CLINICAL STUDY PROTOCOL

Protocol Number: A-101-DPN-201

Version 2.0
28 MARCH 2018

A Phase 2 Open Label Study of A-101 Topical Solution in Subjects with Dermatosis Papulosa Nigra

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PROTOCOL APPROVAL SIGNATURE PAGE

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Chris Powala
Chief Regulatory and Development Officer

28 March 2018
Date

Stuart D. Shanler, MD
Chief Scientific Officer

3/28/18
Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Version Version 2.0 28 MARCH 2018

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 patient or each prospective trial patient's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document used will have the approval of the IRB appropriate for each 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, 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: _____

AMENDMENT HISTORY:

This is the first amendment to the Original Protocol dated 05 MAY 2017**.**

AMENDMENT RATIONALE:

The rationale for Amendment 1 dated 28 MARCH 2018 is to add an additional cohort of subjects (up to an additional 24 subjects) in order to test a different treatment schedule of A-101 Topical Solution 40% for the treatment of DPN lesions.

Protocol Version	**Date**	**Section**	**Revision**
Version 1.0	05 MAY 2017	NA	NA
Version 2.0	28 March 2018	Title Page	Removed "Single Arm" from protocol title; Updated Sponsor Address; Added Kenneth Kostenbader, MD as the Aclaris Safety Monitor
		Protocol Signature Page and Investigator Signature Page	Updated protocol title and version number.
		Synopsis	Updated study design to add cohort 2 as a 2- arm cohort. Clarified the Visit days or cohort 2. Treatment days in cohort 2 changed to Visit 2 (Day 1), Visit 3 (Day 15) and Visit 5 (Day 29).
		Section 3.2.2 Secondary Objective	Corrected the secondary objective to remove safety as a secondary objective. Safety is already included in the primary objective of the study.
		Section 4 Study Design	Study design revised to add cohort 2 as a 2-arm cohort to test a different treatment schedule and to determine whether or not medically abrading the DPN lesion prior to treatment with A-101 40 % Topical Solution affects the treatment outcome.
		Section 4.1 Number of Subjects and Study Centers	Increased the number of subjects to be enrolled to the study with the addition of the second treatment cohort.
		Section 4.2 Duration of Study	Revised the duration of the study to account for addition of 24 subjects being added to the study.
		Section 5.1 Inclusion Criteria	Added an inclusion criteria to ensure that lesions that are identified for treatment are not inflamed or irritated prior to treatment. Also removed the restriction of having the DPN lesions needing to be located in an inconspicuous area based on the safety results obtained from the first treatment cohort.

Protocol Version	Date	Section	Revision
		Section 5.2 Exclusion Criteria	Added an exclusion criteria to exclude subjects with a history of hypertrophic scars.
		Section 6 Study Procedures	Added Table 2 which outlines the study assessment requirements for the cohort 2 subjects.
		Section 7.2 Subject Randomization	Section updated to include randomization information for cohort 2 subjects. Subjects will be randomized to 1 of 2 treatment arms in a 1:2 ratio.
		Section 7.3 Study Medication Packaging, storage and dispensing	The volume fill in the study medication applicator was corrected to reflect the correct volume of 1.5ml.
		Section 7.5 Study Medication Treatment; Section 7.8 Wound care; Section 8.1.1 Standardized Photography; Section 8.1.2 Physician's DPN Lesion Assessment; Section 8.1.3 Lesion Dimensions; Section 8.2 Subject Self-Assessment Scale; Section 9.1 Local Skin Reactions	Updated section to include the treatment information for subjects randomized to the study in cohort 2 [Visit 2 (Day 2), Visit 3 (Day 15) and Visit 5 (Visit 29)] if they meet the criteria for re-treatment.
		Section 9.5.2 Standardized Photography	Deleted section; Section was repeated in Version 1.0 of the document.
		Section 10.2.2 Procedure for reporting a serious adverse event	Updated section with Aclaris's Drug safety monitor.
		Section 12.2 Statistical Analysis of Efficacy Data	Statistical analysis of the efficacy data was updated to reflect how the data from cohort 2 would be analyzed.
		Appendix: Subject Instructions	Updated subject instructions to reflect the changes in the application of Aquaphor for subjects randomized to cohort 2.

Table of Contents

1. SYNOPSIS

Protocol Number: A-101-DPN-201 Synopsis	
Protocol Title:	A Phase 2 Open Label Study of A-101 Topical Solution in Subjects with Dermatosis Papulosa Nigra
Protocol Number:	A-101-201-DPN
Sponsor	Aclaris
Phase of Development	Phase 2

Study Drug Description:

A-101 Solution 40% is hydrogen peroxide that will be supplied in a glass ampule with an applicator to be applied to a dermatosis papulosa nigra (DPN) lesion on subjects with a Fitzpatrick Skin Type of 5 or 6.

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

Study Objectives:

The main objective of this study is to evaluate the safety and efficacy of hydrogen peroxide, A-101 Solution 40% for the treatment of DPN lesions on subjects with a Fitzpatrick Skin Type of 5 or 6.

Study Design:

This is a phase 2 open label study to evaluate the safety of A-101 40% Solution in subjects with DPN. Subjects will be required to have up to four DPN lesions located on the subject's face or neck.

The first cohort of the study will enroll a total of 12 subjects (6 subjects with a Fitzpatrick Skin Type of 5 and 6 subjects with a Fitzpatrick Skin Type of 6) will be enrolled to the study.
The second cohort of the study a total of 24 subjects will be a randomized to a two-arm cohort. Subjects will be randomized to one of the following 2 treatment arms:

- A-101 40% without medically abrading the identified DPN prior to treatment
- A-101 40% with the identified DPN lesions medically abraded prior to treatment

All enrolled/randomized subjects will receive at least one application of A-101 40% solution on up to four target DPN lesions on the subject's face or neck. Subjects in cohort 1 may receive a second application of A-101 40% Solution if the lesions meet the criteria for retreatment at Visit 4 (Day 22). Subjects in cohort 2 may receive up to 3 treatment applications if the lesions meet the criteria for retreatment at Visit 3 (Day 15) and Visit 5 (Day 29). All subjects will be followed on study protocol until Visit 8 (Day 106).

Safety will be evaluated based on clinical laboratory studies (hematology and clinical chemistry), vital signs, urine pregnancy tests, assessment of local skin reactions (LSRs), assessment of adverse events (AEs), and concomitant medication review.

Efficacy will be evaluated based on assessment of each treated Target DPN Lesion based on a four-point Physician's DPN Lesion Assessment Scale. Sites will be required to take standardized color photographs of each of the identified Target DPN Lesions to assist with the documentation of the location of each of the DPN Lesions throughout the study.

Number of Patients to be Enrolled:

A total of 36 subjects will be enrolled to the study. Twelve evaluable subjects will be enrolled to the first cohort (6 subjects with a Fitzpatrick Skin Type of 5 and 6 subjects with a Fitzpatrick Skin Type of 6) and a total of 24 subjects will be randomized to the study in cohort 2.

Number of Study Sites:

This study will be conducted at up to 2 US clinical treatment site.

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

1. Provisions of written informed consent for participation in this study.
2. Male or female ≥ 18 years old.
3. Subject has a clinical diagnosis of dermatosis papulosa nigra (DPN).
4. Subject has a Fitzpatrick Skin Type of 5 or 6.
5. Subject has up to 4 Target DPN Lesions located in an area that has not been previously treated and meets the following requirements as defined below:
    a. Have a clinically typical appearance
    b. Diameter that is between 2mm and less than 5mm
    c. Height that is ≤ 2mm
    d. Have a Physician's DPN Lesion Assessment Score of ≥ 2
    e. Be a discrete lesion
    f. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    g. Not be in an intertriginous fold
    h. Not be on the eyelids
    i. Not be within 5mm of the orbital rim
    j. Not be pedunculated.
    k. Not be inflamed, irritated, or excoriated.
6. Subject chemistry and complete blood count results are within normal limits for the central laboratory. If any of the laboratory values are outside normal limits, the treating investigator must assess the value/s as not clinically significant and document this in the patient's source documents.
7. 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
8. Subject is non-pregnant and non-lactating.
9. 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 of the Target DPN Lesions or which exposes the subject to an unacceptable risk by study participation.
10. 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 DPN lesion.
2. Subject has current systemic malignancy.

3. Subject has a history of hypertrophic scars or keloids
4. Subject has a history of post inflammatory hyperpigmentation lasting longer than 1 year.
5. 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
6. 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 DPN 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-flurouracil (5FU), or ingenol mebutate; 60 days
    - Retinoids; 28 days
    - Microdermabrasion or superficial chemical peels; 14 days
    - Corticosteroids or antibiotics; 14 days.
7. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any Target DPN 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. 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.

Duration of Treatment

The duration of the study participation is anticipated to be a maximum of 127 days per subject. The final visit (Visit 8) has a maximum allowable visit window of 7 days: Study visits for cohort 1 are:

- Visit 1 (Day -13 to 0) screening
- Visit 2 (Day 1) enrollment and study medication treatment
- Visit 3 (Day 8) follow up visit
- Visit 4 (Day 22) follow up visit and second application of study medication if DPN target lesions meets criteria for retreatment
- 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

Study visits for cohort 2 are:

The protocol defined study visits for cohort 2 are:

- Visit 1 (Day -13 to 0) screening

- Visit 2 (Day 1) randomization and study medication treatment
- Visit 3 (Day 15) follow up visit and second application of study medication if DPN target lesions meet criteria for retreatment
- Visit 4 (Day 22) follow up visit
- Visit 5 (Day 29) follow up visit and third application of study medication if DPN target lesions meet criteria for retreatment
- 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 each treated Target DPN Lesion based on a 4- point Physician's DPN Lesion Assessment Scale. Subjects will also evaluate each DPN lesion using a Subject Self-Assessment Scale.

Safety:

Safety will be evaluated based on clinical laboratory studies (hematology and clinical chemistry), vital signs, urine pregnancy tests, assessment of local skin reactions (LSRs), assessment of adverse events (AEs), and concomitant medication review.

Study Drug Administration

A-101 Study medication will be applied to the identified Target DPN lesions during Visit 2 by a member of the investigational site staff. In cohort 1, Target DPN lesions that have not cleared at Visit 4 (Day 22) may be re-treated. In cohort 2, Target DPN lesions may be treated up to 3 times if they meet the criteria for retreatment [Visit 3 (Day 15) and Visit 5 (Day 29)]. Subjects randomized to ARM B in cohort 2 will have their Target DPN Lesions medically abraded prior to treatment with A-101 study medication.

The A-101 40% Solution will be applied to each of the Target DPN Lesions for approximately 15 seconds. Each DPN lesion will be treated up to 3 times while waiting approximately 60 seconds between each application.

Statistical Methods

Efficacy Analysis

Efficacy endpoints will include summary statistics (frequency distributions, proportions, means, medians and standard deviations, as appropriate) by visit for the following parameters: Physician's DPN Lesion Assessment scale results per treated lesion, subject responders defined by Physician's DPN Lesion Assessment scale outcome, and changes from baseline Target lesion diameter. Summaries will also be presented by subject Fitzpatrick Skin Type.

Exploratory Analysis

Exploratory efficacy endpoints will include summary statistics (frequency distributions, proportions, means, medians and standard deviations, as appropriate) by visit for the following parameters: Subject Self-Assessment scale results per treated lesion, and subject responders defined by Subject Self-Assessment scale outcome. Summaries will also be presented by subject Fitzpatrick Skin Type.

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
CBC	Complete Blood Count
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
DPN	Dermatosis Papulosa Nigra
e.g.	for example (Latin; *exempla gratia*)
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_2O_2	Hydrogen Peroxide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	that is (Latin; *id est*)
IPL	Intense Pulsed Laser
IRB	Institutional Review Board
ITT	Intent To Treat
LOCF	Last Observation Carried Forward
LSR	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter

Abbreviation	Term
Mm	Millimeter
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 Operation 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.

Dermatosis Papulosa Nigra (DPN) is a clinical variant of SK primarily affecting individuals of higher Fitzpatrick Skin Types (e.g. Fitzpatrick Type 5 or 6) and is seen in up to 35% of African Americans (Hairston, 1961). Like clinically typical larger SKs, each DPN lesion is a benign epithelial tumor, and histologically, the lesions are indistinguishable from larger SKs. DPN lesions are characterized by small brown or black "spots" typically appearing around the malar and periorbital regions but can also appear on other areas of the face, neck and chest (Kundu, 2017). The lesions can vary in size and number, though typically they begin as minute papules that increase in size to from 1 to 5 mm (or more) and they become more and more numerous over time. DPN does affect women more commonly than men, and, like clinically typical larger SKs, do not spontaneously resolve.

Treatment options for the removal of DPN lesions include scissor excision, shave excision, cryosurgery, electrodesiccation, curettage, dermabrasion, and laser removal. However, with these treatments comes the risk of potential scarring and changes in pigmentation (Kundu, 2017).

While there are existing methods for treating DPN lesions, many require specialized training and the use of expensive equipment, they are often quite painful and may require anesthesia and/or analgesia, and they are often complicated by significant adverse cosmetic outcomes. Both hypopigmentation and hyperpigmentation, which may be transient but is often permanent, are common, particularly when cryosurgery is employed and particularly in individuals of the darker skin types prone to develop DPN. The potential for scarring at the treatment site, particularly with the surgical treatment options, and the typical post-surgical risks of bleeding and infection increase the risk that the sequela from the treatment of these benign, but cosmetically disturbing, lesions may be worse than the lesions themselves. There is a great unmet need for a safe, effective, standardized and less painful treatment for this extremely common condition in patients of darker skin types.

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

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

A-101 (hydrogen peroxide) Solution has been tested in three phase 2 clinical programs and three phase 3 clinical programs in which over 1000 subjects with SK lesions were treated. Data from these studies demonstrated that A-101 Solution 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. Refer to Table 1 for a complete list of completed A-101 clinical trials for the treatment of SK lesions.

Table 1 Summary of Previous Clinical Trials with A-101 Solution in Seborrheic Keratosis

Clinical Study Report	Study Phase	Study Population Countries	Total Randomized or Enrolled/ Completed	Study Design	Treatment Duration	Dose
A-101-SEBK-201	2	At least 4 SK target lesions on the back US	35/34	Single-center, randomized, double-blind, vehicle-controlled, within-subject comparison	Application on Day 1, target lesions meeting criteria were to be retreated on Day 22 (end of study on Day 78)	A-101 solution 25%, 32.5%, 40%, and vehicle
A-101-SEBK-202	2	At least 4 SK target lesions on the trunk/ extremities US	172/169	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group	Application on Day 1, target lesions meeting criteria were to be retreated on Day 22 (end of study on Day 106)	A-101 solution 32.5%, 40%, and vehicle
A-101-SEBK-203	2	1 SK target lesion on the face US	119/116	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group	Application on Day 1, target lesions meeting criteria were to be retreated on Day 22 (end of study on Day 106)	A-101 solution 32.5%, 40%, and vehicle
A-101-SEBK-301	3	4 SK target lesions, including at least 1 on the face and at least 1 on the trunk or extremities US	450/446	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group	Application on Day 1, target lesions meeting criteria were to be retreated on Day 22 (end of study on Day 106)	A-101 solution 40% and vehicle
A-101-SEBK-302	3	4 SK target lesions, including at least 1 on the face and at least 1 on the trunk or extremities US	487/479	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group	Application on Day 1, target lesions meeting criteria were to be retreated on Day 22 (end of study on Day 106)	A-101 solution 40% and vehicle

Clinical Study Report	Study Phase	Study Population Countries	Total Randomized or Enrolled/ Completed	Study Design	Treatment Duration	Dose
A-101-SEBK-303	3	4 SK target lesions on trunk, extremities, and face US	147/139	Open-label	Application on Day 1, target lesions meeting criteria were to be retreated on Days 22, 43, and 64 (end of study on Day 148)	A-101 solution 40%

3. STUDY RATIONALE AND OBJECTIVES

3.1. Rationale

The rationale for this study is to assess safety and efficacy of A-101 Solution 40% when applied to up to 4 DPN Target Lesions in subjects with Fitzpatrick Skin Type 5 or 6.

Aclaris recently completed three phase clinical studies (301, 302, and 303) that demonstrated that A-101 40% Solution is both safe and effective in treating subjects with seborrheic keratosis lesions on the face, trunk and extremities. Based on this data and the classification of DPN lesions as a clinical variant of seborrheic keratosis, a study of A-101 in darker skin type subjects with DPN lesions is warranted.

3.2. Study Objectives

3.2.1. Primary Objective

The main objective of this study is to evaluate the safety and efficacy of hydrogen peroxide, A-101 Solution 40% for the treatment of DPN lesions on subjects with a Fitzpatrick Skin Type of 5 or 6.

3.2.2. Secondary Objective

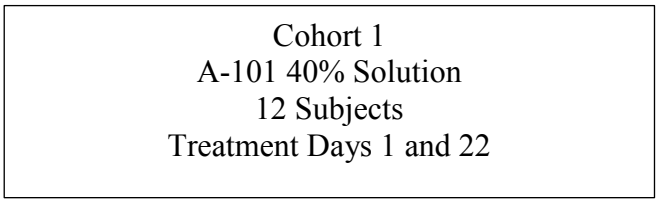
The secondary objective of this study is to assess durability of response.

3.2.3. Exploratory Objective

An exploratory objective of this study is to evaluate the subject's assessment of the treatment with A-101 to DPN lesions using a Subject Self-Assessment Scale.

4. STUDY DESIGN

This is a phase 2 open label study with an initial single arm safety cohort evaluating A-101 40% Topical Solution in subjects with DPN lesions. A second cohort will randomize subjects to two different treatment arms to evaluate different treatment schedules using A-101 40% Topical Solution. Refer to Figure 1: A-101-DPN-201 Study Design. Subjects may have up to 4 Target DPN lesions treated. Lesions that are selected for treatment must be on the subject's face or neck. Subjects will be required to complete a total of 8 study visits.



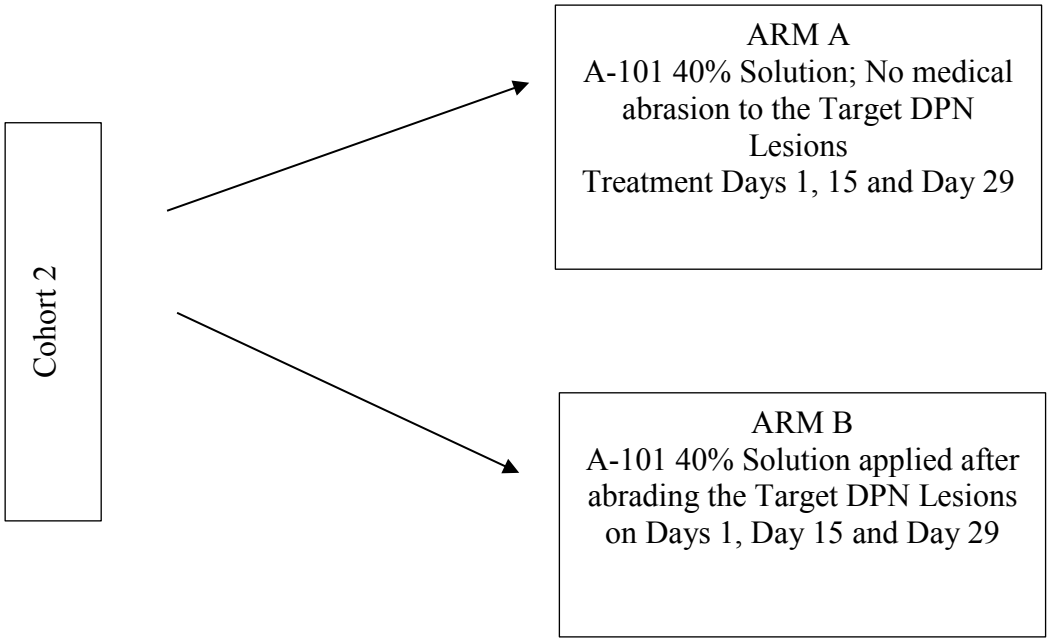


Figure 1: A-101-DPN-201 Study Design

The protocol defined study visits for cohort 1 are:

- Visit 1 (Day -13 to 0) screening
- Visit 2 (Day 1) enrollment and study medication treatment
- Visit 3 (Day 8) follow up visit
- Visit 4 (Day 22) follow up visit and second application of study medication if DPN target lesions meet criteria for retreatment
- 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

The protocol defined study visits for cohort 2 are:

- Visit 1 (Day -13 to 0) screening
- Visit 2 (Day 1) randomization and study medication treatment
- Visit 3 (Day 15) follow up visit and second application of study medication if DPN target lesions meet criteria for retreatment
- Visit 4 (Day 22) follow up visit
- Visit 5 (Day 29) follow up visit and third application of study medication if DPN target lesions meet criteria for retreatment
- Visit 6 (Day 50) follow up visit

- Visit 7 (Day 78) follow up visit;
- Visit 8 (Day 106) follow up visit; end of study

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

4.1. Number of Subjects and Study Centers

Approximately 36 evaluable subjects will be enrolled at up to 2 investigational centers in the US.

4.2. Duration of Study

The duration of study participation is anticipated to be a maximum of 127 days per subject. Subjects will have a total of 8 study visits.
The maximum anticipated duration for the study is 18 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. Provisions of written informed consent for participation in this study.
2. Male or female ≥ 18 years old.
3. Subject has a clinical diagnosis of dermatosis papulosa nigra.
4. Subject has a Fitzpatrick Skin Type of 5 or 6.
5. Subject has up to 4 Target DPN Lesions located on the subject's face or neck that has not been previously treated and meets the requirements as defined below:
    a. Have a clinically typical appearance
    b. Diameter that is between 2mm and less than 5mm
    c. Height that is ≤ 2mm
    d. Have a Physician's DPN Lesion Assessment Score of ≥ 2
    e. Be a discrete lesion
    f. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    g. Not be in an intertriginous fold
    h. Not be on the eyelids
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6. Subject chemistry and complete blood count results are within normal limits for the central laboratory. If any of the laboratory values are outside normal limits, the treating investigator must assess the value/s as not clinically significant and document this in the patient's source documents.
7. 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
8. Subject is non-pregnant and non-lactating.
9. 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 DPN Lesions or which exposes the subject to an unacceptable risk by study participation.

10. 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 DPN lesion.
2. Subject has current systemic malignancy.
3. Subject has a history of hypertrophic scars or keloids
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5. 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
6. 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 DPN 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-flurouracil (5FU), or ingenol mebutate; 60 days
    - Retinoids; 28 days
    - Microdermabrasion or superficial chemical peels; 14 days
    - Corticosteroids or antibiotics; 14 days.
7. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any Target DPN 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. 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
- 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 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 enrolled to the study but does not receive a dose of study drug, then the subject will be replaced.

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

Table 2: Study Procedures for Cohort 1 Subjects

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	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 DPN Lesion Assessment[9]	X	X		X		X	X	X
Subject Self-Assessment Scale[10]	X	X		X		X	X	X
Lesion Dimensions[11]	X	X		X		X	X	X
Standardized Photography[12]	X	X		X		X	X	X
Subject Enrollment		X[13]						
Local Skin Reactions		X[14]	X	X[14]	X	X	X	X
Study Medication Application		X[15]		X[15]				
Wound Care[16]		X		X				
Subject Instructions	X	X	X	X	X	X	X	X
Concomitant therapies[17]		X	X	X	X	X	X	X
Adverse Events[18]		X	X	X	X	X		

[1]Subject inclusion/exclusion criteria will be re-assessed prior to study enrollment during Visit 2.
[2]Investigational 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.
[3]Each subject's skin must be assessed during Visit 1 using the Fitzpatrick Skin Type Assessment. Refer to Section 9.5.1 for the scale.
[4]Vital signs [including temperature, pulse, respiratory rate, blood pressure, and weight (Visit 1 only)] will be measured by a qualified staff member at Visit 1, Visit 2 prior to study enrollment, and at Visit 8.
[5]Prior medications/therapies will be collected for a time-period of 13 days prior to Visit 2. Refer to Section 7.7 for a list of permitted and restricted concomitant medications.

[6]A complete blood count (including hematocrit, hemoglobin, platelet count, red blood cell count, 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.

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

[8]The treating investigator will identify up to 4 Target DPN Lesions. Each lesion that is identified to be treated must be in an inconspicuous area.

[9] The investigator will assess each DPN target lesion based on a 4- point Physician's DPN Lesion Assessment Scale. In order to be eligible for enrollment at Visit 2, the subject must have at least one DPN lesion that is between 2mm and 5 mm in diameter. At Visit 2 and if applicable at Visit 4, the investigator must assess each DPN lesion that is to be treated prior to application of the study medication.

[10] Subjects will use a Subject Self-Assessment Scale to assess each Target DPN Lesion at Screening Visit 1, at Visit 2 prior to application of the study medication, at Visit 4 (prior to study medication, if applicable), at Visit 6, Visit 7 and Visit 8.

[11]The investigator will measure the diameter and thickness of each identified Target DPN Lesions at Visit 1 and prior to enrollment. at Visit 2. At Visit 4 prior to retreatment (if applicable, at Visit 6, Visit 7 and at Visit 8 the investigator will only measure the diameter of each Target DPN Lesion.

[12] 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 DPN lesion that has been treated using the Aclaris supplied camera. All photographs will be sent to a central imaging laboratory.

[13] Subjects will be enrolled to the study at Visit 2 prior to application of study medication. Investigational study staff will re-confirm subject eligibility prior to study enrollment.

[14] Both the investigator and the subject will assess each Target DPN Lesion for symptoms associated with irritation. At Visit 2 and Visit 4, the investigator will assess the Target DPN Lesions prior to application of the study medication and 20 (± 4) minutes after treatment with the study medication. At Visit 2 and Visit 4, the subject will assess the Target DPN Lesions prior to application of the study medication and 10 (±4) minutes after the treatment of the study medication.

[15] A-101 study medication will be applied by the treating physician. All Target DPN Lesions will be treated with study medication following enrollment at Visit 2. If a Target DPN 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 DPN Lesions for at least 6 hours and they must NOT apply any topical products to the Target DPN Lesions for at least 6 hours.

[16]All subjects will be required to apply Aquaphor to all Target DPN Lesions the morning after study medication application. Sites will be provided supplies of Aquaphor by the Sponsor.

[17]All 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.

[18]The reporting period for Serious Adverse Events (SAEs) begins when the subject signs the informed consent. Refer to Section 10 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 5 (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.

Table 3: Study Procedures for Cohort 2 Subjects

Visit	V1 Screening	V2	V3	V4	V5	V6	V7	V8
Treatment Day	-13 to 0	1	15	22	29	50	78	106
Treatment Window	N/A	N/A	+ 4 days	+ 2 days	+4 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	X[4]						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 DPN Lesion Assessment[9]	X	X	X	X	X	X	X	X
Subject Self-Assessment Scale[10]	X	X	X	X	X	X	X	X
Lesion Dimensions[11]	X	X	X	X	X	X	X	X
Standardized Photography[12]	X	X	X	X	X	X	X	X
Subject Randomization		X[13]						
Local Skin Reactions		X[14]	X[14]	X	X[14]	X	X	X
Study Medication Application		X[15]	X[15]		X[15]			
Wound Care[16]		X	X		X			
Subject Instructions	X	X	X	X	X	X	X	X
Concomitant therapies[17]		X	X	X	X	X	X	X
Adverse Events[18]		X	X	X	X	X		

[1]Subject inclusion/exclusion criteria will be re-assessed prior to study enrollment during Visit 2.
[2]Investigational 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.
[3]Each subject's skin must be assessed during Visit 1 using the Fitzpatrick Skin Type Assessment. Refer to Section 9.5.1 for the scale.
[4]Vital signs [including temperature, pulse, respiratory rate, blood pressure, and weight (Visit 1 only)] will be measured by a qualified staff member at Visit 1, Visit 2 prior to study enrollment, and at Visit 8.
[5]Prior medications/therapies will be collected for a time-period of 13 days prior to Visit 2. Refer to Section 7.7 for a list of permitted and restricted concomitant medications.

[6]A complete blood count (including hematocrit, hemoglobin, platelet count, red blood cell count, 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.
[7] Woman of child bearing potential will be required to have a urine pregnancy test at Visit 1, at Visit 2 prior to enrollment and at Visit 8.
[8]The treating investigator will identify up to 4 Target DPN Lesions.
[9] The investigator will assess each DPN target lesion based on a 4-point Physician's DPN Lesion Assessment Scale. In order to be eligible for enrollment at Visit 2, the subject must have at least one DPN lesion that is between 2mm and 5 mm in diameter. The investigator must assess each DPN lesion that is to be treated prior to application of the study medication at Visit 2, if applicable at Visit 3 and Visit 5.
[10] Subjects will use a Subject Self-Assessment Scale to assess each Target DPN Lesion at Screening Visit 1, Visit 2 (prior to application of the study medication), Visit 3 (prior to study medication, if applicable), Visit 4, Visit 5 (prior to study medication, if applicable), Visit 6, Visit 7 and Visit 8.
[11]The investigator will measure the diameter and thickness of each identified Target DPN Lesions at Visit 1 and prior to enrollment. at Visit 2. At Visit 3 (prior to treatment, if applicable), Visit 4, Visit 5 (prior to retreatment if applicable), Visit 6, Visit 7 and Visit 8 the investigator will only measure the diameter of each Target DPN Lesion.
[12] At Visits 1, Visit 2 (prior to study medication application) Visit 3 (prior to study medication application, if applicable), Visit 4, Visit 5 (prior to study medication application if applicable), Visit 6, Visit 7, and Visit 8, a qualified investigational center staff member will take a photograph of each DPN lesion that has been treated using the Aclaris supplied camera. All photographs will be sent to a central imaging laboratory.
[13] Subjects will be enrolled to the study at Visit 2 prior to application of study medication. Investigational study staff will re-confirm subject eligibility prior to study enrollment.
[14] Both the investigator and the subject will assess each Target DPN Lesion for symptoms associated with irritation. At Visit 2, Visit 3 and Visit 5, the investigator will assess the Target DPN Lesions prior to application of the study medication and 20 (± 4) minutes after treatment with the study medication, if applicable. At Visit 2, Visit 3, and Visit 5, the subject will assess the Target DPN Lesions prior to application of the study medication and 10 (±4) minutes after the treatment of the study medication, if applicable.
[15] A-101 study medication will be applied by the treating physician. All Target DPN Lesions will be treated with study medication following enrollment at Visit 2. Subjects randomized to ARM B will be required to have their Target DPN Lesions medically abraded prior to treatment with A-101 study medication. If a Target DPN Lesion meets the criteria for re-treatment as defined in Section 7.5, the lesion will be re-treated at Visit 3, and Visit 5. Following application of study medication, subjects must NOT wash/submerge the Target DPN Lesions for at least 6 hours and they must NOT apply any topical products to the Target DPN Lesions for at least 6 hours.
[16]All subjects will be required to apply Aquaphor to all Target DPN Lesions the morning after study medication application. Sites will be provided supplies of Aquaphor by the Sponsor.
[17]All 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.
[18]The reporting period for Serious Adverse Events (SAEs) begins when the subject signs the informed consent. Refer to Section 10 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 5 (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 medication for this study is A-101 Solution 40%. The study medication solution is clear and colorless solution.

Table 4 Study Medication Information

Study Medication Name	A-101 Solution 40%
Manufacturer	James Alexander Corporation, Blairstown NJ
A-101 concentration (%)	40
Pharmaceutical Form	Solution
Storage Conditions	59ºF to 77ºF (15ºC to 25ºC) protected from excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area
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 15 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 3 times.

7.2. Subject randomization

Cohort 1 of this study is an open label study. Subject randomization is not applicable for this part of the study.

Subjects that are determined to be eligible for treatment in Cohort 2 will be randomized in a 1:2 ratio to one of the following treatment arms.

- ARM A: A-101 40% Solution; No medical abrasion to the Target DPN Lesions Treatment Days 1, 15 and 29
- ARM B: A-101 40% Solution applied after medically abrading the Target DPN Lesions; Treatment Days 1, 15 and 29

7.3. Study medication packaging, storage and dispensing

A-101 Solution 40% 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 1.5 milliliters (mL) of study medication. The ampoule is provided inside a sealed polyethylene tube with a flocked, doe foot applicator on one end.

The investigational site will be supplied with a lot of A-101 Solution 40% labelled appropriately for the study. Investigational sites will be required to maintain full drug accountability for all applicators that are received at the site.

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

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 DPN Target Lesions on the appropriate study subject only.

The treating investigator performing the study medication treatments must comply with the study medication handling warnings. In cohort 1, the treating physician will apply the A-101 Solution 40% to each DPN Target Lesion at Visit 2 and at Visit 4, if applicable.

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

- The DPN 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 DPN 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).

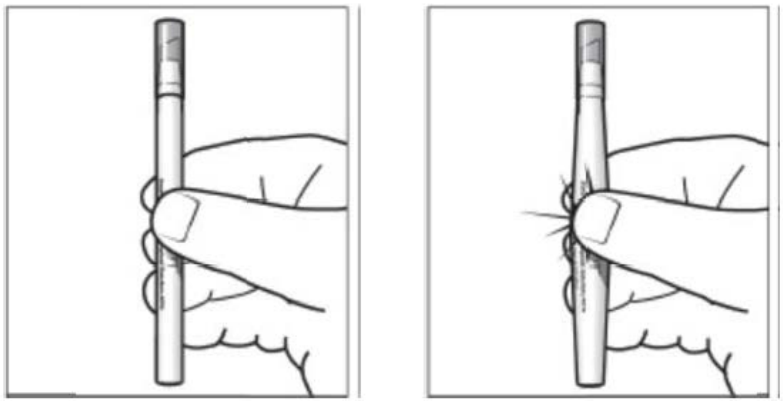
In cohort 2, for those subjects randomized to ARM B, the treating physician will medically abrade the Target DPN Lesion prior to apply the A-101 study medication. All subjects in cohort 2 will be allowed to have up to 3 treatment applications of the A-101 study medication. If subjects meet the criteria as outlined above, subjects in cohort 2 may receive 2 additional study medication applications at Visit 3 (Day 15) and Visit 5 (Day 29).

7.5.1. Preparing the Study Medication for Application

To perform a study medication treatment for a DPN Target Lesion a staff member will select the appropriate study medication applicator. Then follow these instructions:

- 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**
  - 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.
- Activate and prime the applicator:
  - Hold the applicator horizontally with the tip/cap end pointing away from the subject and any staff; ensure the applicator tip protective cap is firmly attached
  - Place the thumbs and forefingers of both hands on the applicator tube at the point on the applicator where indicated
  - Gently but firmly squeeze the applicator tube with your fingers until the glass ampoule is crushed, you should hear an audible "SNAP"
  - Repeatedly squeeze the applicator tube moving your finger location up and down the tube to the tip and back again 2 or 3 times to ensure the glass ampoule containing the study medication has been completely crushed
  - Examine the applicator tube and tip for any wetness or leaking (if the applicator is 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)
  - Hold the applicator in one hand and orient it vertically with the TIP FACING DOWN

- With your other hand, gently flick or tap the applicator tube to ensure any air bubbles have been displaced and the study medication flows downward toward the tip
- Remove the applicator tip protective cap
- Hold the applicator with one hand over a disposable paper free absorbent material (*e.g.*, gauze pad), place your thumb and forefinger approximately 0.5 inch above top of the finger grip on the applicator tube and gently and repeatedly squeeze the applicator tube until you see a drop of study medication visible in the opening of the holed applicator tip. The flow of study medication may be controlled by gently squeezing to apply pressure to the sides of the applicator tube to express more study medication, and by releasing pressure on the tube slow or stop the delivery of the study medication
- The applicator is now ready to use in a treatment. Refer to Figure 2 for a visual diagram of the steps needed to prepare the A-101 study medication applicator.



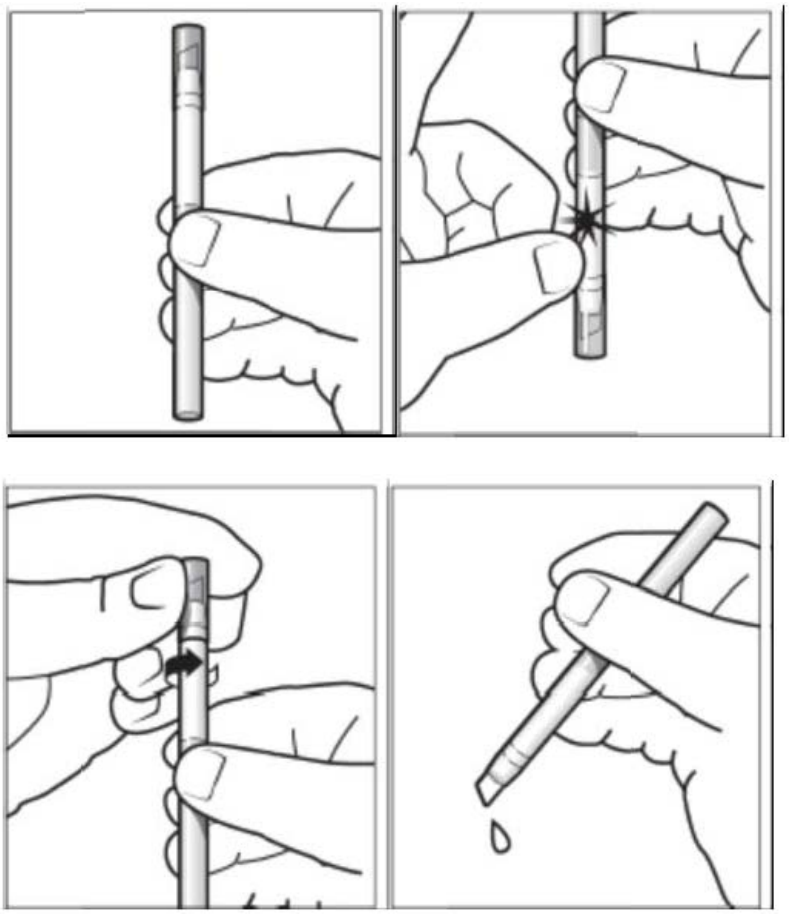


Figure 2: Diagram Showing the Process for Preparing the A-101 study medication applicator

7.5.2. 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
- **Subjects randomized to ARM B of cohort 2 will have their DPN lesions medically abraded prior to the application of the A-101 study medication.
- Using firm pressure, while avoiding squeezing the applicator barrel, apply one drop of study medication onto the DPN lesion and then move applicator around in a circular motion to fully saturate the lesion. Using the smaller Q-tip applicator that is supplied massage the A-101 study medication into the DPN lesion for approximately 15 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 DPN Target Lesion is wet with study medication at the end of the ~15 second application
- Allow the DPN Target Lesion to remain undisturbed for ~60 seconds
- After ~60 seconds repeat the ~15 second application process
- Repeat the application/waiting cycle until the study medication has been applied to the DPN Target Lesion up to 3 times.

Record the number of times each Target DPN Lesion is treated during a treatment visit and record the time the final treatment is completed for the last treated Target DPN Lesion as the Treatment Completion Time.

It is acceptable to treat multiple Target DPN 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 DPN Lesion do not disturb the DPN 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 DPN Lesion with an absorbent pad or dry gauze without wiping or rubbing.

7.5.3. Applying Study Medication to the Neck

To apply the study medication to a Target DPN Lesion on the neck 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 DPN 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

- **Subjects randomized to ARM B of cohort 2 will have their DPN lesions medically abraded prior to the application of the A-101 study medication.
- Using firm pressure, squeezing in the middle of the applicator, apply one drop of study medication onto the DPN lesion and then move applicator around in a circular motion to fully saturate the lesion. Using the smaller Q-tip applicator that is supplied massage the A-101 study medication into the DPN lesion for approximately 15 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 DPN Lesion is fully saturated with study medication at the end of the ~15 second application
- Allow the Target DPN Lesion to remain undisturbed for ~60 seconds
- After ~60 seconds repeat the ~15 second application process
- Repeat the application/waiting cycle until the study medication has been applied to the Target DPN Lesion up to 3 times.

7.6. 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.

7.7. Previous and Concomitant Therapies

7.7.1. Previous therapies

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

7.7.2. 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.

7.7.3. 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**.

7.8. Wound Care

All subjects will be required to apply Aquaphor to the treated Target DPN Lesions beginning the morning after the application of study medication. Sites will be provided with supplies of Aquaphor that may be dispensed to subjects enrolled to the study. Subjects will be instructed to apply a thin layer of Aquaphor 2x's per day, as needed. Subjects will be instructed to stop applying the Aquaphor 12 hours prior Visit 4 (treatment visit, cohort 1 subjects) or 12 hours prior to Visit 3 and Visit 5 for cohort 2 subjects.

8. ASSESSMENTS OF CLINICAL EFFICACY

8.1. Target Lesion Identification

At Visit 1, the investigator will identify up to 4 Target DPN Lesions located on the subject's body.

At Visit 1, each Target Lesion must:

- Have a clinically typical appearance
- Have a Physician's DPN Lesion Assessment score of ≥ 2
- Have a diameter that is between 2 mm and less than 5 mm
- Have a height or thickness that is ≤2mm
- Be a discrete lesion
- Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
- Not be in an intertriginous fold
- Not be on the eyelids
- Not be within 5mm of the orbital rim
- Not be pedunculated.
- Not be inflamed, irritated, or excoriated.

Record the approximate location of each Target DPN Lesion on the appropriate body chart in the CRFs. Also, identify the body area (*i.e.*, face, neck) for each Target DPN Lesion in the CRFs. Number the Target DPN 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 to identify the Target DPN Lesions.

8.1.1. Standardized photography

At Visits 1, 2, 3 (prior to retreatment, if applicable for cohort 2 subjects ONLY), 4 (prior to retreatment, if applicable for cohort 1 subjects ONLY), 5 (prior to retreatment, if applicable for cohort 2 subjects ONLY), 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 DPN Lesion and to assist with relocating the Target DPN Lesion and the Target DPN 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 DPN Lesion Assessment

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

At Visits 1, 2, 3 (cohort 2 ONLY), 4 (cohort 1 ONLY), 5 (cohort 2 ONLY), 6, 7 and 8, the investigator will assess the Target DPN Lesion using the scale below and report the one integer that best describes the severity of the Target DPN Lesion. At Visit 2, and if appropriate at Visit 4 for cohort 1 subjects or Visit 3 and Visit 5 for cohort 2 subjects, the investigator must complete the Physician's DPN Lesion Assessment prior to the study medication treatment.

Table 5: Physician's DPN Lesion Assessment Definitions

Physician's DPN Lesion Assessment	
Grade	Descriptor
0	Clear: no visible DPN lesion;
1	Near Clear: a slightly visible DPN lesion; lesion may be macular
2	Small: a visible DPN lesion with a diameter of less than 3 mm
3	Large: a visible DPN lesion that is elevated with a diameter of ≥3 mm

At Visit 1 and Visit 2, for the subject to be eligible for enrollment to the study the identified DPN lesions must have a Physician's Lesion Assessment of grade ≥ 2.

8.1.3. Lesion Dimensions

At Visit 1 and at Visit 2 prior to enrollment the Investigator will be required to measure the diameter and thickness of each Target DPN Lesion. For subjects enrolled to cohort 1 the investigator will measure the diameter of each Target DPN Lesion using the ruler at Visit 4 (prior to retreatment, if applicable), Visit 6, Visit 7 and Visit 8. For subjects randomized to cohort 2, the investigator will measure the diameter of each Target DPN Lesion t Visit 3 (prior to retreatment if applicable), Visit 4, Visit 5 (prior to retreatment if applicable) Visit 6, Visit 7 and Visit 8.

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

- A diameter that is between 2 mm and less than 5 mm.
- A height or thickness that is ≤ 2 mm.

8.2. Subject Self-Assessment Scale

For subjects enrolled to cohort 1, each subject will use the Subject Self-Assessment Scale to assess each Target DPN Lesions at the following visits: Visit 1, Visit 2 (prior to treatment), Visit 4 (prior to treatment), Visit 6, Visit 7 and Visit 8. For subjects randomized to cohort 2, each subject will use the Subject Self-Assessment Scale to assess each Target DPN Lesion at the following visits: Visit 1, Visit 2 (prior to treatment), Visit 3 (prior to retreatment, if applicable), Visit 4, Visit 5 (prior to retreatment, if applicable) Visit 6, Visit 7 and Visit 8.

Subject Self-Assessment Scale	
Grade	**Descriptor**
0	No Visible DPN Lesion
1	Mild; Slightly raised DPN lesion
2	Moderate; Obviously raised DPN lesion
3	Severe; Prominent DPN lesion

8.3. 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 DPN 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 DPN Lesions to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the Target DPN Lesions, if excessive exposure cannot be avoided
- Bring the subject instruction sheet with them to each visit.

On study visit days, the subjects should:

- When appropriate for the Target DPN 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 DPN 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 DPN Target Lesions for at least 6 hours
    - Apply any topical products to the Target Lesions for at least 6 hours.
- Apply Aquaphor to the Target DPN Lesions the morning after the treatment visits (Visit 2 and Visit 4, cohort 1, or Visit 2, Visit 3 and Visit 5, cohort 2

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 Target DPN Lesion during the study medication treatment process
- White Petrolatum USP for protecting sensitive areas during study medication treatments for Target Lesions on the face
- Individual subject supplies of Aquaphor for Wound Care.

- 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
- Small Q-tip applicators
- 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 study following safety assessments according to the schedules noted below.

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 DPN Lesion site, which includes the Target DPN Lesion and the area immediately surrounding the Target DPN Lesion.

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 DPN Lesion site respectively.

The investigator will assess the LSR signs as follows:

- Visits 2 and 4 (cohort 1) and Visits 2, 3 and 5 (cohort 2):
  - For each Target DPN Lesion site report the severity for all signs prior to any study medication treatment

  - For every treated Target DPN 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 (cohort 1) and Visits 4 and 6-8 (cohort 2):
  - For each Target DPN Lesion site, report the severity for all signs.

The subject will assess the LSR symptoms as follows:

- Visits 2 and 4 (cohort 1) and Visits 2, Visit 3 and Visit 5 (cohort 2):
  - For each Target DPN 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 DPN 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 (cohort 1) and Visits 4 and 6-8 (cohort 2):
  - For each Target DPN 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 6 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, Visit 4 (cohort 1 ONLY) prior to treatment and at Visit 8. The following items will be measured:

- Body temperature
- Pulse rate
- Respiration rate

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

Any measure that is, in the opinion of the investigator, abnormal AND clinically relevant (CR) must be recorded as history if found prior to the first study medication 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 CR or not clinically relevant (NCR) 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 7.5 mL of blood will be collected for each chemistry sample and 3ml of blood will be collected for the complete blood count (CBC). 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/email. The investigator must review all laboratory reports in a timely manner and note NCS or CS to define the clinical significance 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 enrolled to the study 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 (Section 11) 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 (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 7 Fitzpatrick Skin Type Scoring System

Skin Type Classification	Description
Type I	always burns, never tans
Type II	usually burns, tan less than average (with difficulty)
Type III	sometimes mild burn, tan about average
Type IV	rarely burn, tan more than average (with ease)
Type V	very rarely burns, tans very easily
Type VI	never burns, never tans

(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.

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 CR 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, or
- Is a congenital anomaly/birth defect
- Is an important medical event.

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

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

Important medical events are those that may not be immediately life threatening, result in death or hospitalization, but are clearly of major clinical significance and may jeopardize the subject or require intervention to prevent one of the outcomes listed in the SAE definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization.

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 6. Non-serious adverse events that occur between the time the subject was consent 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 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 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 Drug Safety Monitor of the SAE by telephone:

Kenneth Kostenbader, MD
Aclaris Therapeutics, Inc.
640 Lee Road, Suite 200
Wayne, PA 19087
Telephone: 484-329-2176
Serious Adverse Event Facsimile: 484-324-2359
Email: kkostenbader@aclaristx.com

3. Within 24-hours complete, as fully as possible, an AE CRF and an SAE form; fax or e-mail the forms and any other relevant information (*e.g.*, concomitant medication CRF, medical history CRF, laboratory test results) to the Drug Safety Monitor.
4. Monitor and document the progress of the SAE until it resolves or, if not resolved after the subject's last study visit, until in the opinion of the investigator the AE reaches a clinically stable outcome with or without sequelae AND the investigator and Drug Safety Monitor agree that the SAE is satisfactorily resolved.
5. Inform the Drug Safety Monitor of SAE updates by telephone followed by an SAE form update sent by fax or by e-mail.
6. Comply with the appropriate regulatory requirements and Aclaris Therapeutics, Inc. instructions regarding reporting of the SAE to the responsible Institutional Review Board (IRB) or Ethics Committee (EC).

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 minilaparotomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. Women who are WOCBP and are using an active method of birth control, are practicing abstinence or where the partner is sterile (*e.g.*, vasectomy), should be considered to be WOCBP.

All WOCBP must use an 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).

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 Considerations

The results of this first DPN study are intended to provide the data required for sample size estimation for future studies.

12.2. Statistical Analysis of Efficacy Data

Efficacy summaries and analyses (where appropriate) will be based on the per protocol (PP) population of all treated subjects completing all treatment visits and Visit 8 with no major protocol violations. In addition, efficacy summaries may be presented for the intent to treat (ITT) population of all treated subjects with at least one post-baseline visit, using last observation carried forward (LOCF) to impute missing data. Efficacy endpoints will include summary statistics (frequency distributions, proportions, means, medians and standard deviations, as appropriate) by visit for the following parameters: Physician's DPN Lesion Assessment scale results per treated lesion, subject responders defined by Physician's DPN Lesion Assessment scale outcome, and changes from baseline treated lesion diameter.

Comparative inferential analyses will be conducted for data collected from subjects in Cohort 2. The primary efficacy comparisons between the two Cohort 2 treatment groups will be made on the per-subject mean change across all treated lesions in Physician's DPN Lesion Assessment scale from baseline to the final visit using an ANCOVA model. A similar secondary analysis will be performed on the pre-subject mean percent of treated lesions that are clear (PLA=0), and a similar analysis based on clear or near-clear lesions (PLA < 2). Another secondary analysis will be performed on subject responders with all treated lesion PLA scores = 0, as well as a similar analysis on subject responders with all treated lesion PLA scores < 2. An analysis of change from baseline lesion diameter will be conducted using the same methodology as the primary efficacy analysis. All analyses will be conducted at each post-baseline visit where possible. Summaries will also be presented by subject Fitzpatrick Skin Type.

12.3. Exploratory Analysis

Exploratory efficacy endpoints will include summary statistics (frequency distributions, proportions, means, medians and standard deviations, as appropriate) by visit for the following parameters: Subject Self-Assessment scale results per treated lesion, and subject responders defined by Subject Self-Assessment scale outcome. Analyses similar to the secondary analyses described above will be conducted on the Subject Self-Assessment scale results. Summaries will also be presented by subject Fitzpatrick Skin Type. Summaries will be based on the PP population

12.4. Statistical Analysis of Safety Data

Safety analyses will include descriptive statistics calculated on the safety parameters using the ITT population. The proportion of subjects with treatment-emergent adverse events will be tabulated and presented by study treatment group 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.

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

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 patients 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), use of prohibited medications,

A **protocol violation** is defined as any divergence from the protocol-specific inclusion/exclusion criteria, use of any prohibited medications to treat an identified DPN target lesion or a divergence from 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 patients 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 study monitor is the primary association between the sponsor/CRO and each investigator. The main responsibilities of the study monitors are to visit each investigator before, during, and after the study to ensure adherence to the protocol that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before their participation in the study.

The study monitors will contact each investigator and visit the study center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs, corresponding subject medical records, study medication dispensing records and study medication storage area, and any other documents considered source documentation) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic case report forms (eCRFs) are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the eCRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor/CRO personnel may, on request, accompany the study monitor on visits to the study center. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

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.

All required study data will be collected from primary source documents (or direct electronic capture from validated instrument operating systems, where applicable) by appropriately designated and trained personnel at the clinical facility, and CRFs must be completed for each patient screened consistent with the data source. Patients' actual identity will be coded appropriately and should not be discernible from the data provided on the CRF. CRF content will be verified against data sources by the study monitor,and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the Investigator at the clinical site. This approval acknowledges the Investigator's review and declaration that the data are complete and accurate.

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. All steps and actions taken regarding data management and quality assurance will be documented in a data handling report. 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. The investigational site must retain the original signed consent and provide a copy to the patient.

14.2. Ethical Conduct of the Study

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

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 and date of birth only.

All Sponsor personnel will handle patients' data in a confidential manner in accordance with applicable regulations governing clinical research. Patients' records will be inspected only in connection with this research project. Information generated as a result of a patient'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, patients will not be individually identified but will be referred to only by the study assigned number and the patient's date of birth.

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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 Instructions

A-101-DPN-201 SUBJECT INSTRUCTION SHEET

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

Contact:_____ Telephone:_____

DURING THE STUDY:

- Continue your routine cleansing regimen except avoid vigorous scrubbing of the Target DPN 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 DPN 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 DPN 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.
- Apply Aquaphor to each of the DPN Target Lesions beginning the morning after Visit 2 (Day 1) and Visit 4 (Day 22, if applicable, cohort 1) or after Visit 3 (Day 15) and Visit 5 (Day 29) for cohort 2 subjects, if applicable.

STUDY VISIT SCHEDULE:

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

16. References

Calonje, E. (2012). Dermatosis papulosa nigra. In E. Calonje, *McKee's Pathology of the Skin* (p. 1028). Elsevier.

Fitzpatrick, T. (1988). The Validity and Practicality of Sun Reactive Skin Types I through VI. *Arch Dermatology*, 869-871.

Hairston, M. (1961). Dermatosis Papulosa Nigra. *Archives of Dermatology*, 655-658.

Kundu, S. L. (2017, February 28). *Dermatology Education: Dermatosi Papulosa Nigra (DPN)*. Retrieved from Skin of Color Society: http://skinofcolorsociety.org/dermatology-education/1399-2

Lupo, M. P. (2007). Dermatosis Papulosis Nigra: Treatment Options. *Journal of Drugs in Dermatology*, 29-30.