CLINICAL STUDY PROTOCOL

Protocol Number: A-101-WART-202

05 December 2017
Amendment 2
Version 3

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP STUDY OF A-101 TOPICAL SOLUTION APPLIED ONCE A WEEK IN SUBJECTS WITH COMMON WARTS

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PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: **A-101-WART-202**

Protocol Title: **A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of A-101 Topical Solution Applied Once a Week in Subjects with Common Warts**

Protocol Version: **Version 3.0 05 December 2017**

Chris Powala
Chief Operating Officer

12-4-2017
Date:

Stuart D. Shanler, MD
Chief Scientific Officer

12/4/17
Date:

INVESTIGATOR SIGNATURE PAGE

Protocol Number: A-101-WART-202

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Protocol Version **Version 3.0: 05 December 2017**

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

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

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

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

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

_____

Investigator Name (print)

_____ _____

Investigator's Signature **Date**

Table of Contents

1. SYNOPSIS

Protocol Number A-101-WART-202 Synopsis	
Protocol Number:	**Protocol Title:** A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of A-101 Topical Solution Applied Once a Week in Subjects with Common Warts
Sponsor: Aclaris	**Phase of Development:** **Phase 2**
Study Drug Description: A-101 Solution (45%) is a hydrogen peroxide solution that will be supplied in a glass ampule with an applicator to be applied to common warts (verruca vulgaris) on the trunk or extremities. The study drug, A-101 (hydrogen peroxide) 45% Topical Solution (hereafter referred to as A-101) is a colorless solution that must be stored at room temperature (15-25º C or 59 -77 º F). The blinded vehicle solution is packaged to match the active study drug and will be stored under the same conditions.	
Study Objectives: **Primary:** The main objective of this study is to evaluate the clinical effect of A-101 45% vs Vehicle when applied to 1 common Target Wart (verruca vulgaris) on the trunk or extremities. **Secondary**: The secondary objectives of this study include: • Evaluate the clinical effect of A-101 45% when applied to all treated Warts (Target plus Non-Target Warts) • Duration of response in all treated Warts (Target Warts plus Non-Target Warts) • Safety of A-101 45%	
Study Design: This is a phase 2, randomized, multicenter study to evaluate the safety and efficacy of A-101 45% vs Vehicle in subjects with common warts on the trunk or extremities. Subjects may have up to a total of 4 treated common warts located on their trunk or extremities. Investigators will be required to identify 1 Target Wart for treatment with A-101 study medication. An additional 3 Non-Target Warts may be treated and followed throughout the study protocol therapy. All identified Common Warts will be treated once a week for 8 weeks. Subjects will be followed for 3 months after the last weekly treatment. Approximately 120 evaluable subjects will be randomized to one of 2 treatment arms in a 1:1 ratio. The duration of study participation is anticipated to be up to a maximum of 155 days per subject. All subjects will be followed for at least 12 weeks after the last study medication treatment. Safety will be evaluated based on clinical laboratory studies (hematology and clinical chemistry), vital signs, assessment of local skin reactions (LSRs), assessment of adverse events (AEs), and concomitant medication review.	

Efficacy will be evaluated based on assessment of each Target and Non-Target Wart according to the Physician Wart Assessment (PWA). Sites will be required to take standardized color photographs of each Target and Non-Target Wart to assist with the documentation of the location of each of the wart throughout the study.

Number of Patients to be Enrolled:

Approximately 120 evaluable subjects will be randomized to the study.

Number of Study Sites:

This study will be conducted in the US only at approximately 15 treatment centers.

Inclusion Criteria:

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

1. Subject is able to comprehend and is willing to sign an informed consent/assent for participation in this study.
2. Male or female ≥ 8 years old.
3. Subject has a clinical diagnosis of common warts.
4. Subject has up to 1 Target Wart and up to 3 additional Non-Target Warts located on the trunk or extremities. The identified Target and Non-Target Warts must meet the requirements as defined below:
    a. Each wart must have a longest axis that is ≥ 3mm and ≤ 8 mm and have a thickness of ≤3mm
    b. Each wart must be a discrete lesion
    c. Each wart must be present for at least 4 weeks
    d. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    e. Not be in an intertriginous fold
    f. Be the only common wart present when the circular cutout template is centered over the wart
5. The Target and Non-Target Warts must have a PWA ≥ 2.
6. Subject chemistry and complete blood count results are within normal limits. If any of the laboratory values are outside normal range, the treating investigator must assess the value/s as NOT clinically significant and document this in the subject's medical chart in order for the subject to be eligible for randomization.
7. Woman of childbearing potential (WOCBP) 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 or Non-Target Warts 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 warts on the trunk or extremities.
2. Subject is immunocompromised (e.g., due to chemotherapy, systemic steroids, genetic immunodeficiency, transplant status, etc.).
3. Subject has periungual, subungual, genital, anal, mosaic, plantar, flat, or filiform wart as a Target

or Non-Target Wart.

4. Subject has a history of Human Immunodeficiency Virus (HIV) infection.
5. Subject has had any Human Papilloma Virus (HPV) vaccine within 1 year prior to Visit 2
6. Subject has used any of the following intralesional therapies within the specified period prior to Visit 2
    - Immunotherapy (e.g., *Candida* antigen, mumps antigen, *Trichophyton* antigen); 8 weeks
    - Anti-metabolite therapy (e.g., bleomycin, 5-fluorouracil); 8 weeks
7. Subject has used any of the following systemic therapies within the specified period prior to Visit 2:
    - Immunomodulatory/immunosuppressant therapy (e.g., etanercept, alefacept, infliximab); 16 weeks
    - Glucocorticosteroids (inhaled and intra-nasal steroids are permitted); 28 days
8. Subject has used any of the following topical therapies within the specified period prior to Visit 2 on, or in a proximity to any Target or Non-Target Warts, 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
    - Immunotherapy (e.g., imiquimod, squaric acid dibutyl ester[SADBE], etc); 12 weeks
    - Liquid nitrogen, electrodesiccation, curettage; 60 days
    - Hydrogen peroxide; 90 days
    - Anti-metabolite therapy (e.g., 5-fluorouracil); 8 weeks
    - Retinoids; 90 days
    - Over-the-counter (OTC) wart therapies; 28 days
9. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any Target or Non-Target Warts 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
10. Subject has a history of sensitivity to any of the ingredients in the study medications.
11. 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.
12. 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 155 days per subject. The final visit (Visit 13) has a maximum allowable visit window of 7 days: Study visits are:

- Visit 1 (Day -13 to 0) screening
- Visit 2 (Day 1) randomization; study medication treatment
- Visit 3 (Day 8) study medication treatment
- Visit 4 (Day 15) study medication treatment
- Visit 5 (Day 22) study medication treatment
- Visit 6 (Day 29) study medication treatment
- Visit 7 (Day 36) study medication treatment
- Visit 8 (Day 43) study medication treatment
- Visit 9 (Day 50) study medication treatment

- Visit 10 (Day 57) follow up evaluations, no Target or Non-Target Wart retreatment
- Visit 11 (Day 78) follow up evaluations, no Target or Non-Target Wart retreatment
- Visit 12 (Day 106) follow up evaluations, no Target or Non-Target Wart retreatment
- Visit 13 (Day 134) follow up evaluations, no Target or Non-Target Wart retreatment; end of study

Criteria for Evaluation

Efficacy:
The investigator will evaluate the severity of each Target and Non-Target Wart using the Physician Wart Assessment (PWA)

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

Study Drug Administration

Study drug medication will be applied to each Target and Non-Target Wart meeting the requirements for treatment/retreatment during Visits 2 through 9. The study drug will be applied by the subject in the presence of the treating physician or a member of the investigational site staff who is a trained healthcare professional. Subjects between the ages of 8 and 17 years of age will have their A-101 study medication applied by the investigational research staff.

Study medication must be applied to each of the Target and Non-Target Warts for approximately 15 seconds. The treated warts must remain undisturbed for approximately 15 seconds. This treatment cycle may be repeated up to 3 times to each Target and Non-Target Wart.

Statistical Methods

Efficacy Analysis
The primary efficacy analysis will be a comparison between treatment groups based on the mean change in Target Wart PWA from Baseline (Visit 2) to Visit 10, using Analysis of Covariance with Baseline PWA as the covariate. Secondary efficacy analyses will include comparisons between treatment groups based on the following: the proportion of subjects with the Target Wart Clear (PWA = 0) at Visit 10 using Fisher's Exact Test; the proportion of subjects with all treated warts Clear at Visit 10 using a Cochran-Mantel-Haenszel test stratified by number of treated warts; and the mean of per-subject percentages of all treated warts that are clear at Visit 10 using Analysis of Variance. Durability of response in the Active treatment group will be evaluated by calculating the proportion of those treated warts achieving a PWA status of Clear at Visit 10 which continue to maintain a PWA status of Clear at Visit 13. This analysis will be performed separately for Target Warts, and for all treated warts. The 95% confidence limits around the calculated proportions will also be calculated in order to estimate the population lower limit value of the observed sample proportions.

Safety Analysis
Safety endpoints for adverse events (AEs) include the following: incidences of all treatment-emergent AEs (TEAEs) and all serious AEs (SAEs); by severity, by relationship to study drug and discontinuation of patients from study due to AEs. Safety endpoints for AEs, clinical laboratory tests, vital signs, and physical examinations and local skin reactions will be specified in the statistical analysis plan (SAP). All safety endpoints will be summarized using descriptive statistics.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
°C	Degrees Centigrade
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Clinically Significant
e.g.	for example, (Latin; *exempla gratia*)
EC	Ethics Committee
eCRF	Electronic Case Report Form
°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
PP	Per Protocol
PWA	Physician Wart Assessment
SAE	Serious Adverse Event
SI	Subject Identifier
SK	Seborrheic Keratosis
SOP	Standard Operating Procedure
US	United States
WOCBP	Women of childbearing potential

2. INTRODUCTION

2.1. Summary

Warts are benign proliferations of the skin and mucosa that are caused by infection of keratinocytes by subtypes of the human papilloma virus (HPV) family. Cutaneous HPV subtypes are a subset of this large group of the DNA papillomavirus family that is capable of infecting humans and causing cutaneous lesions. HPVs are ubiquitous in the environment and infection occurs most commonly through direct contact with individuals who harbor the virus clinically (evident lesions) or subclinically, indirectly through exposure to contaminated surfaces, or even by autoinoculation of virus from individual lesions to adjacent uninfected skin. Cutaneous manifestations of HPV infection include common warts (verruca vulgaris), palmar and plantar warts, mosaic warts, flat warts, and butcher's warts. Common warts are generally small, rounded, hyperkeratotic, exophytic dome-shaped papules or nodules and are typically associated with HPV subtypes 1, 2 or 4 though other subtypes are reported. Lesions are most commonly located on the fingers (including periungual and subungual regions), dorsal surfaces of the hands, and sites prone to trauma (*e.g.*, knees, elbows), but commonly occur at virtually any other anatomical location, potentially spreading by autoinoculation from the finger/hand lesions.

In immunocompetent individuals, many common cutaneous warts (up to 2/3rds in some reports) may spontaneously resolve in less than 2 years. However, they often persist for many years, may be large and/or cosmetically unsightly (*e.g.*, face, hands), spread to distant anatomical regions by autoinoculation, be painful and/or prone to trauma, and, importantly, provide a significant reservoir of HPV infection in the community, placing (especially immunocompromised) individuals at risk for significant morbidity.

There are currently no specific antiviral therapies available to treat cutaneous HPV infection and there is no FDA-approved topical treatment for cutaneous common warts. Existing therapies, many of which are off-label uses of drugs approved for other indications, and many of which have never undergone the drug approval process, are of unproven safety and/or efficacy, and are generally directed towards either the direct physical destruction of the lesions with locally destructive or ablative modalities such as cryotherapy, electrosurgery, curettage, application of acids (*e.g.*, salicylic acid, trichloroacetic acid); locally cytotoxic therapies, such as topical podophyllin, cantharidin, topical or intralesional 5-fluorouracil, or bleomycin; topical immunomodulatory or immunotherapy (*e.g.*, topical imiquimod, intralesional candida antigen, topical squaric acid dibutyl ester) or lesion removal. Several of these therapies are also available as over-the-counter (OTC) wart therapies in lesser exposures than used in the office setting (*e.g.*, topical salicylic acid preparations, home freezing kits). Systemic therapy with agents such as cimetidine, and even local occlusion with duct tape have also been anecdotally reported to be effective in some cases. While these methods may achieve cure in some cases, many require multiple visits to a physician's office, and may require providers with specialized training and the use of expensive equipment. Such procedures can be painful, may require anesthesia and/or analgesia, and they can be complicated by adverse cosmetic outcomes including scarring at the treatment site, as well as the typical post-surgical risks of bleeding and infection. No one therapy is consistently effective in all cases and, in fact, there is great variability among practitioners in the methods employed using each of these techniques with great variability of the results.

Hydrogen peroxide (H_2O_2) is a compound that is ubiquitous in the environment. It is the simplest peroxide and a potent oxidizing agent commonly used in innumerable household goods including chlorine-free bleaches, general-purpose cleaning products, and disinfectants. Additionally, H_2O_2 has been employed as the oxidizing component in hair dyes, and has been used in oral hygiene products and tooth-whitening systems for many years. In industry, it is employed in the treatment of wastewater. In high concentrations, it is used in bleaching paper, pulp, and textiles. Clinically, in addition to its use as an oral topical agent noted above, H_2O_2 is widely employed at low concentrations (*e.g.*, 3%-6%) as a wound irrigant and topical antiseptic/disinfectant, and has been in use medicinally since its introduction into clinical practice by Richardson in 1858. (Schumb WC 1955) (Chan HP 2008) (Richardson, On Peroxide of Hydrogen, or Ozone, or Water as a Remedy: Continued from a Research Commenced in the Year 1858 1891) (Richardson, On Peroxide of Hydrogen, or Ozone, or Water, as a Remedy: Continued from Research Commenced in the Year 1858 1891) (Richardson, On the Introduction of Peroxide of Hydrogen as a Medicine 1866) (Watt BE 2004)(Zonios 2007).

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

An investigator-initiated, single-site, double-blind, vehicle-controlled, parallel-group proof-of-concept trial: "A randomized, double-blind, vehicle-controlled, parallel group study of hydrogen peroxide solution in adult subjects with common warts of the hand (WART-01), was conducted utilizing once weekly applications (maximum of four applications) of A-101 (hydrogen peroxide) 40% topical solution or placebo (vehicle) topical solution to investigate the potential utility of a 40% hydrogen peroxide topical solution for the treatment of common warts on the hands. A total of 15 subjects received 4 study medication applications. One subject achieved complete clearance of the Target Wart during the investigation, and data from this pilot study demonstrated a statistically significant trend towards clearing warts in the A-101 40% group when compared with the vehicle. It was the Investigator's opinion that "1 or 2 additional treatments may clear the warts as most A-101 40% treated warts were "Near Clear" at the end of the four-week study". The administration of A-101 40% over four applications one week apart showed no untoward effects and the treatment was well tolerated by all subjects. The data and clinical observations suggest that a larger study allowing greater than four drug applications and evaluating additional doses of A-101 topical solution are warranted.

2.2. Study Rationale

A phase 2 clinical trial was conducted in which subjects were randomized to receive A-101 40%, A-101 45% or Vehicle for the treatment of common warts. Study A-101-WART-201 randomized a total of 98 subjects with a clinical diagnosis of common warts. Subjects received up to 8 weekly treatments with A-101 study medication.

The primary and secondary efficacy endpoints of the mean change from baseline to Visit 10 on the Physician Wart Assessment (PWA) and the proportion of PWA responders at Visit 10, which was defined as target warts judged to be clear or to be clear or mild, demonstrated superiority of A-101 45%, but not 40%, versus vehicle.

Both concentrations of A-101 evaluated were well tolerated. The only TEAEs considered to be treatment-related were application site pain for 2 subjects (all events were considered to be mild and resolved on the same day without intervention) and chlamydial infection for 1 subject. There were no clinically significant changes during the study in laboratory evaluations or vital signs.

A-101 solution 45% demonstrated superiority versus the matching A-101 solution vehicle (and A-101 40%) in physician evaluations of efficacy in treating target warts on the trunk or extremities and was well tolerated with occurrence of local skin reactions that were generally transient. Based on these results a phase 2 study comparing A-101 45% vs Vehicle is warranted.

3. OBJECTIVES

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is to evaluate the effectiveness of A-101 45% compared to vehicle when applied to 1 common target wart on the trunk or extremities.

3.1.2. Secondary Objective

The secondary objectives of this study include:

- Evaluate the clinical effect of A-101 45% when applied to all treated warts (Target plus Non-Target Warts)
- Duration of response in all treated warts (Target Warts plus Non-Target Warts)
- Safety of A-101 45%

4. STUDY DESIGN

This is a phase 2, randomized, multi-center, study designed to evaluate the safety and efficacy of A-101 45% compared to Vehicle in subjects with common warts on the trunk or extremities.

During the study, the investigator will identify 1 eligible Target Wart and up to 3 additional Non-Target Warts on each subject on the trunk or extremities. All Target and Non-Target Warts will be treated weekly for 8 weeks.

Subjects will be required to complete a total of 13 study visits. The protocol defined study visits are:

- Visit 1 (Day -13 to 0) screening
- Visit 2 (Day 1) randomization; study medication treatment
- Visit 3 (Day 8) study medication treatment
- Visit 4 (Day 15) study medication treatment
- Visit 5 (Day 22) study medication treatment
- Visit 6 (Day 29) study medication treatment
- Visit 7 (Day 36) study medication treatment
- Visit 8 (Day 43) study medication treatment
- Visit 9 (Day 50) study medication treatment
- Visit 10 (Day 57) follow up evaluations, no Target or Non-Target Wart retreatment
- Visit 11 (Day 78) follow up evaluations, no Target or Non-Target Wart retreatment
- Visit 12 (Day 106) follow up evaluations, no Target or Non-Target Wart retreatment
- Visit 13 (Day 134) follow up evaluations, no Target or Non-Target Wart retreatment; end of study

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

A completed evaluable subject is a subject that misses no more than 3 treatment visits, completes Visit 10 and Visit 13 (end of study visit), has had all Target Warts assessed at these visits and has not had a protocol violation documented during the study.

4.1. Number of Subjects and Study Centers

Approximately 120 evaluable subjects will be randomized to one of two treatment arms at approximately 15 investigational centers in the US.

4.2. Duration of Study

The anticipated time for study enrollment is 3 months. The duration of study participation is anticipated to be a maximum of 155 days per subject. Subjects will have a total of 13 study visits. The maximum anticipated duration for the study is approximately 8 months.

5. STUDY ENTRY CRITERIA

5.1. Inclusion Criteria

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

1. Subject is able to comprehend and is willing to sign an informed consent/assent for participation in this study.
2. Male or female ≥ 8 years old.
3. Subject has a clinical diagnosis of common warts.
4. Subject has up to 1 Target Wart and up to 3 additional Non-Target Warts located on the trunk or extremities. The identified Target and Non-Target Warts must meet the requirements as defined below:
    a. Each wart must have a longest axis that is ≥ 3mm and ≤ 8 mm and have a thickness of ≤3mm
    b. Each wart must be a discrete lesion
    c. Each wart must be present for at least 4 weeks
    d. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    e. Not be in an intertriginous fold
    f. Be the only common wart present when the circular cutout template is centered over the wart
5. The Target and Non-Target Warts must have a PWA ≥ 2
6. Subject chemistry and complete blood count results are within normal limits. If any of the laboratory values are outside normal range, the treating investigator must assess the value/s as NOT clinically significant and document this in the subject's medical chart in order for the subject to be eligible for randomization.
7. Women of childbearing potential (WOCBP) 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 and Non-Target Warts 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 warts on the trunk or extremities.
2. Subject is immunocompromised (e.g., due to chemotherapy, systemic steroids, genetic immunodeficiency, transplant status, etc.)
3. Subject has periungual, subungual, genital, anal, mosaic, plantar, flat, or filiform wart as a Target or Non-Target Wart
4. Subject has a history of Human Immunodeficiency Virus (HIV) infection
5. Subject has had any Human Papilloma Virus (HPV) vaccine within 1 year prior to Visit 2
6. Subject has used any of the following intralesional therapies within the specified period prior to Visit 2
    a. Immunotherapy (e.g., *Candida* antigen, mumps antigen, *Trichophyton* antigen); 8 weeks
    b. Anti-metabolite therapy (e.g., bleomycin, 5-fluorouracil); 8 weeks
7. Subject has used any of the following systemic therapies within the specified period prior to Visit 2:
    a. Immunomodulatory/immunosuppressant therapy (e.g., etanercept, alefacept,infliximab); 16 weeks
    b. Glucocorticosteroids (inhaled and intra-nasal steroids are permitted); 28 days
8. Subject has used any of the following topical therapies within the specified period prior to Visit 2 on, or in a proximity to any Target or Non-Target Warts, that in the investigator's opinion interferes with the study medication treatment or the study assessments:
    a. LASER, light or other energy based therapy (e.g., intense pulsed light [IPL], photo-dynamic therapy [PDT]; 180 days
    b. Immunotherapy (e.g., imiquimod, squaric acid dibutyl ester[SADBE], etc.) 12 weeks
    c. Liquid nitrogen, electrodesiccation, curettage; 60 days
    d. Hydrogen peroxide; 90 days
    e. Anti-metabolite therapy (e.g., 5-fluorouracil); 8 weeks
    f. Retinoids; 90 days
    g. Over-the-counter (OTC) wart therapies; 28 days
9. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any Target or Non-Target Warts that, in the investigator's opinion, interferes with the study medication treatment or the study assessments:
    a. Cutaneous malignancy; 180 days
    b. Sunburn; currently
    c. Pre-malignancy (e.g., actinic keratosis); currently
10. Subject has a history of sensitivity to any of the ingredients in the study medications.

11. 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.
12. 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/assent withdrawal for study participation
- Change in compliance with an inclusion/exclusion criteria
- Use of a prohibited medication (through Visit 13)
- 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 within 24 hours of the decision to remove the subject from the study.

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

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

5.4. Withdrawal Procedures

If a subject withdraws from the study prior to Visit 13, the reason for and the date of withdrawal from the study must be recorded on the eCRF. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring of the subject will continue until the event has resolved or stabilized, until the patient is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

5.5. Subject Replacement

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

Subjects that are determined to be screen failures may be rescreened for the study and if determined to be eligible for the study they may be randomized using the same subject identifier.

5.6. Subject Identifier (SI)

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

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

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

6. STUDY PROCEDURES

The schedule of study activities (including assessments, tests, exams, disease assessments, and study drug administration) beginning with screening and continuing through the end of study are outlined in Table 1. A written, signed informed consent form (ICF)/assent must be obtained from each subject prior to performing any study related procedure (e.g., vital signs, clinical laboratory sampling, urine pregnancy test or photography).

Table 1: Study Procedures

Visit	V1 Screening	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Treatment Day	-13 to 0	1	8	15	22	29	36	43	50	57	78	106	134
Treatment Window	N/A	N/A	±1 day	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days	+4 days	±7 days	±7 days	+7 days
Study Procedures													
Informed Consent/Assent	X												
Inclusion Criteria/Exclusion Criteria	X	X[1]											
Subject Identifier	X[2]												
Medical history/demographics	X												
Fitzpatrick Skin Type Assessment	X[3]												
Vital Signs	X[4]								X				X
Prior Medications/Therapies	X[5]												
Clinical Chemistry and CBC[6]	X								X				X
Urine Pregnancy Test[7]	X	X							X				X
Target Wart Identification[8]	X												
Physician's Wart Assessment[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Target Wart Dimensions[10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized Photography[11]	X	X		X					X	X			X
Subject Randomization		X[12]											
Local Skin Reactions		X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X	X	X	X	X
Study Medication Application[14]		X	X	X	X	X	X	X	X				
Weighing of Study Medication Applicators[15]		X	X	X	X	X	X	X	X				
Subject Instructions	X	X	X	X	X	X	X	X	X	X	X	X	

Concomitant therapies[16]		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[17]		X	X	X	X	X	X	X	X	X	X		

[1]Subject inclusion/exclusion criteria will be re-assessed prior to randomization 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, height and weight (Visit 1 only)] will be measured by a qualified staff member at Visit 1, Visit 9 and Visit 13.

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

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

[7] Woman of child bearing potential will be required to have a urine pregnancy test at Visit 1, at Visit 2 prior to randomization, Visit 9 and Visit 13.

[8]The treating investigator will identify 1 Target Wart and up to 3 additional Non-Target Warts on the trunk and extremities.

[9] The investigator will use the Physician Wart Assessment (PWA) to assess each Target and Non-Target Warts. The investigator must assess the Target and Non-Target Warts prior to application of the study medication at Visit 2-Visit 9. In order to be eligible for randomization at Visit 2, the subject must have a PWA grade ≥ 2.

[10] The investigator will measure the dimensions (longest diameter and thickness) of the Target and Non-Target Warts at Visit 1 and prior to randomization at Visit 2. In order for the subject to be randomized at Visit 2 each Target and Non-Target Wart must have the specific dimensions outlined in Section 8.1. At Visits 3-13 the investigator will measure the diameter of each Target and Non-Target Wart.

[11] At Visits 1, Visit 2 (prior to study medication application), Visit 4 prior to study medication application, Visit 9, Visit 10 and at Visit 13, a qualified investigational center staff member will take a photograph of each Target and Non-Target Wart using the Aclaris supplied camera. All photographs will be sent to a central imaging laboratory.

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

[13] The investigator and subject will assess each Target Wart for local skin reactions associated with irritation at Visits 2-13. At Visit 2-Visit 9, the investigator and subject will assess the Target and Non-Target Warts for LSRs prior to the application of the study medication. The subject will assess LSRs 10 (±4) minutes after the application of A-101 study medication and the investigator will assess for LSRs 20 (± 4) minutes after application of A-101 study medication. Refer to Section 9.1 for the complete list of Local Skin Reaction signs and symptoms.

[14]The investigator will apply the A-101 study medication to subject 8 to 17 years of age. Subjects 18 years of age and older will apply their A-101 study medication in the presence of the treating physician or a member of the investigational study staff that has been trained on the protocol. All Target and Non-Target Warts will be treated with study medication following randomization at Visit 2. If a Target or Non-Target Wart meets the criteria for re-treatment as defined in Section 7.6 the lesion will be re-treated at Visit 3-9. Following application of study medication, subjects must NOT wash/submerge the Target or Non-Target Warts for at least 6 hours and they must NOT apply any topical products to the Target or Non-Target Warts for at least 6 hours.

[15]Sites will be required to weigh all A-101 study medication applicators before and after treatment and document the weight of each applicator in the subject's eCRF.
[16]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 or Non-Target Warts within 12 hours prior to any study visit.
[17]The reporting period for Serious Adverse Events (SAEs) begins when the subject signs the informed consent and continues through Visit 11. Refer to Section 10.1.2 for instructions on the reporting of SAEs. Non-serious clinical adverse events will be collected following the application of the study medication at Visit 2. Non-serious adverse events that occur between the time of consent and study medication application will be documented as medical history. All safety reporting (AEs and SAEs) will conclude at Visit 11 (approximately 28 days after last study medication application) except for clinical adverse events related to local skin reactions.

7. STUDY TREATMENT

7.1. Investigational Study Medication

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

Table 2 Study Medication Information

Study Medication Name	A-101 45%	Vehicle
Manufacturer	James Alexander Corporation, Blairstown NJ	
A-101 concentration (%)	45	0
Pharmaceutical Form	Solution	
Storage Conditions	15ºC to 25ºC or 59ºF to 77ºF protected from excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area*	
Route	Topical	
Frequency	A-101 Study Medication will be applied once a week for 8 weeks.	
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/Non-Target Wart for approximately 15 seconds. Allow each Target/Non-Target Wart to remain undisturbed for approximately 15 seconds. Repeat the application/waiting cycle until the study medication has been applied to each Target and Non-Target Wart up to 3 times.	
Activated Applicators	Activated applicators are stable for 4 hours at room temperature (15ºC to 25ºC or 59ºF to 77ºF)	

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

7.2. Subject Randomization

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

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

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

7.3. Study medication packaging, storage and dispensing

A-101 45% and matching Vehicle will be provided by Aclaris Therapeutics, Inc. and labelled according to the local law and legislation.

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

Each subject kit will be packaged with 10 treatment applicators. The outside of each subject kit will be labelled with a two part, three panel, double blind label. One part (one-panel) of the label remains attached to the Subject Kit, the other part (two-panel tear-off) is separated and attached to the subject's Label Page CRF when the subject is randomized.

A-101 study medication must be stored in a location where there is limited access to the investigational study medication at room temperature (15ºC to 25ºC or 59ºF to 77ºF) 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 randomized 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. Weighing of Study Medication Applicators

Sites will be required to weigh each A-101 study medication applicator before all Target and Non-Target Warts are treated. The used applicators will be weighed again after all warts have been treated. The weight of the applicators will be documented in the subject's eCRF. Sites will be supplied with a scale to weigh each applicator.

7.6. Study Medication Treatment

The study medications are for external, topical use on the Target and Non-Target Warts on the appropriate study subject only.

The investigational center staff member must comply with the study medication storage conditions outlined in Section 7.1.

At Visit 2, the investigational study staff will select the appropriate study medication applicator for treatment of a specific subject. Subjects ages 18 years of age and older will apply the appropriately labeled A-101 study medication to all Target and Non-Target Warts in the presence of the treating investigator or investigational staff that has been trained on the protocol. Investigational study staff will apply A-101 study medication to subjects between the ages of 8 and 17.

At Visit 3-9, any Target or Non-Target Wart that has a **PWA grade of >0** and **ONLY Target Warts or Non-Target Warts that have a PWA grade of >0**, must receive study medication treatment UNLESS either of the following criteria apply to the Target or Non-Target Wart:

- The Target or the Non-Target Wart has a pre-treatment LSR grade of 3 (severe) for any sign or symptom AND the grade has increased compared to the previous visit.
- The Target or the Non-Target Wart is, in the investigator's opinion, not appropriate for a retreatment (the investigator must note the reason on the subject's Comments CRF page).
- The Target or the Non-Target Wart, in the Investigator's opinion, cannot be visualized so the Investigator cannot assess the PWA.

Following treatment with the A-101 study medication applicator, all used applicators must be disposed of in a biohazardous container.

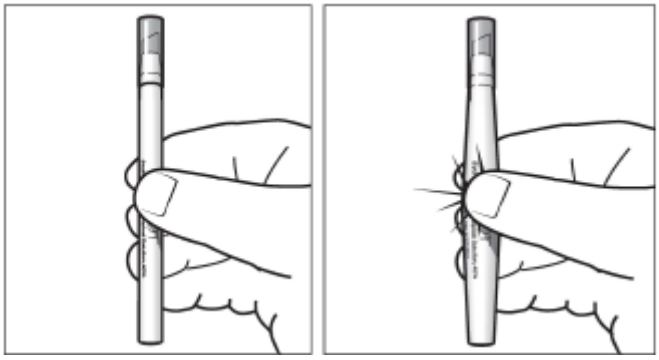
7.6.1. Preparing the Study Medication for Application

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

- Investigational Study Staff member will prepare the A-101 study medication applicator for all subjects, regardless of age by:
    - Washing their 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**
    - Complete the study medication applicator label as instructed
    - Visually inspect the applicator for damage:
        - If the applicator appears damaged do not use it for the treatment, contact the study monitor for disposal instructions and select another unused applicator for treatment.

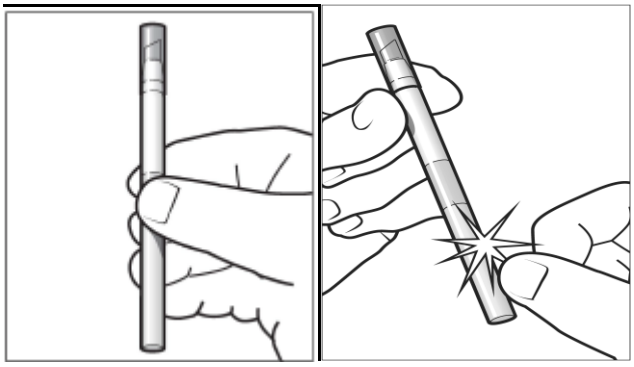
If the applicator is intact, proceed with the applicator preparation process as outlined in Figure 1.

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



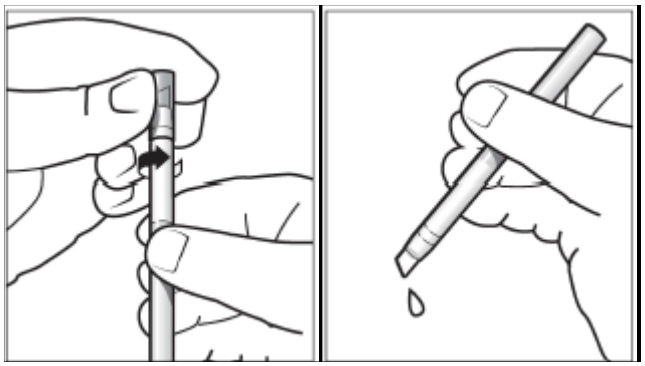
Step 1: Hold the Study Medication applicator so that the applicator cap is pointing up.

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



Step 3: Remove the cardboard sleeve.

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



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

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

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

7.6.2. Applying Study Medication to Target and Non-Target Warts on the Trunk and Extremities

Subjects that are between the ages of 8 and 17 will have their A-101 study medication applied by the investigational study staff and the staff will follow the application process outlined below for all Target and Non-Target Warts.

Subjects 18 years of age and older will apply their A-101 study medication to his/her identified Target and Non-Target Warts in the presence of the treating physician or member of the investigational staff.

The following instructions will be used by all individuals applying A-101 study medication to all Target and Non-Target Warts:

- Do not apply the study medications to eyes, nose, mouth, mucous membranes, or open wounds
- Thoroughly cleanse the Target and Non-Target Warts by firmly rubbing with a swab/wipe wetted with 70% isopropyl alcohol
- Using firm pressure and with the tip of the applicator held over the wart, squeeze in the middle of the applicator to apply one drop of study medication onto the Target Wart. Using the smaller side of the applicator tip, move the applicator around in a circular motion to fully saturate the lesion. Apply the study medication 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 that each identified wart is fully saturated with study medication at the end of the ~15 second application
- Allow the treated wart to remain undisturbed for ~15 seconds

- After ~15 seconds repeat the ~15 second application process
- Repeat the application/waiting cycle until the study medication has been applied to each identified Wart up to 3 times.

Document the number of times each identified wart is treated during a treatment Visit.

After all identified warts have been treated, the subject must be instructed not to disturb any of the treated warts until just prior to the post-application LSR evaluation.

Just prior to the post-application LSR evaluation the investigational study staff should absorb any remaining A-101 study medication and dry the Target and Non-Target Warts and the surrounding skin without wiping orrubbing

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

7.7. Dose modification

If a subject refuses to allow a study medication initial treatment or retreatment the investigator must report the visit number, visit date, Target Wart 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.

7.8. Previous and Concomitant Therapies

7.8.1. Previous therapies

During Visit 1, the investigator or designee will question the subject to ensure they have not used any excluded therapies within the specified period prior to Visit 1 to any of the Target or Non-Target Warts:

- Intralesional Therapy
  - Immunotherapy (e.g., *Candida* antigen, mumps antigen, *Trichophyton* antigen) 8 weeks
  - Anti-metabolite therapy (e.g., bleomycin, 5-fluorouracil); 8 weeks
- Systemic Therapy
  - Immunomodulatory/immunosuppressant therapy (e.g., etanercept, alefacept, infliximab); 16 weeks
  - Glucocortico-steroids (inhaled and intra-nasal steroids are permitted); 28 days
- Topical Therapy
  - LASER (e.g., pulsed-dye laser [PDL], light (e.g., intense pulsed light [IPL], photodynamic therapy [PDT], other energy based therapy); 180 days
  - Immuno-therapy (e.g., imiquimod, squaric acid dibutyl ester [SADBE], etc.); 12 weeks
  - Anti-metabolite therapy (e.g., 5-fluorouracil); 8 weeks
  - Retinoids; 90 days
  - Liquid nitrogen, electrodesiccation, curettage; 60 days
  - Over-the-counter (OTC) wart therapies; 28 days

7.8.2. Concomitant therapies

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

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

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

7.8.3. Prohibited therapies

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

- Intralesional Therapy
  - Immunotherapy (e.g., *Candida* antigen, mumps antigen, *Trichophyton* antigen)
  - Anti-metabolite therapy (e.g., bleomycin, 5-fluorouracil);
- Systemic Therapy
  - Immunomodulatory/immunosuppressant therapy (e.g., etanercept, alefacept, infliximab);
  - Glucocortico-steriods (inhaled and intra-nasal steroids are permitted);
- Topical Therapy
  - LASER (e.g., pulsed-dye laser [PDL], light (e.g., intense pulsed light [IPL], photodynamic therapy [PDT], other energy based therapy);
  - Immuno-therapy (e.g., imiquimod, squaric acid dibutyl ester [SADBE], etc.);
  - Anti-metabolite therapy (e.g., 5-fluorouracil);
  - Retinoids;
  - Liquid nitrogen, electrodesiccation, curettage;
  - Over-the-counter (OTC) wart therapies;

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 or Non-Target Warts within **12 hours prior** to any study visit (Note: routine cleansing products are allowed).

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

7.9. Breaking the Blind

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

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

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

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

8. ASSESSMENTS OF CLINICAL EFFICACY

8.1. Target and Non-Target Wart Identification

At Visit 1, the investigator will identify one Target Wart and up to 3 additional Non-Target Warts on the trunk or extremities for each subject for treatment and evaluation.

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

- The front and back of the torso from the clavicle to the hips, including the buttocks and excluding the genitals and anus
- The arms from the shoulder to the fingertips, excluding periungual and subungual areas
- The legs from the hip to the ankles (including the dorsal side of the foot).

At Visit 1, each Target and Non-Target Wart must:

- Have a longest axis that is ≥3mm and ≤8mm
- Have a thickness ≤3mm
- Be a discrete lesion
- Be, when centered in the circular cutout of the provided template, the only common wart present (Refer to Figure 2)
- Not be periungual, subungual, genital, anal, mosaic, plantar, flat or filiform.
- Not be covered with hair which, in the Investigator's opinion, would interfere with the study medication treatments or the study evaluations
- Not be in an area that may be occluded (*e.g.*, by clothing or footwear or in a skin fold).

Record the location of the Target and Non-Target Wart on the body charts in the CRFs indicating landmarks and distances to assist with confirming the location of the Target and Non-Target Warts at subsequent visits.

At Visit 1, the Investigator and an investigational staff member will identify each Target and Non-Target Wart by placing 2 identification (ID) stickers approximately 180 degrees opposite each other with the identified wart in the center of the area outlined by the provided circular template (diagram not to scale):

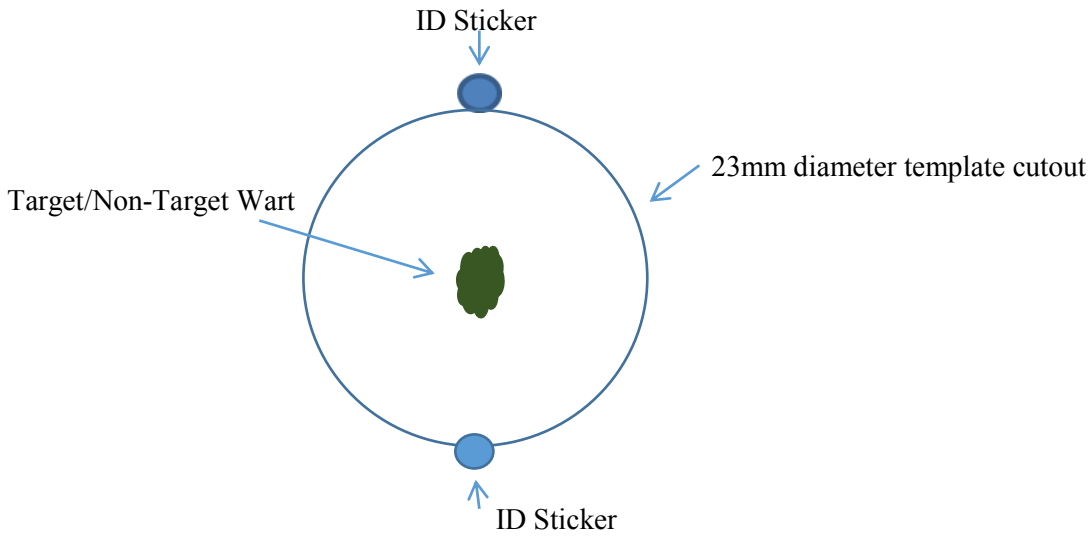


Figure 2 Target/Non-Target Wart Identification

At Visits 2-13, an investigational staff member (other than the evaluating investigator) will confirm the location of each Target/Non-Target Wart using an appropriate combination of the Visit 1 hard-copy reference prints, Visit 2 photographs and the body charts. The staff member will identify the Target/Non-Target Warts by placing 2 appropriately colored ID stickers, with the Target/Non-Target Wart number written on one sticker, approximately 180 degrees opposite each other with the identified wart in the center of area outlined by the provided circular template.

8.2. Standardized photography

At Visits 1, 2, 4, 9, 10, and 13 a qualified investigational center staff member will take standardized color photographs of each Target and Non-Target Wart.

The photographs are to document the appearance and location of the subjects' Target and Non-Target Warts. 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 application.

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

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.

8.3. Physician's Wart Assessment (PWA)

The Physician's Wart Assessment (PWA) is the Investigator's assessment of the severity of each Target and Non-Target Wart at a particular time point. The Investigator should NOT refer to any other assessments to assist with this evaluation. This evaluation IS NOT a comparison with the PWA at any other visit.

At every study visit, the Investigator will assess the Target and Non-Target Warts and report the one integer that best describes the Target and Non-Target Wart severity using the following scale. At any visit where a study medication treatment is performed, the PWA must be completed prior to the treatment.

Physician's Wart Assessment	
Grade	**Descriptor**
0	Clear: No visible wart. No further treatment is indicated
1	Near Clear: A visible wart that is less than 3mm in maximal diameter (or length)
2	A visible wart ≥ 3mm and <6 mm in maximal diameter (or length)
3	A visible wart ≥ 6mm in maximal diameter (or length)

At Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized each Target and Non-Target Wart must have a PWA grade ≥ 2.

At Visits 3-9, Target and Non-Target Warts must have a PWA > 0 to be retreated. If the Investigator cannot assess the PWA for a Target or Non-Target Wart (*e.g.*, the Target /Non-Target Wart cannot be visualized because of an LSR such as edema, scabbing, etc.) she/he must report the reason in the subject's CRFs. The Target/Non-Target Wart must not be retreated at that visit, and the subject should be seen at the next scheduled visit.

8.4. 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/Non-Target Warts (*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/Non-Target Warts to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the Target/Non-Target Warts, if excessive exposure cannot be avoided
- Avoid activities that might irritate the Target/Non-Target Wart
- Avoid the use of self-tanning lotions and spray tans.
- Bring the subject instruction sheet with them to each visit.

On study visit days, the subjects should:

- When appropriate for the Target/Non-Target Wart 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/Non-Target Wart within **12 hours** prior to the visit (Note: routine cleansing products are allowed)
- After the completion of any study visit where a study medication treatment was performed DO NOT:
    - Wash/submerge the Target or Non-Target Warts for at least **6 hours**
    - Apply any topical products to the Target or Non-Target Warts for at least **6 hours**.

8.5. Other Study Supplies

Aclaris Therapeutics, Inc. will provide:

- An appropriate ruler, or other instrument, for measuring the thickness of all Target/Non-Target Warts dimensions
- Templates for use when identifying Target/Non-Target Warts
- 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
- Scales to weigh all treatment 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 the following safety assessments according to the schedules noted below.

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

9.1. Local Skin Reactions (LSR)

The LSR assessment is the Investigator's assessment of the signs and the subject's assessment of the symptoms associated with irritation at the Target/Non-Target Wart site (*i.e.*, the Target/Non-Target Wart and the skin immediately surrounding the Target/Non-Target Wart exposed to study medication). The Investigator may refer to previous photographs to assist with these assessments only after the PWA has been performed.

The Local Skin Reaction signs to be assessed are:

- Erythema
- Edema
- Erosion
- Ulceration
- Vesicles/bullae
- Excoriations
- Scabbing.

The Local Skin Reaction symptoms to be assessed (by the Subject) are:

- Stinging/burning
- Pruritus (itch).

At Visits 2-13, the Investigator will evaluate the LSR signs at the Target/Non-Target Wart site(s) as follows:

- At visits where a study medication treatment or retreatment is performed:
  - Perform an LSR assessment prior to any study medication application
  - For treated Target and Non-Target Warts perform an LSR assessment 20 (±4) minutes after the Treatment Completion Time.

At Visits 2-13, the Subject will assess the LSR symptoms at the Target/Non-Target Wart site(s) as follows:

- At visits where a study medication treatment or retreatment is performed:
  - Perform an LSR assessment prior to any study medication application
  - For every treated Target and Non-Target Wart 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.

- At visits where no study medication treatment is performed:
  - Perform an LSR assessment.

The Investigator and subject should report the one integer that best describes the severity of each LSR sign or LSR symptom for the Target and Non-Target Wart sites using the scale below.

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 9 and Visit 13. The following items will be measured:

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

Any measure that is, in the opinion of the investigator, abnormal AND clinically significant (CS must be recorded as history if found prior to the first study medication treatment or as an AE if found after the first study medication treatment begins (Section 10.1).

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

9.3. Clinical laboratory sampling

Non-fasting blood samples for clinical laboratory analysis will be collected by a qualified staff member at Visit 1, Visit 9 and Visit 13. Approximately 7.5 mL of blood will be collected for each chemistry sample and 3 ml 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. The investigator must review all laboratory reports in a timely manner and note NCS or CS to define the clinical relevance of any result that is outside the normal range for the laboratory. The investigator must date and initial every laboratory report.

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

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

9.4. Urine pregnancy tests

The investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at Visit 1, at Visit 2 prior to randomization, Visit 9 and Visit 13.

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

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

9.5. Other Evaluations

9.5.1. Demographics and medical history

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

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

Table 3 Fitzpatrick Skin Type Scoring System

Skin Type Classification	Description
Type I	always burns, never tans (pale white; blond or red hair; blue eyes; freckles)
Type II	usually burns, tans minimally (white; fair; blond or red hair; blue, green, or hazel eyes)
Type III	sometimes mild burn, tans uniformly (cream white; fair with any hair or eye color)
Type IV	burns minimally, always tans well (moderate brown)
Type V	very rarely burns, tans very easily (dark brown)
Type VI	Never burns, never tans (deeply pigmented dark brown to darkest brown)

(Fitzpatrick 1988)

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

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

9.5.2. Standardized photography

At Visits 1, 2, 4, 9, 10 and 13, a qualified investigational center staff member, other than the investigator, will take standardized color photographs of each Target and Non-Target Wart.

The photographs are to document the location of the Target and Non-Target Warts and to assist with relocating the Target/Non-Target Warts. The Target/Non-Target Wart 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, and subject positioning relative to the camera and camera settings are used for each photograph.

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

10. ADVERSE EVENTS

10.1. Definitions

10.1.1. Adverse events (AE)

- An adverse event (AE) is any untoward medical occurrence in a patient that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product and does not necessarily have a causal relationship to the study drug. An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study (or any concurrent disease), whether or not considered related to the study drug. Accordingly, an adverse event could include any of the following:
- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (NOTE: A condition, recorded as pre-existing, that is intermittently symptomatic [e.g., headache] and which occurs during the study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or any washout phase of the study
- laboratory or diagnostic test abnormalities occurring after the start of the study (i.e., after screening and once confirmed by repeat testing) that results in the withdrawal of the patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant. NOTE: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events, but will be recorded to monitor data from patients who do not meet screening criteria.

Worsening of any of the Target or Non-Target Wart 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 or Non-Target Wart related AE, question the subject in detail to determine if there are any confounding factors (*e.g.*, irritation by clothing or activity, sunburn) for any such AE.

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

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

10.1.2. Serious adverse event (SAE)

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

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

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

Inpatient hospitalization is considered to have occurred if the subject is admitted to the hospital on an in-patient basis, even if released the same day. Prolongation of hospitalization is defined as an additional night stay in the hospital. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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

10.1.3. Adverse event reporting period

The investigator must start reporting non-serious AEs starting with the subject's first study medication treatment continuing until Visit 11. Non-serious adverse events that occur between the time the subject was consented and the first application of study medication will be reported as medical history.

Reporting for SAEs begins after the subject signs the informed consent and continues until Visit 11 (regardless of relationship to study medication). If a subject experiences a SAE after Visit 11 that is deemed by the investigator to be related to study medication, the investigator must report this to the Sponsor using the study specific SAE report form.

10.1.4. Severity

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

Mild – Awareness of signs or symptom, but easily tolerated

Moderate – Discomfort, enough to cause interference with usual activity

Severe – Incapacitating with inability to perform usual activity.

10.1.5. Relationship to study medication

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

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

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

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

10.2. Reporting Procedures

10.2.1. Procedures for reporting adverse events

At each post enrollment visit, the investigator or designee will question the subject to elicit AEs using a non-directive question such as "Has there been any change in your health since the previous study visit?"

The Investigator/designee will monitor the subject for at least 20 minutes after the Treatment Completion Time at any visit during which a study medication treatment is performed to elicit AEs in a similar manner.

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

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

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

10.2.2. Procedure for reporting a serious adverse event

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

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

Evyan Cord-Cruz, MD
Symbio
Main Number: 631-403-5126
Office Number: 516-338-0647
Mobile Number: 516-982-0677
Serious Adverse Event Facsimile: 484-324-2359
Email: ecruz@symbioresearch.com

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

10.2.3. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from study drug at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time. The patient will be monitored until the event has resolved or stabilized, until a determination of a cause unrelated to the study drug or study procedure is made, or until the patient is referred to the care of a local health care professional. The investigator must inform

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

11. PREGNANCY

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

All WOCBP must use an active method of birth control during the course of the study, in a manner such that risk of failure is minimized.

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/assent form documenting this discussion. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period).

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

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

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

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size and Power Consideration

Based on efficacy results from the previous study and the active study medication specified in the current protocol for the same indication, sample size for the current study is anticipated to provide greater than 90% power to achieve statistical significance in the primary efficacy analysis.

12.2. Statistical Analysis of Efficacy

Primary and secondary efficacy analyses will be performed on the Per-Protocol population, defined as all randomized subjects who missed no more than 3 treatment visits, completed Visit 10 (primary analysis) and Visit 13 (secondary analysis), and who have not had a major protocol violation over that time period, including the use of a clinically relevant quantity of a prohibited medication as determined by the study Medical Monitor. No missing data imputation will be used for these analyses.

Visit 10 is considered to be the primary efficacy endpoint. In addition, some analyses will also be conducted at earlier and subsequent visits, and treated as exploratory analyses. Some sensitivity efficacy analyses may also be re-performed on the Intent to Treat population, defined as those randomized subjects who have at least one post-baseline visit with required efficacy data collection and who completed Visit 10 with required collection of efficacy data. For those analyses, missing efficacy data for intermediate visits will be imputed using the last observation carried forward (LOCF) procedure. A determination as to the performance of analyses using the Intent to Treat population will be based on the number and pattern of visits missed by randomized subjects. Exploratory analyses using models specified below may also be performed for separate age groups, depending on enrollment outcomes.

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

After the last randomized subject has completed Visit 10 the database will be validated, locked through Visit 10 and unblinded for the purpose of analyzing efficacy data through Visit 10. Those analyses are not considered to be interim analyses as the results will be final. Data will continue to be collected through Visit 13 for all subjects, and the full database will subsequently be locked for efficacy analysis (including durability of response) beyond Visit 10, and for the analysis of safety and all other clinical data.

The primary efficacy analysis will be a comparison between treatment groups based on the mean change in Target Wart PWA from Baseline (Visit 2) to Visit 10, using Analysis of Covariance with Baseline PWA as the covariate.

Secondary efficacy analyses will include comparisons between treatment groups based on the following: the proportion of subjects with the Target Wart Clear (PWA = 0) at Visit 10 using Fisher's Exact Test; the proportion of subjects with all treated warts Clear at Visit 10 using a Cochran-Mantel-Haenszel test stratified by number of treated warts; and the mean of per-subject percentages of treated warts that are clear at Visit 10 using Analysis of Variance. The number of treated warts Clear at Visit 10 will also be analyzed using a Cochran-Mantel-Haenszel test stratified by number of treated warts.

Durability of response in the Active treatment group will be evaluated by calculating the proportion of those treated warts achieving a PWA status of Clear at Visit 10 which continue to maintain a PWA status of Clear at Visit 13. This analysis will be performed separately for Target Warts, and for all treated warts. The 95% confidence limits around the calculated proportions will also be calculated in order to estimate the population lower limit value of the observed sample proportions.

Exploratory analyses will be conducted using a subset of the above analysis models, based on the following baseline wart classifications: warts that are determined to be treatment-naive vs. recalcitrant.

12.3. Statistical Analysis of Safety Data

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

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

12.4. Interim Analysis

An interim Analysis will not be conducted for this study.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Protocol Amendments

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

13.2. Protocol Deviations, Violations and Exceptions

A **protocol deviation** is non-adherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study. Deviations include study procedures that occurred outside the treatment windows (except for treatment application days).

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

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

13.3. Training

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

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

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

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

13.4. Monitoring

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

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

13.5. Data Management

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

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

13.6. Quality Assurance

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

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

13.7. Record Retention

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

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

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

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

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

14. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

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

This protocol and any accompanying material, including information that will be provided to prospective patients (such as advertisements, patient information sheets, or study descriptions used to induce study participation or obtain informed consent/assent) 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/assent 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/assent 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/assent(s) from each prospective patient interested in participating in this study before performing any study-related procedures. Written informed consent must be obtained after adequate, thorough, and clear explanation of the aims, methods, objectives, and potential hazards of the study, as well as any use of the patient's genetic information from the study. The Investigator must use the most current Central IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient and the person obtaining consent and each page not signed must be initialed and dated by the patient. The investigational site must retain the original signed consent and provide a copy to the patient.

14.2. Ethical Conduct of the Study

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

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

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

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

14.3. Regulatory Documents

The investigator must maintain a study file containing current and complete regulatory documentation in compliance with the current ICH E6 GCP guideline. This file will be reviewed as part of the routine monitoring for this study.

14.4. Contractual Requirements

A contractual agreement will be signed between Aclaris Therapeutics, Inc. and each investigator. This document will contain supplemental information, including financial terms, confidentiality, study schedule, third party responsibility, and publication rights.

15. APPENDICES

15.1. Subject Instruction Sheet

A-101-WART-202 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:_____

THROUGHOUT THE STUDY:

- Continue your routine cleansing regimen except avoid vigorous scrubbing of the Target and Non-Target Warts (*e.g.*, abrasive cleansing pads, abrasive cleansers, etc.)
- Continue your routine skin care products
- Avoid exposing the Target and Non-Target Warts to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the warts, if excessive exposure cannot be avoided
- Avoid activities that might irritate the Target or Non-Target Warts
- Bring this subject instruction sheet with you to each visit.

STARTING WITH VISIT 2:

- On visit days, do not apply any topical products (*e.g.*, moisturizers, sunscreens) to the Target and Non-Target Warts, except for routine cleansing products, within 12 hours prior to the visit
- After any study visit where a study medication treatment occurred do not:
  - Wash/submerge the warts for at least 6 hours after the treatment
  - Apply any topical products to the wart for at least 6 hours
  - Occlude, bandage or otherwise cover the wart treatment area (loose-fitting clothing is permissible) for at least 6 hours.

STUDY VISIT SCHEDULE:

VISIT 2: Date: Time:	VISIT 3: Date: Time:
VISIT 4: Date: Time:	VISIT 5: Date: Time:
VISIT 6: Date: Time:	VISIT 7: Date: Time:
VISIT 8: Date: Time:	VISIT 9: Date: Time:
VISIT 10: Date: Time:	VISIT 11: Date: Time:
VISIT 12: Date: Time:	VISIT 13: Date: Time:

THANK YOU FOR FOLLOWING THESE INSTRUCTIONS

16. References

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