CLINICAL STUDY PROTOCOL

Protocol Number: A-101-WART-301

THWART 1: A PHASE 3 RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP STUDY OF A-101 TOPICAL SOLUTION APPLIED TWICE A WEEK IN SUBJECTS WITH COMMON WARTS

Version 1.0: 21May2018
Version 2.0 09 July 2018
Amendment 1 Version 3: 11 September 2018
Amendment 2 Version 4: 12 October 2018
Amendment 3 Version 5: 14 February 2019

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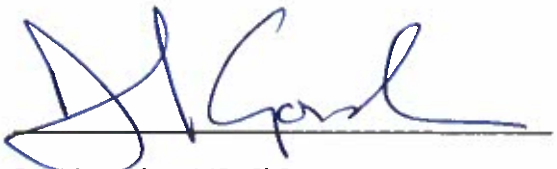
PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: A-101-WART-301

Protocol Title : THWART 1: A Phase 3 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of A-101 Topical Solution Applied Twice a Week in Subjects with Common Warts

Protocol Version: Version 5 14 February 2019



David Gordon, MB, ChB

Chief Medical Officer

2/14/19

Date:

INVESTIGATOR'S AGREEMENT

Protocol Number: A-101-WART-301

Protocol Title: THWART 1: A Phase 3 Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group Study of A-101 Topical Solution Applied Twice a Week in Subjects with Common Warts

Protocol Version **Version 5 14 February 2019**

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/Assent 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 immediately 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**

1. AMENDMENT RATIONALE

Amendment 3

The protocol dated 12 October 2018 was amended to update the medical monitor contact information, as well as provide an update to the stats section.

Amendment 2

Amendment 2 dated 12 Sep 2018 of the protocol A-101-WART-301 has been amended to include subjects ≥ 1 years of age and to clarify the application procedures for younger subjects randomized to the study. This change in inclusion criteria is at the request of the FDA following a review of the pediatric plan for this program.

Amendment 1

The protocol dated 09 July 2018 has been amended to change the patient instruction sheet, to provide updated information on how to return the used applicators to the site for final accountability. The rationale for this change is to simplify the instructions provided for any product which may remain in the applicator after it is applied at home, by removing the need to express any remaining product and the need to use a sharps container for disposal. The protocol was also amended to clarify that cantharidin has a 28 day wash out window prior to joining the study, and that the concomitant use of cantharidin is prohibited while on study. Lastly, the study title has been updated throughout the document to include the branded study name, THWART.

1.1. Protocol Changes

Protocol Version	Date	Section	Revisions
Version 2.0	09 July 2018	NA	Original Protocol
Version 3.0	10 September 2018		
		Title	THWART 1, the branded study name, has been added to the study title throughout the document.
		Synopsis	Revised exclusion criteria number 7 to clarify the wash out period for cantharidin use prior to study entry.
		Section 8.2	Revised exclusion criteria number 7 to clarify the wash out period for cantharidin use prior to study entry.

Protocol Version	Date	Section	Revisions
		Section 10.7	Language added to instruct all subjects/guardians that nitrile examination gloves must be worn during the application of A-101 study medication
		Section 11.1	Revised the previous therapy list to clarify the wash out period for cantharidin use prior to study entry.
		Section 11.3	Revised the prohibited medication list to include cantharidin use while on study as prohibited.
		Section 12.5	Added nitrile gloves to the list of clinical supplies
		Appendix 1	Revised the patient instruction sheet to simplify the instructions regarding disposal of the A-101 study medication applicator at home. Additionally, typos and formatting were updated to provide clarity.
Version 4	12 Oct 2018	Synopsis, Inclusion criteria #2, Section 7.1, Table 2 Footnote 14 and 15, Section 10.5 and Section 10.7	The age range for eligibility was broadened to subjects ≥ 1 years of age.
		Section 10.7, Table 2 Footnote 14, Section 11.3, Section 12.4 and Appendix 1	Added clarification that parents/guardians should ensure that children should not put a treated area in their mouth or eyes until the treated area is dry post-application. If the area is not dry 10 minutes after the application, the parent is advised to blot the area dry.
Version 5	14 Feb 2019	Cover page	The medical monitor information has been updated to the current medical monitor.
		Section 10.6	The language was updated to reflect that unused study medication will be disposed of after final accountability.
		Section 15	The stats section of the protocol has been updated to reflect the planned statistical analyses that will be performed.

2. SYNOPSIS

Protocol Number A-101-WART-301 Synopsis	
Protocol Number: **A-101-WART 301**	THWART 1: A Phase 3 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of A-101 Topical Solution Applied Twice a Week in Subjects with Common Warts
Sponsor: **Aclaris Therapeutics**	**Phase of Development:** **Phase 3**

Study Drug Description:

A-101 Solution contains 45% hydrogen peroxide that will be supplied in a single use applicator to be applied directly to common warts (verruca vulgaris) twice a week.

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 primary objective of this study is to evaluate the effectiveness of A-101 45% compared to Vehicle when applied twice weekly to common warts.

Secondary:

The secondary objectives of this study include:

- Duration of response
- Onset of action of A-101 45%.
- Safety of A-101 45%.

Study Design:

This is a phase 3, multicenter, randomized vehicle controlled, double blind parallel group study to evaluate the safety and efficacy of A-101 45% vs Vehicle in subjects with common warts. Investigators

will be required to identify at least 1 and up to 6 clearly identifiable common warts for treatment with A-101 study medication. All identified common warts will be treated twice a week for up to 8 weeks (maximum of 16 treatment applications). Subjects will be followed for 12 weeks after Visit 9.

Approximately 500 subjects will be randomized to one of 2 treatment arms in a 1:1 ratio. Of the 500 subjects randomized, approximately 100 subjects will be between 1 and 17years of age. The duration of study participation is anticipated to be up to a maximum of 158 days per subject.

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

Efficacy will be evaluated based on assessment of each identified common wart according to the Physician Wart Assessment (PWA)scale. The Investigator should NOT refer to any other assessments or previous assessments to assist with this evaluation.

Sites will be required to take standardized color photographs to assist with the documentation of the appearance and location of each identified common wart throughout the study. These photographs are not to be used when performing the PWA.

Number of Patients to be Enrolled:

Approximately 500 subjects will be randomized to the study.

Number of Study Sites:

This study will be conducted in the US only at approximately 25 treatment centers.

Inclusion Criteria:

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

1. Subject or legal guardian is able to comprehend and is willing to sign an informed consent/assent for participation in this study.
2. Male or female ≥ 1 year old.
3. Subject has a clinical diagnosis of common warts (verruca vulgaris).

4. Subject has at least 1 and up to 6 clearly identifiable common warts located on the trunk or extremities that meet the requirements as defined below:
    a. Have a longest axis that is ≥3 and ≤8 mm and have a thickness of ≤3mm
    b. Be a discrete lesion, i.e. each wart meeting the entry criteria is clearly separated from other warts.
    c. 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. Periungual, subungual, genital, anal, mosaic, plantar, flat and filiform warts are excluded from treatment and evaluation. If a subject has these types of warts, but also has warts that meet the inclusion criteria, the subject will NOT be excluded from the study.
5. Each common wart identified for treatment must have a PWA ≥ 2.
6. Subject's 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. 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 the identified common warts or which exposes the subject to an unacceptable risk by study participation.
8. Subject is willing and able to follow all study instructions and to attend all study visits.
9. Subject must be the only individual in a household participating in the study.

Exclusion Criteria:

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

1. Subject has clinically atypical common warts.
2. Subject is immunocompromised (*e.g.*, due to chemotherapy, systemic steroids, genetic immunodeficiency, transplant status, etc.).
3. Subject has a history of Human Immunodeficiency Virus (HIV) infection.
4. Subject has had any Human Papilloma Virus (HPV) vaccine within 6 months prior to Visit 1.
5. 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
6. 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

- Glucocortico-steroids (inhaled and intra-nasal steroids are permitted); 28 days

7. Subject has used any of the following topical therapies within the specified period prior to Visit 2 on or in the proximity to any of the common warts identified for treatment 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], photodynamic 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
    - Antimetabolite therapy (*e.g.*, 5-fluorouracil); 8 weeks
    - Retinoids; 90 days
    - Over-the-counter (OTC) wart therapies and cantharidin; 28 days
8. 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 of the common warts identified for treatment 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
9. Subject has a history of sensitivity to any of the ingredients in the study medications.
10. Subject has any current skin or systemic 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.
11. Participation in another therapeutic investigational drug/device trial in which administration of an investigational treatment occurred within 30 days prior to Visit 1.
12. Subject has an active malignancy.
13. Subjects viewed by the Principal Investigator as not being able to complete the study.

Duration of Treatment

The duration of the study participation is anticipated to be a maximum of 157 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 60) follow up evaluations, no identified Wart retreatment
- Visit 11 (Day 78) follow up evaluations, no identified Wart retreatment
- Visit 12 (Day 106) follow up evaluations, no identified Wart retreatment
- Visit 13 (Day 137) follow up evaluations, no identified Wart retreatment; end of study

Study Endpoints:

*Primary Efficacy Endpoint***:**

The primary efficacy endpoint is the proportion of subjects whose identified common warts are determined to be clear on the PWA scale (PWA=0) at Visit 10 (Day 60).

Secondary Efficacy Endpoint:

The secondary efficacy endpoints are:

- Proportion of subjects whose identified common warts are clear on the PWA scale (PWA =0) at Visit 13 (Day 137; last follow-up evaluation).
- Mean per-subject percent of all warts that are clear on the PWA scale at Visit 13 (Day 137)
- Proportion of subjects with a single wart at baseline whose wart is clear on the PWA scale (PWA=0) at Visit 10 (Day 60)
- Median time for subjects to achieve clearance (PWA=0) of all treated common warts.

Criteria for Evaluation

Efficacy:

The investigator will evaluate the severity of the identified Warts using the Physician Wart Assessment (PWA) scale.

Safety:

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

Study Drug Administration

Study drug medication will be applied to each identified common wart which meets the requirements for retreatment twice a week for up to 8 weeks (maximum of 16 applications). At Visit 2, subjects

who are 18 years of age or older will apply the A-101 study medication in the presence of the treating physician or a member of the investigational site staff who is a trained healthcare professional. The second weekly application of the A-101 study medication will be applied by the subject at home. Subjects between the ages of 1 and 17 years of age will have their A-101 study medication applied in the office by a parent or legal guardian in the presence of the treating physician or a member of the investigational site staff. The second weekly A-101 study medication application will be applied at home by a parent or a legal guardian.

Study medication must be applied to each identified common wart for approximately 15 seconds. The treated wart must remain undisturbed for an additional approximately 15 seconds. This treatment cycle must be repeated up to 3 times to the common wart. If severe erythema and edema develop, then the treatment cycle should be discontinued for that specific treatment application.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation	Term
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
°C	Degrees Celcius
CBC	Complete Blood Count
CDMS	Clinical Data Management System
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
e.g.	for example, (Latin; *exempla gratia*)
EC	Ethics Committee
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
H_2O_2	Hydrogen Peroxide
ICF	Informed Consent Form

Abbreviation	Term
ICH	International Conference on Harmonization
ID	Identification
i.e.	that is (Latin; *id est*)
IPL	Intense Pulsed Light
IRB	Institutional Review Board
ITT	Intent to Treat
LDH	Lactate Dehydrogenase
LSR	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
Mm	Millimeter
NCS	Not Clinically Significant
OTC	Over-The-Counter
PDL	Pulsed-dye Laser
PDT	Photodynamic Therapy
PWA	Physician Wart Assessment
SADBE	Squaric Acid Dibutyl Ester
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Subject Identifier
SOP	Standard Operating Procedure
US	United States
w/w	Weight-to-weight

5. INTRODUCTION

5.1. 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 sub-clinically, 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, 1955) (Chan, 2008) (Richardson, 1866) (Richardson, 1891) (Watt, 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.

5.2. Study Rationale

Aclaris has conducted three (3) Phase 2 studies to determine the dose response and dose frequency of A-101 (H_2O_2) Topical Solution in patients with common warts. The three studies conducted are identified below and they represent data collected from 406 subjects.

- **Study A-101-WART-201:** A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group, Study of A-101 Solution in Subjects with Common Warts (n=90).
- **Study A-101-WART-202:** A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of A-101 Topical Solution Applied Once a Week in Subjects with Common Warts (n=157).
- **Study A-101-WART-203:** A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of A-101 Topical Solution Applied Twice a Week in Subjects with Common Warts (n=159).

The results from Study A-101-WART-201 evaluated two concentrations of A-101 (H_2O_2) Topical Solution: 40% and 45% (w/w) compared with vehicle. The 45% (w/w) concentrations demonstrated clinically and statistically significant results in clearing warts while the 40% concentration had no effect when compared with vehicle. Therefore, A-101 40% topical solution was judged to be an ineffective concentration and not evaluated in further Phase 2 studies.

The results from Study A-101-WART-202, which evaluated a 45% (w/w) concentration of A-101 (H_2O_2) Topical Solution when treating a single target wart and up to 3 additional warts showed that the 45% concentration applied once weekly resulted in a clinically and statistically significant clearing of warts at the end of the treatment period (Day 56) and at the end of a 12-week post-treatment follow-up (Day 134).

The results from Study A-101-WART-203, which evaluated a 45% concentration of A-101 (H_2O_2) Topical Solution administered twice weekly to a single target wart and up to 5 additional warts showed that the 45% (w/w) concentrations resulted in clinically and statistically significant clearing of the target wart and all treated warts at the end of the treatment period (Day 56) and at the end of a 12-week, post-treatment follow-up (Day 134). The results from Study WART-203 were clinically and statistically significant clearance of warts at the end of the treatment period (Day 56) and at the end of a 12-week post-treatment follow-up (Day 134), with consistently earlier and stronger results than the data from Study WART-202 which incorporated a once weekly dose regimen.

A-101 (H_2O_2) 45% (w/w) Topical Solution administered once weekly and twice weekly was well tolerated. Treatment emergent adverse events were predominantly mild and unrelated to study medication. Local Skin Reactions (LSRs) were predominantly mild and transient. The LSRs of pruritus and stinging reported by subjects, and crusting, edema, erythema, and scaling reported by the investigator following treatment generally resolved by Visit 13 (Day 134). There were no clinically significant changes during the study in laboratory evaluations or vital signs.

6. OBJECTIVES

6.1. Study Objectives

6.1.1. Primary Objective

The primary objective of this study is to evaluate the effectiveness of A-101 45% compared to Vehicle when applied twice weekly to common warts.

6.1.2. Secondary Objectives

The secondary objectives of this study include:

- Duration of response to A-101 45% compared to Vehicle.
- Onset of action of A-101 45% compared to Vehicle.
- Safety of A-101 45%.

7. STUDY DESIGN

This is a phase 3, multicenter, randomized, vehicle controlled, double blind parallel group study designed to evaluate the efficacy and safety of A-101 45% compared to Vehicle in subjects with common warts.

During the study, the investigator will identify at least 1 and up to 6 common warts to be treated twice a week for up to 8 weeks (maximum of 16 treatment applications)

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 60) follow up evaluations, no identified Wart retreatment
- Visit 11 (Day 78) follow up evaluations, no identified Wart retreatment
- Visit 12 (Day 106) follow up evaluations, no identified Wart retreatment
- Visit 13 (Day 137) follow up evaluations, no identified Wart retreatment; end of study

*The second weekly application will be applied by the subject/parent/legal guardian at home (Day 4, 11, 18, 25, 32, 39, 46, and 53).

Refer to Table 2 for a complete list of protocol required study assessments.

7.1. Number of Subjects and Study Centers

Approximately 500 subjects will be randomized to one of two treatment arms at approximately 25 investigational centers in the US. Of the 500 subjects randomized, approximately 100 subjects will be between 1 and 17 years of age.

7.2. Duration of Study

The anticipated time for study enrollment is approximately 3 months. The duration of study participation is anticipated to be a maximum of 157 days per subject. Subjects will have a total of 13 study visits. The maximum anticipated duration for the study is approximately 10 months.

8. STUDY ENTRY CRITERIA

8.1. Inclusion Criteria

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

1. Subject or legal guardian is able to comprehend and is willing to sign an informed consent/assent for participation in this study.
2. Male or female ≥ 1 year old.
3. Subject has a clinical diagnosis of common warts (verruca vulgaris).
4. Subject has at least 1 and up to 6 clearly identifiable common warts located on the trunk or extremities that meet the requirements as defined below:
    a. Have a longest axis that is ≥3 and ≤8 mm and have a thickness of ≤3mm
    b. Be a discrete lesion, i.e. each wart meeting the entry criteria is clearly separated from other warts.
    c. 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. Periungual, subungual, genital, anal, mosaic, plantar, flat and filiform warts are excluded from treatment and evaluation. If a subject has these types of warts, but also has warts that meet the inclusion criteria, the subject will NOT be excluded from the study.
5. Each common wart identified for treatment must have a PWA ≥ 2.
6. Subject's 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. 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 the identified common warts or which exposes the subject to an unacceptable risk by study participation.
8. Subject is willing and able to follow all study instructions and to attend all study visits.
9. Subject must be the only individual in a household participating in the study.

8.2. Exclusion Criteria

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

1. Subject has clinically atypical warts.
2. Subject is immunocompromised (*e.g.*, due to chemotherapy, systemic steroids, genetic immunodeficiency, transplant status, etc.).
3. Subject has a history of Human Immunodeficiency Virus (HIV) infection.
4. Subject has had any Human Papilloma Virus (HPV) vaccine within 6 months prior to Visit 1.
5. 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

6. 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
    - Glucocortico-steroids (inhaled and intra-nasal steroids are permitted); 28 days
7. Subject has used any of the following topical therapies within the specified period prior to Visit 2 on, or in the proximity to any of the common warts identified for treatment, 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], photodynamic 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
    - Antimetabolite therapy (*e.g*., 5-fluorouracil); 8 weeks
    - Retinoids; 90 days
    - Over-the-counter (OTC) wart therapies and cantharidin; 28 days
8. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in the proximity to any of the common warts identified for treatment 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
9. Subject has a history of sensitivity to any of the ingredients in the study medications.
10. Subject has any current skin or systemic 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.
11. Participation in another therapeutic investigational drug/device trial in which administration of an investigational treatment occurred with 30 days prior to Visit 1.
12. Subject has an active malignancy.
13. Subjects is viewed by the Principal Investigator as not being able to complete the study.

8.3. Removal of Subjects from Study Therapy

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

- Unacceptable adverse event
- Subject unwilling or refusal to continue with the protocol defined study visits and/or consent withdrawal for study participation
- Change in compliance with an inclusion/exclusioncriteria
- Use of a prohibited medication (through Visit 13)
- 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. CRA 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

8.4. 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.

8.5. Subject Replacement

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. A screen failure is a subject that signs an informed consent form for participation in the study but is determined not to be eligible for the study prior to the subject being randomized to the study.

8.6. Subject Identifier (SI)

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

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

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

9. STUDY PROCEDURES

The schedule of study activities (including assessments, tests, exams, disease assessments, and study drug administration) beginning with screening and continuing through the end of study are outlined in Table 2 . A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study related procedure (*e.g.*, vital signs, clinical laboratory sampling, or photography).

Table 2: 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	60	78	106	137
Treatment Window	N/A	N/A	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	+4 days	±7 days	±7 days	+7 days
Study Procedures													
Informed Consent	▲												
Inclusion Criteria/Exclusion Criteria	▲	▲[1]											
Subject Identifier	▲[2]												
Medical history/demographics	▲												
Fitzpatrick Skin Type Assessment	▲[3]												
Vital Signs	▲[4]								▲				▲
Prior Medications/Therapies	▲[5]												
Clinical Chemistry and CBC[6]	▲												▲
Common Wart Identification[7]	▲												
Physician's Wart Assessment[8]	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲

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	60	78	106	137
Treatment Window	N/A	N/A	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	+4 days	±7 days	±7 days	+7 days
Common Wart Dimensions[9]	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Standardized Photography[10]	▲	▲[11]		▲		▲			▲	▲	▲	▲	▲
Subject Randomization		▲[12]											
Local Skin Reactions		▲[13]	▲[13]	▲[13]	▲[13]	▲[13]	▲[13]	▲[13]	▲	▲	▲	▲	▲
Study Medication Application[14]		▲	▲	▲	▲	▲	▲	▲	▲				
Study Medication Application at Home[15]			A-101 Study Medication will be applied at home on Days 4, 11, 18, 25, 32, 39, 46, 53. A window of +1 day is allowed.										
Subject Instructions	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	
Concomitant therapies[16]		▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	
Adverse Events[17]		▲	▲	▲	▲	▲	▲	▲	▲	▲	▲		

[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.

[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 14 days prior to Visit 2. Refer to Section 11 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]The treating investigator will identify at least 1 and up to 6 common warts located on the trunk or extremities that meet the inclusion criteria outlined in Section 7.

[8] The investigator will use the Physician Wart Assessment (PWA) scale to assess each identified common wart. The investigator must assess the identified common warts prior to application of the study medication at Visit 2-Visit 9. In order to be eligible for randomization at Visit 2, each common wart must have a PWA grade ≥ 2.

[9] The investigator will measure the dimensions (longest axis and thickness of the common wart) at Visit 1 and prior to randomization at Visit 2. In order for the subject to be randomized at Visit 2 the identified common warts must have the specific dimensions outlined in Section 12.1. The investigator will be required to measure the longest axis of each common wart at Visits 2-13.

[10] At Visits 1, Visit 2, 4, 6, and 9 (prior to study medication application), and Visit 10-13, a qualified investigational center staff member will take a photograph of each identified common wart using the Aclaris supplied camera. All photographs will be sent to a central imaging laboratory.

[11]At a sub-set of investigational sites (up to 3 sites), subjects randomized at these sites will have additional standardized photographs taken of their common warts at the following time-points: V2-10 minutes post application, 1-hour post application and 24 hours post application.

[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 identified common wart for local skin reactions associated with irritation at Visits 2-13. At Visit 2-Visit 9, the investigator and subject will assess each identified common wart for LSRs prior to the application of the study medication. Refer to Section 13.1 for the complete list of Local Skin Reaction signs and symptoms.

[14] During in-office visits, 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. Subjects ages 1 to 17 will have their A-101 study medication applied by a parent/legal guardian in front of the treating physician or a member of the investigational study staff during in-office visits. If the identified common wart meets the criteria

for re-treatment as defined in Section 10.6 the lesion will be re-treated at Visits 3-9. Following application of study medication, subjects must NOT wash/submerge the treated wart for at least 6 hours and they must NOT apply any topical products to the treated common warts for at least 6 hours. Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated area is not completely dry 10 minutes after the application, the area should be blotted dry.

[15]All subjects will receive their second weekly treatment of the A-101 study medication at home on Days 4, 11, 18, 25, 25, 32, 39, 46, 53 as determined by the PWA assessment performed during the in-office visit. Subjects ages 1 to 17 will have their A-101 study medication applied by a parent or legal guardian. All subjects will need to document the application of A-101 study medication in a subject diary. The second weekly treatment will depend on the PWA performed during the in-office visit that week. If the identified common wart meets the criteria for re-treatment during the in-office visit, then the subject/parent/guardian will perform the second weekly treatment at home.

[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 the identified common wart 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 Section 14.1.2 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 and through Visit 11. 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.

10. STUDY TREATMENT

10.1. Investigational Study Medication

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

Table 3: 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	59ºF to 77ºF (15ºC to 25ºC) 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 twice a week for 8 weeks.	
Duration of Administration	Apply study medication to each identified common wart for approximately 15 seconds. Allow each treated wart to remain undisturbed for approximately 15 seconds. Repeat the application/waiting cycle until the study medication has been applied to each identified common wart up to 3 times.	
Activated Applicators	Activated applicators are stable for 4 hours at room temperature (59ºF to 77ºF or 15ºC to 25ºC)	

10.2. 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 and stratified by investigational study site. Sites will be shipped study medication in blocks of 4. Once a subject is determined to have met all inclusion criteria and does not meet any of the exclusion criteria, the site will pull the next sequential drug kit from their supply and enter the drug kit number into the EDC system.

10.3. Study medication packaging, storage, and dispensing

A-101 45% and matching Vehicle will be provided by Aclaris Therapeutics, Inc. and labeled according to applicable regulatory requirements.

The study medication will be packaged in single use applicators. The ampoule is provided inside a sealed polyethylene tube with a flocked, doe foot applicator on one end.

Subject kits will contain 20 study medication applicators. The blinded subject kits will remain at the investigational site and the site staff will dispense a study medication applicator to the subject for the at home treatment visit. The outside of each subject kit and each individual treatment applicator will be labelled in compliance with applicable regulatory requirements.

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

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

10.4. 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 CRA at the completion of the study and all unused study medication will be disposed of after final accountability.

10.5. Study Medication Treatment

The study medications are for external, topical use only and are to be applied only to those subjects that have been properly consented and randomized to the study.

The investigational center staff member must comply with the study medication storage conditions outlined in Section 10.1

During Visit 2-Visit 9 (if the identified common wart meets the criteria for retreatment), 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 the identified common wart in the presence of the treating investigator or investigational staff that has been trained on the protocol. The second weekly application of the A-101 study medication will be applied by the subject at home (Days 4, 11, 18, 25, 32, 39, 46, and 53). The second weekly treatment will be determined by the PWA assessment performed during the in-office visit. If the identified common wart meets the criteria for retreatment, then the subject will apply the A-101 study medication at home.

Subjects between the ages of 1 and 17 years of age will have their A-101 study medication applied in the office by a parent or legal guardian in the presence of the treating physician or a member of the investigational site staff during Visit 2-Visit 9. The second weekly A-101 study medication application will be applied at home by a parent or a legal guardian (Days 4, 11, 18, 25, 32, 39, 46, and 53). The second weekly treatment will be determined by the PWA assessment performed during the in-office visit. If the wart meets the criteria for retreatment, then the subject will apply the A-101 study medication at home.

Retreatment Criteria:

At Visit 3-9, if the identified common wart has a **PWA grade of >0** then the subject will receive re-treatment with the A-101 study medication treatment. However, treatment with the A-101 study medication should not be applied if any of the following criteria apply to the identified common wart:

- The common 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 common 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 common wart, in the Investigator's opinion, cannot be visualized so the Investigator cannot assess the PWA.

If the identified common wart meets the criteria for re-treatment during the in-office visit (PWA>0), then the subject/parent/legal guardian should treat the common wart at home on the protocol defined at home treatment days (Days 4, 11, 18, 25, 32, 39, 46, 53. A window of +1 day is allowed). If the subject is unable to tolerate treatment the day of an at home treatment visit due to severe skin irritation, then the treatment should be held and the investigational site should be notified.

Subjects whose identified common wart(s) is assessed at a particular visit (V3-V9) to be a PWA=0 will not have the that common wart re-treated at that visit (or retreated at the second at home application that week).

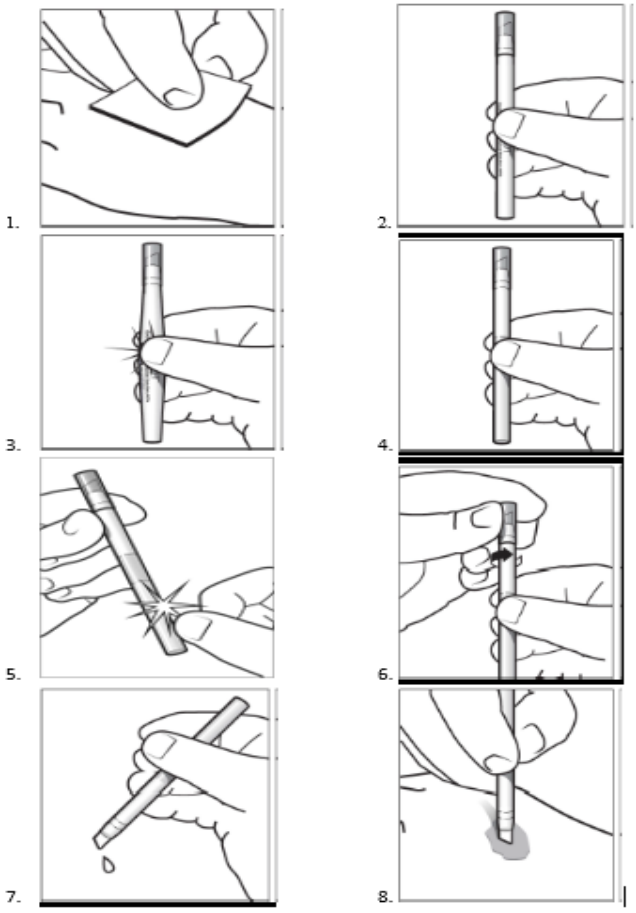
10.6. Preparing the Study Medication for Application

To perform a study medication treatment for the identified common wart a staff member will select the appropriate study medication applicator from the identified subject's kit. The following instructions outline the procedure for application of the study medication to the identified common wart. During each in-office treatment visit, the Investigational Study Staff will be responsible for reviewing the following instructions with the subject/parent/legal guardian and ensure that they understand how to properly prepare the applicator and apply the A-101 study medication.

- For the in-office treatment applications, the 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 nitrile or vinyl examination gloves during the treatment; **latex gloves are prohibited**
    - Visually inspect the applicator for damage:
        - If the applicator appears damaged do not use it for the treatment, contact the study monitor for disposal instructions and select an unused applicator with the next highest number for the treatment

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

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



1. Each common wart should be cleaned using an alcohol wipe prior to application of A-101 45%.
2. Hold the applicator so that the applicator cap is pointing up.
3. Crush the ampule in the applicator by applying pressure to the center of the barrel of the applicator.
4. Remove the sleeve.
5. Tap the barrel of the applicator to ensure the solution is free of the crushed ampule.
6. Gently remove the cap by twisting while pulling away from the applicator.
7. Express a single drop of A-101 45% so that the tip of the applicator becomes wet.
8. Apply the solution to the identified warts in a circular motion.

All subjects will be supplied with treatment application instruction sheets at the completion of each in-office visit.

10.7. Applying Study Medication

All subjects that are between the ages of 1 and 17 will have their A-101 study medication applied by a parent/legal guardian. Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated area is not completely dry 10 minutes after the application, the area should be blotted dry. . For in-office visits, the subject's parent or legal guardian will apply the A-101 study medication in front of a member of the investigational study staff to ensure there is a clear understanding regarding how the study medication should be handled.

Subjects 18 years of age and older will apply their A-101 study medication to his/her identified common warts in the presence of the treating physician or member of the investigational staff during in-office visits. The second weekly application will be performed at home.

The following instructions will be used by all subjects/parents/legal guardians applying A-101 study medication to all identified common warts:

- Do not apply the study medications to eyes, nose, mouth, mucous membranes, or open wounds
- Wear nitrile or vinyl examination gloves during the treatment; **latex gloves are prohibited (All subjects will be supplied with nitrile or vinyl examination gloves to be used for at home applications)**
- Thoroughly cleanse the common wart 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 common 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 the identified common 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.
- If severe erythema and edema develop, then the treatment cycle should be discontinued for that specific treatment application.
- Absorb any remaining A-101 study medication and dry the common wart and the surrounding skin without wiping or rubbing.

10.8. Dose Modification

If a subject refuses to have a study medication treatment the investigator must report the visit number, visit date, and state the reason the subject refused to allow treatment 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.

10.9. 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.

11. PREVIOUS AND CONCOMITANT THERAPIES

11.1. Previous Therapy

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 2 to the identified common 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); 6 months
    - Immuno-therapy (*e.g.*, imiquimod, squaric acid dibutyl ester [SADBE], etc.); 12 weeks
    - Antimetabolite therapy (*e.g.*, 5-fluorouracil); 8 weeks
    - Retinoids; 90 days
    - Liquid nitrogen, electrodesiccation, curettage; 60 days
    - Over-the-counter (OTC) wart therapies and cantharidin; 28 days

11.2. Concomitant Therapies

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

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

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

11.3. Prohibited Therapies

During the course of this study, subjects are prohibited from using the following treatment therapies to treat the identified common 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 and cantharidin.

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 identified common 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 treated common wart for at least **6 hours** and must not apply any topical products to the treated common wart for at least **6 hours.** Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated area is not completely dry 10 minutes after the application, the area should be blotted dry.

12. ASSESSEMENTS OF CLINICAL EFFICACY

12.1. Common Wart Identification

At Visit 1, the investigator will identify at least one 1 and up to 6 common warts for treatment and evaluation.

At Visit 1, each identified common wart must:

- Have a longest axis that is ≥3 mm and ≤8 mm
- Have a thickness ≤3mm
- Be a discrete lesion, i.e. each wart meeting the entry criteria must be clearly separated from other warts
- Be present for at least 4 weeks
- Not be a periungual, subungual, genital, anal, mosaic, plantar, flat or filiform wart
- Not be in an intertriginous fold
- 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 each identified common wart on the body charts in the CRFs indicating landmarks and distances to assist with confirming the location of the identified common wart at subsequent visits.

12.2. Standardized Photography

At Visits 1, 2, 4, 6, 9-13 a qualified investigational center staff member will take standardized color photographs of each identified common wart.

Subjects at a sub-set of investigational sites (up to 3) will have additional standardized photographs taken of their each identified common wart at the following time-points:

- V2: 10 minutes post application
- V2: 1-hour post application
- V2: 24-hour post application

The photographs are to document the appearance and location of the each identified common wart. 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 common wart 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.

12.3. Physician's Wart Assessment (PWA)

The Physician's Wart Assessment (PWA) is the Investigator's assessment of the severity of each identified common 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 performed at any other visit.

At every study visit, the Investigator will assess each identified common wart and report the one integer that best describes the common 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 visit.

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 3 mm in maximal diameter (or length)
2	A visible wart ≥ 3 mm and < 6 mm in maximal diameter (or length)
3	A visible wart ≥ 6 mm in maximal diameter (or length)

The physician is encouraged to use a ruler or caliper and to feel the wart or skin area to help his/her assessment.

At Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized each identified wart must have a PWA grade ≥ 2.

At Visits 3-9, identified common warts must have a PWA > 0 to be retreated. If the Investigator cannot assess the PWA for a common wart (*e.g.*, the common 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 identified common wart must not be retreated at that visit, and the subject should be seen at the next scheduled visit. All at home treatment visits will be based on the PWA score during the in-office visit.

Refer to Appendix 2 for the PWA Site Manual.

12.4. Subject Instructions

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

Throughout the study, the subjects should:

- Continue their routine cleansing regimen except they should avoid vigorous scrubbing of the identified common 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 identified common warts to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the common warts, if excessive exposure cannot be avoided
- Avoid activities that might irritate the common warts.
- Avoid the use of self-tanning lotions and spray tans near the common warts.
- Bring the subject instruction sheet and subject diary with them to each visit.
- Follow all instructions for the proper application of the A-101 study medication when applying product at home.

On study visit days, the subjects should:

- 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 identified common 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 treated common wart for at least **6 hours**
    - Apply any topical products to the treated common wart for at least **6 hours**.

12.5. Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated area is not completely dry 10 minutes after the application, the area should be blotted dry.Other Study Supplies

Aclaris Therapeutics, Inc. will provide:

- An appropriate ruler, or other instrument, for measuring of all common wart dimensions;
- Supplies and instructions for collecting, labeling, shipping and result reporting for the clinical laboratory tests from ACM Laboratories;
- Nitrile examination gloves
- Equipment, supplies and training for taking standardized photographs;

13. ASSESMENT 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.

13.1. Local Skin Reactions (LSRs)

The LSR assessment is the Investigator's assessment of the signs and the subject's assessment of the symptoms associated with irritation at the identified common wart site (*i.e.*, the common wart and the skin immediately surrounding the common 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 each identified common wart site as follows:

- At visits where a study medication treatment or retreatment is performed:
    - Perform an LSR assessment prior to any study medication application

      and

At Visits 2-13, the Subject will assess the LSR symptoms at the identified common wart site as follows:

- At visits where a study medication treatment or retreatment is performed:
    - Perform an LSR assessment prior to any study medication application

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 common wart site using the scale below:

Local Skin Reactions	
Grade	**Descriptor**
0	None; No signs or symptoms present.
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated.
3	Severe or medically significant but not immediately life threatening; disabling; limiting self-care of activities of daily living.

13.2. 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;
- Heart 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.

13.3. Clinical Laboratory Sampling

Non-fasting blood samples for clinical laboratory analysis will be collected by a qualified staff member at Visit 1 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 each 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
- 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
- Uric acid
- Hemoglobin
- Platelet count
- Red blood cell morphology
- Red blood cell count
- White blood cell count
- White blood cell differential
  - % & absolute
  - Basophils
  - Eosinophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

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.

13.4. 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 4: 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, TB, 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.

14. ADVERSE EVENTS

14.1. Definitions

14.1.1. Adverse Events (AEs)

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 identified common 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 common 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.

14.1.2. Serious Adverse Events (SAEs)

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.

14.1.3. 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.

14.1.4. 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.

14.1.5. 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.

14.2. Reporting Procedures

14.2.1. 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.

14.2.2. Procedure for Reporting Serious Adverse Events

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 Aclaris of the SAE:

Serious Adverse Event Facsimile: 484-324-2359

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 Drug Safety Monitor agree that the SAE is satisfactorily resolved.
5. Inform the Drug Safety Monitor of SAE updates by telephone followed by an SAE form update sent by fax or by e-mail.

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).

14.2.3. 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.

15. STATISTICAL CONSIDERATIONS

15.1. Sample Size and Power Considerations

Based on efficacy results from study A-101-WART-203 with the same active study medication and treatment plan specified in the current protocol for a comparable patient population and indication, an overall per-wart clearance rate of at least 26% for Active compared with 9% for Vehicle is anticipated. Assuming a distribution of treated warts per subject comparable to the Phase 2 study results, statistical modeling provided a forecast of an advantage in subject responder rates (all treated warts with PWA=0) for Active over Vehicle groups of at least 11 percentage points. This leads to a required sample size for the current study of approximately 500 subjects to provide greater than 90% power to achieve statistical significance in the primary efficacy analysis. This projection takes into account the impact of the anticipated subject dropout rate on power for the primary efficacy analysis, based on the Intent-to-Treat (ITT) population and planned missing data imputation procedures.

Additionally, a simulation was conducted in a manner that accounted for the distribution of multiple warts, the treatment effect in clearance between the different warts and the correlation in wart clearance among multiple warts. Specific details of the simulation are described in the SAP. Results of this simulation indicate that data from 500 subjects (250 per group) will provide 97% power to demonstrate the superiority of 45% A-101 topical solution over vehicle for the primary endpoint.

15.2. Analysis of Populations

The populations used for analyses will be defined as follows:

- Intent-to-Treat Population (ITT): The ITT population includes all randomized subjects.
- Per-Protocol Population (PP): The PP Population includes all subjects who received at least one application of study medication and have no major protocol violations.
- Safety Population: The Safety population includes all subjects who received at least one application of study medication.

15.3. Statistical Analysis of Efficacy

The ITT population will be used for primary and secondary efficacy analyses and summaries. The ITT population is defined as all subjects randomized to the study and analyzed as randomized. The Per-Protocol (PP) population will be used for sensitivity analyses for the primary efficacy analysis and all secondary efficacy analyses included in the hierarchical testing procedure. Details on all analyses discussed below will be provided in the study Statistical Analysis Plan (SAP).

The primary efficacy analysis will be a treatment comparison of A-101 45% compared to Vehicle at Visit 10 (Day 60). It will be based on the proportion of subjects who achieve complete clearance (PWA=0) of all identified common warts. A Cochran Mantel Haenszel

(CMH) test stratified by the baseline number of treated warts will be used to perform the primary efficacy comparison between treatment groups, with 2-tail alpha set at 0.05. The analysis will be based on the ITT population. Any identified common wart for a randomized subject that has missing data at the endpoint visit will be treated as not Clear for the purpose of the primary efficacy analysis.

The first sensitivity analysis for the primary endpoint will be an analysis based upon the PP population. This analysis will use the same CMH model described for the primary analysis. A second sensitivity analysis will be conducted for the primary endpoint using the same CMH model for the ITT population that includes the imputation of missing PWA data using a fully conditionally specified (FCS) regression-based Multiple Imputation (MI) procedure. To assess the impact of missing data imputation on the primary analysis results a tipping point analysis will be conducted. This analysis will shift the treatment coefficient in the regression model used in the MI procedure to impose a worse mean maximum PWA for the A-101 45% arm and a better mean maximum PWA for the vehicle arm. Details of this tipping point analysis will be specified in the SAP. In addition, a model similar to the primary analysis model but stratified instead by Study Center will be performed as a sensitivity analysis including a Breslow-Day test to evaluate heterogeneity across sites.

Four secondary efficacy analyses will be performed and tested in a hierarchical Fixed-Sequence step-down method to control alpha among secondary efficacy variables. The predefined order of the tests is specified to be the order of these analyses as presented below. All analyses will be conducted at the same alpha level (2-tail alpha = 0.05). The results of the second analysis will only be reported if the first analysis reaches statistical significance at alpha = 0.05. The results of the third analysis will only be reported if the first and second analyses reach statistical significance, each at alpha = 0.05. The results of the fourth analysis will only be reported if the first, second and third analyses reach statistical significance, each at alpha = 0.05. Each of the analyses will focus on the outcome of identified common warts at specified time points.

The first secondary analysis will evaluate the effectiveness of A-101 45% compared to Vehicle at Visit 13 (Day 137). It will be based on the proportion of subjects who achieve complete clearance (PWA=0) of all identified common warts. A Cochran Mantel Haenszel (CMH) test identical to the primary efficacy analysis model and stratified by the number of treated warts at baseline will be used to perform the comparison between treatment groups, with 2-tail alpha set at 0.05. Any randomized subject with missing data at the Day 137 visit will be treated as not Clear for the purpose of this secondary efficacy analysis. Sensitivity analyses specified for the primary efficacy analysis will also be performed for this efficacy time point, including missing data imputation impact analyses, the tipping point analysis, and the site heterogeneity analysis.

The second secondary efficacy analysis will be based on a comparison between A-101 45% and Vehicle of the mean per-subject percent of treated warts that are Clear (PWA=0) at Visit 13 (Day 137), using an analysis of variance (ANOVA) model with 2-tail alpha set at 0.05.

The third secondary efficacy analysis will be a comparison between A-101 45% and Vehicle of the proportion of subjects with a single wart at baseline, whose wart is Clear (PWA=0) at Visit 10, using a CMH test stratified by investigator site, with 2-tail alpha set at 0.05.

The fourth secondary efficacy analysis will a comparison between A-101 45% and Vehicle s with respect to the median time to achieve onset of Clearance (PWA=0) for all treated warts. It will be conducted as a comparison of median time for a subject to first achieve Clearance (PWA=0) of all treated warts, using a log rank test with 2-tail alpha set at 0.05. This will be a Kaplan-Meier time-to-event analysis providing standard survivor functions and comparisons of time-to-event curves using the log rank test, where time-to-event curves will be compared with two-tail alpha = 0.05, and median time to event will be presented for each treatment group. For each subject the time to achieve onset of complete treated wart Clearance will be calculated from the date of randomization to the earliest visit date when all treated warts are clear. In the event a subject does not attain complete wart Clearance, that subject's time-to-event data will be treated as censored for the Kaplan-Meier analysis.

15.4. Statistical Analysis of Safety Data

Descriptive statistics will be calculated on the safety parameters using the Safety Population and using actual treatment received. 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.

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. The version of MedDRA to be used for the analysis of this study will be specified in the Statistical Analysis Plan.

15.5. Interim Analysis

No interim analyses are planned for this study.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. 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 IRB/EC, 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.

16.2. Protocol Violations

A **protocol violation** is defined as any divergence from the protocol-specific inclusion/exclusion criteria, subject is administered a prohibited medication, 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.

16.3. 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.

16.4. 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.

16.5. Data Management

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

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

16.6. 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.

16.7. 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.

17. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

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

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

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

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

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

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

The Investigator is responsible for obtaining written, informed consent(s) from each prospective patient interested in participating in this study before performing any study-related procedures. Written informed consent must be obtained after adequate, thorough, and clear explanation of the aims, methods, objectives, and potential hazards of the study, as well as any use of the patient's genetic information from the study. The Investigator must use the most current Central IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient and the person obtaining consent and each page not signed must be initialed and dated by the patient. The investigational site must retain the original signed consent and provide a copy to the patient.

17.2. 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.

17.3. 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.

17.4. 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.

18. REFERENCES

1. Chan HP, Maibach HI, 2008. "Hydrogen Peroxide, Blanching, and Skin: an Overview". Cutaneous and Ocular Toxicology, 307-309.
2. Fitzpatrick, TB. 1988. "The Validity and Practicality of Sun Reactive Skin Types I through VI." Arch Dermatology 869-871.
3. Richardson. 1866. "On the Introduction of Peroxide of Hydrogen as a Medicine." The Lancet 87 (2220):300.
4. Richardson. 1891. "On Peroxide of Hydrogen, or Ozone, or Water as a Remedy: Continued from a Research Commenced in the Year 1858." The Lancet 137(3527):760-763.
5. Richardson. 1891. "On Peroxide of Hydrogen, or Ozone, or Water, as a Remedy: Continued from Research Commenced in the Year 1858." The Lancet 137(3526):707-709
6. Schumb WC, Satterfield CN, and Wentworth RL. 1955. Hydrogen Peroxide. New York: Reinhold Publishing Comp.
7. Watt BE, Proudfoot AT, Vale JA. 2004 . "Hydrogen Peroxide Poisoning (Review)." Toxicological Reviews 51-57.
8. Zonios. 2007. "Probing Skin Interaction with Hydrogen Peroxide Using Diffuse Reflectance Spectroscopy." Physicis in Medicine and Biology 269-278.

APPENDIX 1. A-101-WART-301 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 identified common warts (*e.g.*, abrasive cleansing pads, abrasive cleansers, etc.).
- Continue your routine skin care products.
- Avoid exposing the identified common warts to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the wart, if excessive exposure cannot be avoided.
- Avoid activities that might irritate the identified common warts.
- Bring this subject instruction sheet and subject diary with you to each visit.

STARTING WITH VISIT 2:

- On visit days, do not apply any topical products (*e.g.*, moisturizers, sunscreens) to the identified common wart, 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 treated common warts for at least **6 hours** after the treatment
    - Apply any topical products to the treated common warts for at least **6 hours**
    - Occlude, bandage or otherwise cover the common wart treatment area (loose-fitting clothing is permissible) for at least **6 hours**.

      Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated area is not completely dry 10 minutes after the application, the area should be blotted dry**.**

STUDY MEDICATION: The study medication provided to you is only to be used as instructed.

Please ask your doctor or staff if you have any questions about its use.

STUDY VISIT SCHEDULE:

VISIT 2:	VISIT 3:

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

At Home Study Administration Days:

- Do not apply any topical products (*e.g.*, moisturizers, sunscreens) to the identified common wart, except for routine cleansing products, within **12 hours** prior to the administration.
- After application of the study medication do not:
    - Wash/submerge the treated common wart for at least **6 hours** after the treatment
    - Apply any topical products to the treated common wart for at least **6 hours**
    - Occlude, bandage or otherwise cover the common wart treatment area (loose-fitting clothing is permissible) for at least **6 hours**.

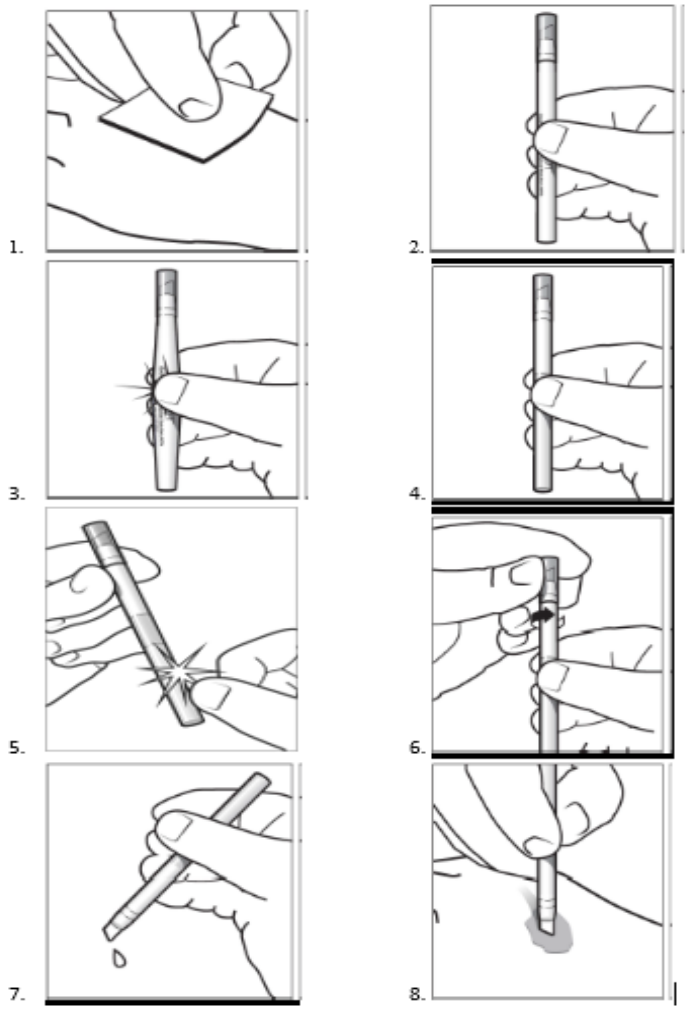
Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated

area is not completely dry 10 minutes after the application, the area should be blotted dry.

At Home Study Medication Application:

- Wash your hands prior to completing study medication treatment.
- Visually inspect the applicator for damage. If the applicator appears damaged do not use it for the treatment.
- Do not apply the study medications to eyes, nose, mouth, mucous membranes, or open wounds.
- Wear nitrile examination gloves during the treatment that were provided to you by your doctor. Latex gloves are prohibited
- Thoroughly cleanse the identified common wart by firmly rubbing with a swab/wipe wetted with 70% isopropyl alcohol that was provided to you by your doctor.
- 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 identified common wart. Using the smaller side of the applicator tip, firmly 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 the each identified wart is fully saturated with study medication at the end of the approximately 15 second application.
- Allow the treated wart to remain undisturbed for approximately 15 seconds.
- After approximately 15 seconds repeat the approximately 15 second application process.
- Repeat the application/waiting cycle until the study medication has been applied to the identified common wart up to 3 times.
- Absorb any remaining A-101 study medication and dry the treated common wart and the surrounding skin without wiping or rubbing.
- Document, in your treatment diary, the number of times the identified common wart is treated during a treatment.
- After applying the study medication, the cap should be put back on the applicator, the used applicator should be put in one of the used nitrile gloves (after removal), knotted at the end and placed in a biohazard bag. The biohazard bag, with the used applicator in the glove, should be placed in the plastic bag you brought the applicator home in, and returned to the site for accountability.

Diagram Showing the Process for Preparing A-101 Study Medication



1. The common wart should be cleaned using an alcohol wipe prior to application of A-101 45%.
2. Hold the applicator so that the applicator cap is pointing up.
3. Crush the ampule in the applicator by applying pressure to the center of the barrel of the applicator.
4. Remove the sleeve.
5. Tap the barrel of the applicator to ensure the solution is free of the crushed ampule.
6. Gently remove the cap by twisting while pulling away from the applicator.
7. Express a single drop of A-101 45% so that the tip of the applicator becomes wet.
8. Apply the solution to the common wart in a circular motion.

APPENDIX 2. PWA SITE USER MANUAL

THE PHYSICIAN'S WART ASSESSMENT (PWA)

To Assess Common Warts on the Trunk or Extremities

ACLARIS THERAPEUTICS

For Clinical Research

THE PHYSICIAN'S WART ASSESSMENT (PWA)

To Assess Common Warts on the Trunk or Extremities

INTRODUCTION

Aclaris Therapeutics developed the PWA to facilitate and standardize the rating of common warts in clinical research settings.

The purpose of the PWA is to guide the physician's overall global assessment of the target wart in order to determine the: (a) presence/absence of a wart and (b) extent to which the wart is getting better or not. Though the tool will be used for comparative purposes, the physician should only consider the wart **RIGHT NOW** when making his/her assessment.

The physician will use his or her clinical judgement and the wart size *guidelines* to rate the wart under observation on a four-point scale.

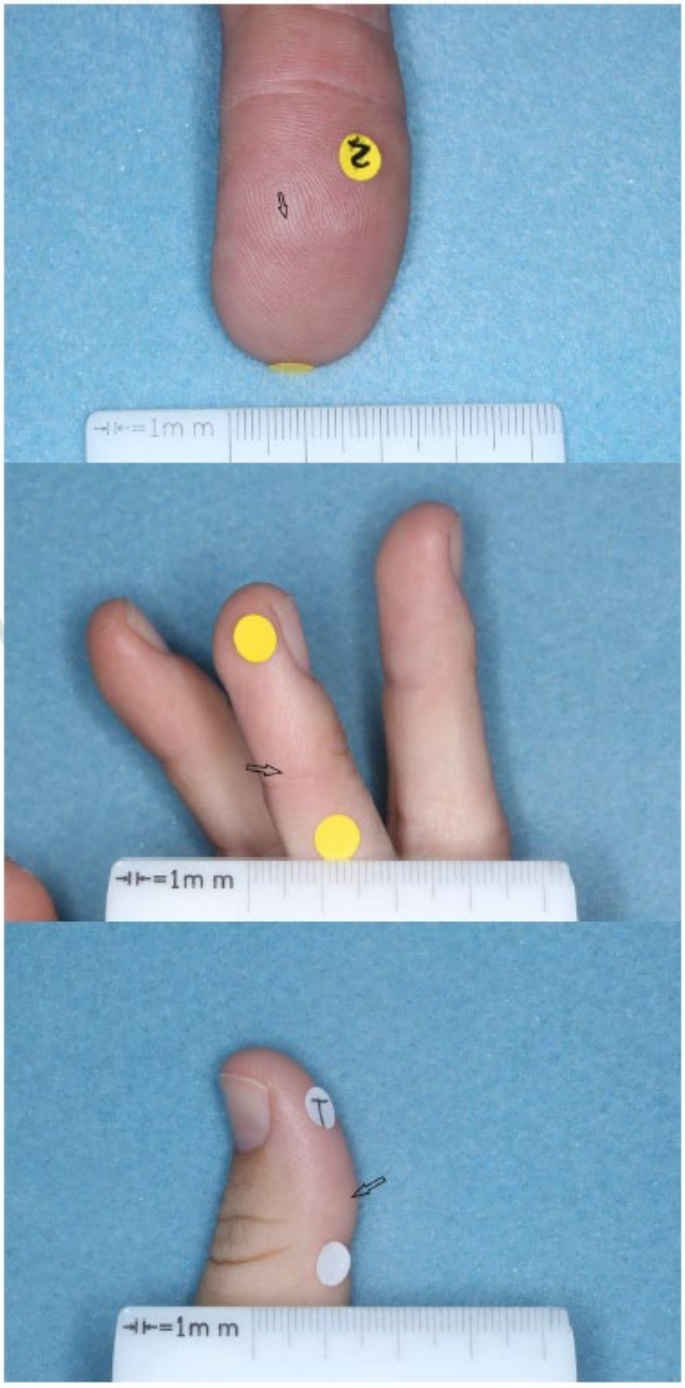
Grade	Descriptor
0	Clear: No visible wart. No further treatment is indicated.
1	Near Clear: A visible wart <3mm in maximal diameter (or length).
2	A visible wart ≥3mm and <6mm in maximal diameter (or length).
3	A visible wart ≥6mm in maximal diameter (or length).

The photographic illustrations provided in this guide are examples of each wart severity grade and can be used to help the physician determine the appropriate grading for the wart under evaluation.

In addition, the physician is encouraged to use a ruler or caliper and to feel the wart or skin area to help make his/her determination.

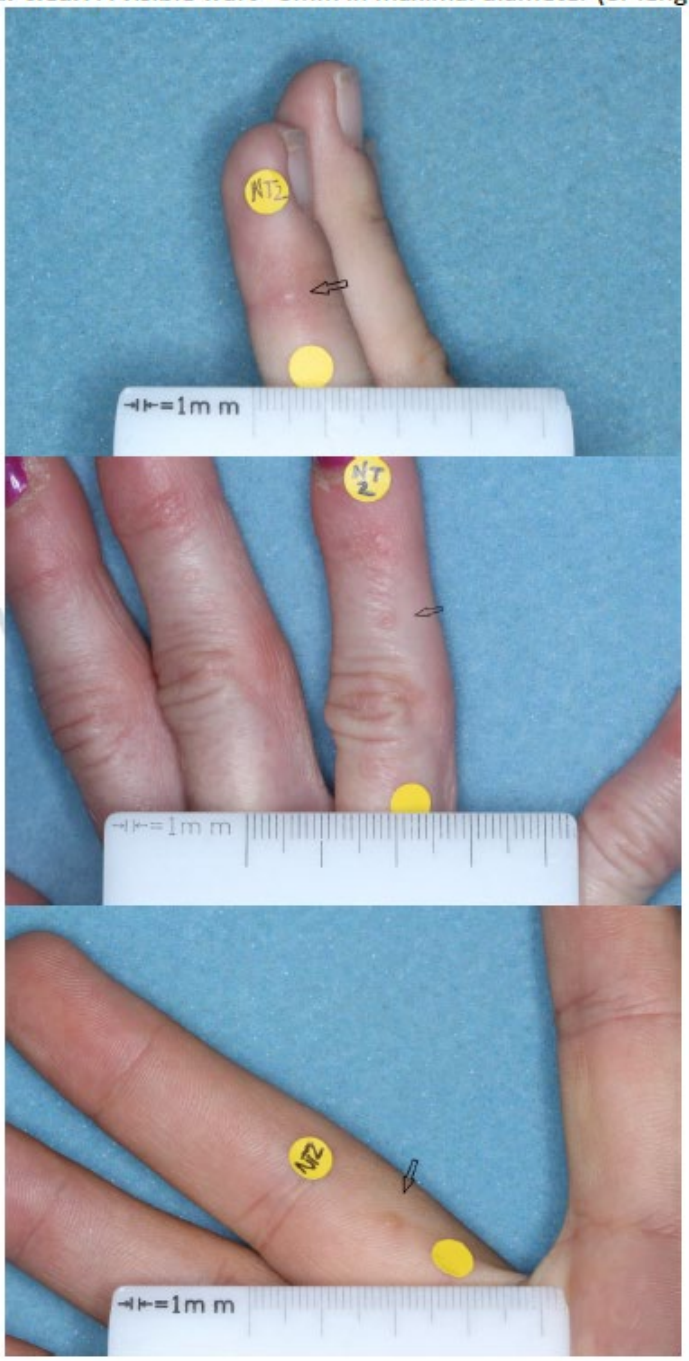
GRADE 0

Clear: No visible wart. No further treatment is indicated.



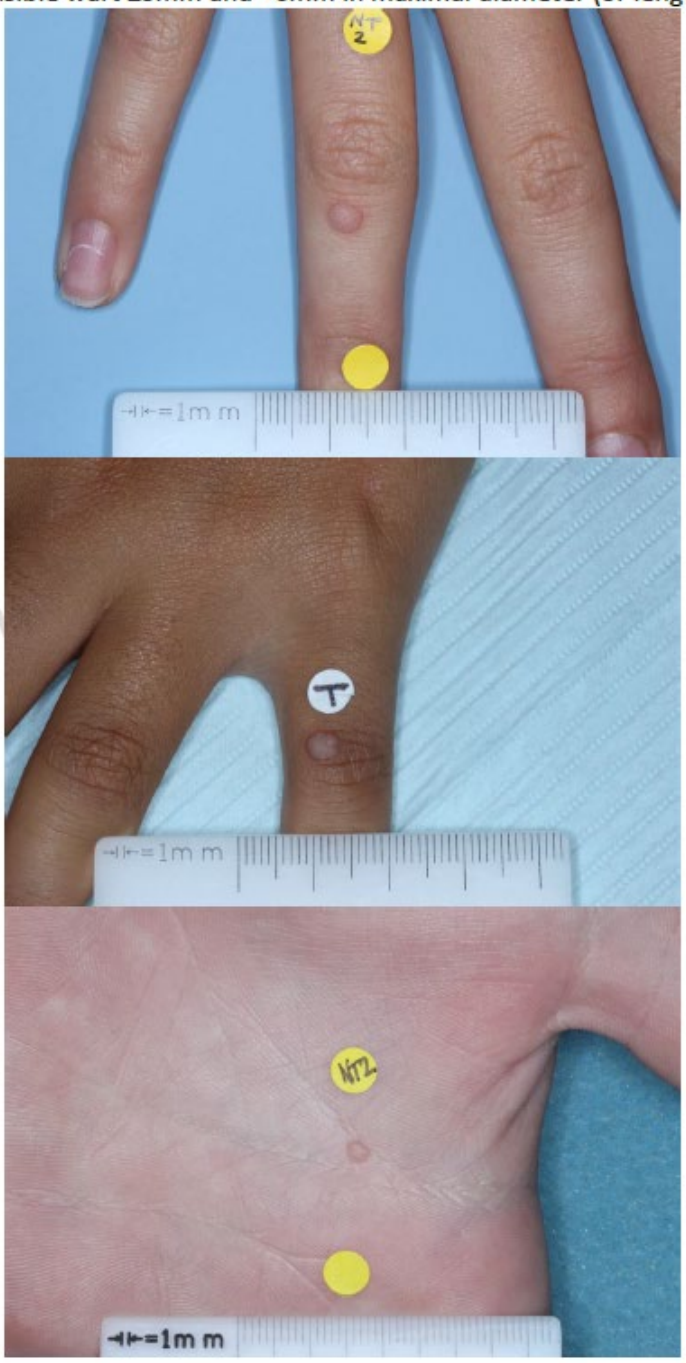
GRADE 1

Near clear: A visible wart <3mm in maximal diameter (or length).



GRADE 2

A visible wart ≥3mm and <6mm in maximal diameter (or length).



GRADE 3

A visible wart ≥6mm in maximal diameter (or length).