CLINICAL STUDY PROTOCOL

Protocol Number: A-101-WART-303

A PHASE 3 OPEN LABEL SAFETY STUDY OF A-101 TOPICAL SOLUTION FOR THE TREATMENT OF COMMON WARTS

Version 2: 20 December 2018
Version 3: 14 February 2019

Sponsor

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PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: A-101-WART-303

Protocol Title: A Phase 3 Open Label Safety Study of A-101 Topical Solution for the Treatment of Common Warts

Protocol Version 3: 14 February 2019

2-14-19

David Gordon, MB, ChB — Date:

Chief Medical Officer

INVESTIGATOR'S AGREEMENT

Protocol Number: A-101-WART-303

Protocol Title: A Phase 3 Open Label Safety Study of A-101 Topical Solution for the Treatment of Common Wart**s**

Protocol Version 3: 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**

Protocol Version	Date	Section	Revisions
Version 1	12 October 2018	NA	Original Protocol
Version 2	20 December 2018	Protocol Cover Page	Sponsor contact information has been updated.
		Synopsis, Section 7.1	Added Inclusion criteria 7, identified warts must have a longest axis of ≤8 mm.
		Table 3, Footnote 2	A typo in footnote 2 was corrected.
		Section 9.1	Added clarification that identified warts must have a longest axis of ≤8 mm. Removed any minimum size requirements, there are no minimum size or thickness requirements for warts to be eligible for entry to this protocol.
		Table 4	Protected from was added to the storage conditions for the investigational product. Additionally, the footnote that any excursion from the storage conditions must be reported to Aclaris.
		10.8	Added a sentence to clarify that all at home treatment applications must be recorded on the subject diary.
		10.9	Biohazard bag was changed to Ziptop bag.
		12.1	Added clarification that subjects should remain in the clinic for 20 minutes after any in office application to ensure any local skin reactions are appropriately documented as adverse events.
		Appendix 1	Revised the patient instruction sheet to simplify the instructions regarding the at home disposal of used A-101 applicators.
			Typos and formatting have been updated through out.

Protocol Version	Date	Section	Revisions
Version 3	14 February 2019	Synopsis, Exclusion 7 Section 7.2, Exclusion 7	Clarified that the use of hydrogen peroxide while in the A-101-WART-301 or A-101-WART-302 study was not exclusionary.
		Table 2	Visit 8 was updated to EOS (End of Study) the visit name was updated for continuity between the treatment groups.
		Table 2	A footnote 6 was added to table 2 to clarify that IP should only be dispensed at visit 5, if the subject has warts that did not clear during the 8-week treatment cycle or if new warts have appeared.
		Table 3	Visit 5 was updated to EOS (End of Study) the visit name was updated for continuity between the treatment groups.
		Section 9.2	The thickness of a wart is not a measurement which we require to be noted for this study.
		Section 10.4	This section was updated to note that any unused IP will be disposed of after final accountability has been performed.
		Section 13.2.2	An update was made to this section to reflect that SAEs will be entered in to the Axiom database rather than requiring SAEs to be faxed in.
		Section 14	The statistics section has been updated to reflect the statistical analyses that will be completed for the study.
		Section 7.6	Updated the language on subject numbering to clarify that subjects will retain the subject number from the parent study.
		Throughout	Formatting has been updated throughout.

1. SYNOPSIS

Protocol Number A-101-WART-303 Synopsis	
Protocol Number: **A-101-WART 303**	A Phase 3 Open Label Safety Study of A-101 Topical Solution for the Treatment of 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).

Study Objectives:

Primary:

The primary objective of this study is to evaluate the long-term safety of A-101 45% when applied twice weekly to common warts.

Secondary:

The secondary objectives of this study include:

- Efficacy of A-101 45% in the treatment of recurrent and/or further treatments for new warts
- Duration of response of A-101 45%
- Onset of action of A-101 45%

Study Design:

This is a phase 3, open label, long term safety study of A-101 Topical Solution 45% in subjects with common warts.

In order to be eligible for A-101-WART-303, subjects must have completed protocol treatment on either the A-101-WART-301 or A-101-WART-302 study.

Subjects that have complete clearance of all warts at the end of A-101-WART-301 or A-101-WART 302 may enter into the A-101-WART-303 study following completion of the Visit 1 assessments. These subjects will be followed every 6 weeks to assess for a recurrence or development of new common warts. If a recurrence occurs or a new wart develops these subjects may return to the investigational site to receive A-101 Topical Solution 45% twice a week for an additional 8 weeks.

Subjects that have warts that have not cleared at the completion of A-101-WART-301 or A-101-WART 302 may enter into the A-101-WART-303 study following completion of the Visit 1 assessments and will receive A-101 Topical Solution 45% twice a week for 8 weeks. If at the completion of the initial 8-week treatment course with A-101 Topical Solution 45% the identified warts are not clear, subjects may continue to receive repeated 8-week treatment course with A-101 Topical Solution 45% twice a week. The final 8-week treatment course must be initiated by Day 122.

Safety will be evaluated based on clinical laboratory studies (hematology and clinical chemistry), assessment of local skin reactions (LSRs), assessment of adverse events (AEs), 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.

Number of Patients to be Enrolled:

Approximately 400 subjects will be enrolled to the study.

Number of Study Sites:

This study will be conducted in the US only at approximately 50 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. Subject must have completed study participation in either A-101-WART 301 or A-101-WART 302.
3. Male or female ≥ 1 year old.

4. Subject has or has had a clinical diagnosis of common warts (verruca vulgaris).
5. 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.
6. Subject is willing and able to follow all study instructions and to attend all study visits.
7. Identified warts must have a longest axis of ≤8 mm.

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 (other than IP from the 301/302 study)
    - 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 (other than the Aclaris 301 or 302 study) 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 anticipated time for study enrollment is approximately 3 months. The duration of study participation is a maximum of 184 days per subject. The maximum anticipated duration for the study is approximately 9 months.

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, concomitant medications, as well as through the assessment of local skin reactions, and skin examinations.

Study Drug Administration

Subjects with identified common warts (up to 6) will apply the A-101 Topical Solution 45% to each identified common wart which meets the requirements for treatment twice a week for up to 8 weeks per treatment (maximum of 16 applications). Eight week treatment courses may be repeated.

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 should 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.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 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

4. INTRODUCTION

4.1. 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.

4.2. Study Rationale

The rationale for the dose selection and treatment design of A-101-WART 301 and A-101-WART-302 and this open label, long term safety study is based on data collected from three completed (3) Phase 2 studies which assessed dose response and dose frequency of A-101 (H_2O_2) Topical Solution in patients with common warts. All three studies demonstrated good efficacy and safety of H_2O_2 45% for the treatment of 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)

On the basis of these successful Phase II studies, Aclaris has progressed to phase III with studies A-101-WART 301 and A-101-WART-302. These studies will assess efficacy and safety of 8 weeks of treatment and 12 weeks of post treatment follow up. Aclaris recognizes that many patients may require multiple treatment courses and there is therefore a need to assess the long-term safety of topical H_2O_2 45%. A-101-WART-303 is therefore designed to assess the long-term safety of patients who were initially treated in studies A-101-WART-301 and A-101-WART-302.

5. OBJECTIVES

5.1. Study Objectives

5.1.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety of A-101 45% when applied twice weekly to common warts.

5.1.2. Secondary Objectives

The secondary objectives of this study include:

- Efficacy of A-101 45% in the treatment of recurrent and/or further treatments for new warts
- Duration of response of A-101 45%
- Onset of action of A-101 45%

6. STUDY DESIGN

This is a phase 3, open label, long term safety study of A-101 Topical Solution 45% in subjects with common warts.

In order to be eligible for A-101-WART-303, subjects must have completed protocol treatment on either the A-101-WART-301 or A-101-WART-302 study.

Subjects that have complete clearance of all warts at the end of A-101-WART-301 or A-101-WART 302 may enter into the A-101-WART-303 study following completion of the Visit 1 assessments. These subjects will be followed every 6 weeks to assess for a recurrence or development of new common warts. If a recurrence occurs or a new wart develops these subjects may return to the investigational site to receive A-101 Topical Solution 45% twice a week for an additional 8 weeks.

Subjects that have warts that have not cleared (or were not treated) at the completion of A-101-WART-301 or A-101-WART 302 may enter into the A-101-WART-303 study following completion of the Visit 1 assessments will receive A-101 Topical Solution 45% twice a week for 8 weeks. Subjects may continue to receive A-101 Topical Solution 45% twice a week for 8 weeks if their warts are not clear at the end of the 8-week treatment period but the 8 weekly treatments must be initiated by Day 122.

Visit 1 of A-101-WART-303 can be the same day as Visit 13 of either A-101-WART-301 or A-101-WART 302.

All subjects will be required to remain on study for a total of 6 months.

During the study, the investigator may identify from 1 to 6 common warts (during a 8 week treatment period) to be treated twice a week for up to 8 weeks (maximum of 16 treatment applications). An 8-week treatment course may be repeated.

Refer to **Table 2** and **Table 3** and for a complete list of protocol required study assessments.

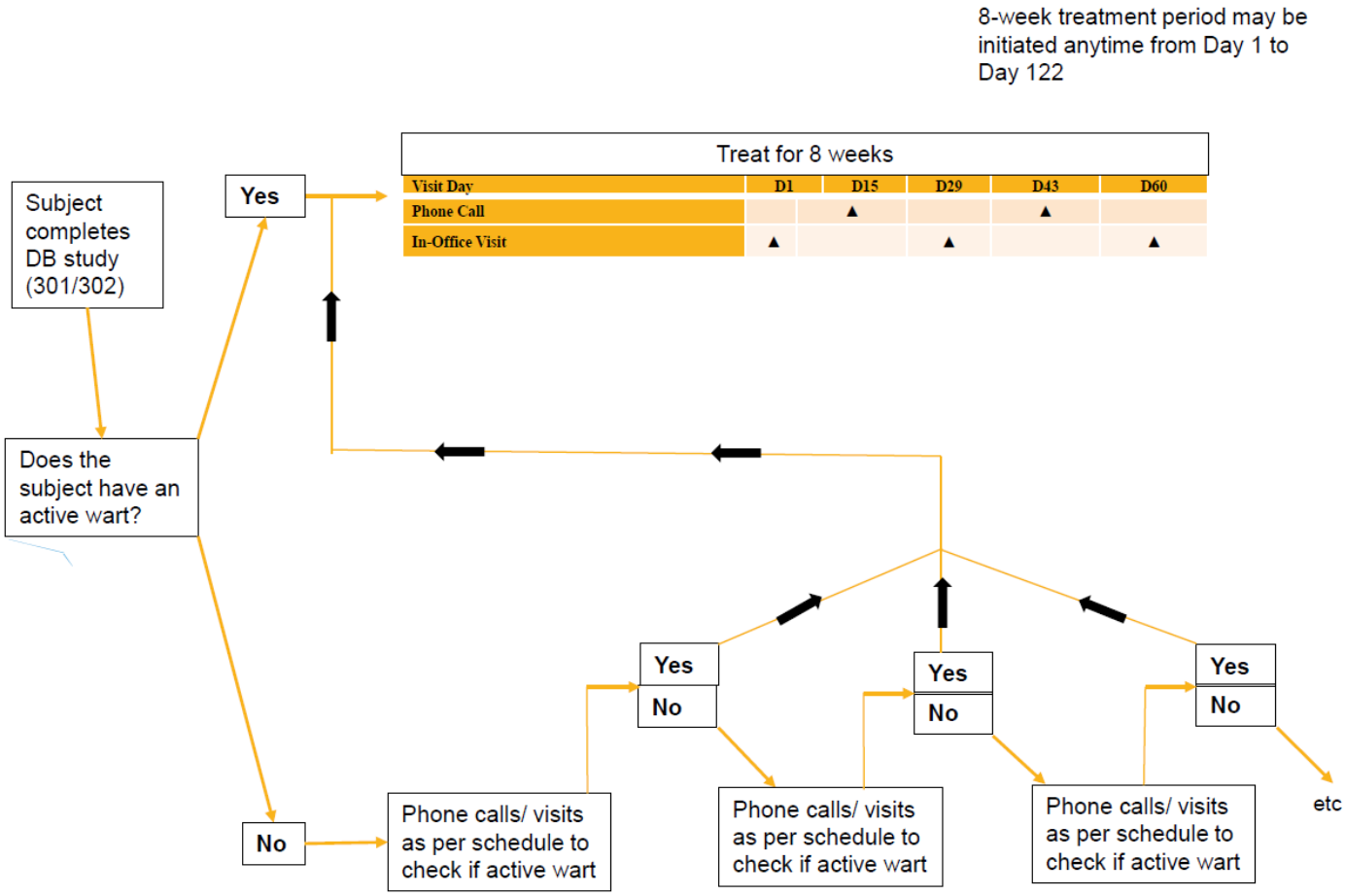


Figure 1 WART 303 Study Diagram for Treatment

6.1. Number of Subjects and Study Centers

Approximately 400 subjects will be enrolled to the study at approximately 50 investigational centers in the US.

6.2. Duration of Study

The anticipated time for study enrollment is approximately 3 months. The duration of study participation is a maximum of 184 days per subject. The maximum anticipated duration for the study is approximately 9 months.

7. STUDY ENTRY CRITERIA

7.1. 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. Subject must have completed study participation in either A-101-WART 301 or A-101-WART 302.
3. Male or female ≥ 1 year old.
4. Subject has or has had a clinical diagnosis of common warts (verruca vulgaris).
5. 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.
6. Subject is willing and able to follow all study instructions and to attend all study visits.
7. Identified warts must have a longest axis of ≤8 mm.

7.2. 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 (other than IP from the 301/302 study)
- 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 (other than the Aclaris 301 or 302 study) 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.

7.3. 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/exclusion criteria
- 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

7.4. Withdrawal Procedures

If a subject withdraws from the study prior to Day 182 (6-month time-point), the reason for withdrawal 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.

7.5. 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.

7.6. Subject Identifier (SI)

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

The SI format will be NNN-NN-NNN where the first 3 digits associate the subject with either the 301 or 302 study, the middle 2 digits are the investigational center site number (using leading zeroes, as appropriate) and the final 3 digits are the subject number which was assigned during the parent study. For example, the SI for the second subject previously treated on the A-101-WART-301 study that signs an informed consent at site number 04 would be 301- 04-002.

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

8. 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 and Table 3 . A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study related procedure.

Table 2: Study Procedures for Subjects with Common Warts at Visit 1

Visit	V1	V2	V3	V4	V5	V6	V7	EOS
Visit Day	Day 1	Day 15	Day 29	Day 43	Day 60	Day 102	Day 144	Day 182
Visit Windows		+3 Days	+ 3 Days	+ 3 Days	+ 3 Days	+ 3 Days	+ 3 Days	+ 2 Days
In Office Visit	▲[1]		▲		▲			▲
Phone Call		▲[4]		▲[4]		▲[4]	▲[4]	
Informed Consent	▲							
Inclusion Criteria/Exclusion Criteria	▲							
Clinical Chem / CBC[2]								▲
Common Wart Identification	▲[3]							
Common Wart Dimensions	▲		▲		▲			▲
Physician's Wart Assessment	▲		▲		▲			▲
Local Skin Reactions	▲		▲		▲			▲
Study Medication Application[5]	▲	▲	▲	▲				
Study Medication Dispensing and Instructions for at home application	▲		▲		▲[6]			

Visit	V1	V2	V3	V4	V5	V6	V7	EOS
Concomitant therapies		▲	▲	▲	▲	▲	▲	▲
Adverse Events	▲	▲	▲	▲	▲	▲	▲	▲

[1]Visit 1 of A-101-WART 303 may occur on the same day as Visit 13 of A-101-WART 301 or A-101-WART 302.

[2] Subjects who do not have their Visit 1 assessment on Visit 13 of A-101-WART 301 or A-101-WART-302 will have to have a clinical chemistry and a complete blood count drawn and sent to the central laboratory for analysis. 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.

[3] Warts that are identified for treatment must meet the requirements as outlined in Section 9.1.

[4] Investigational site staff will be required to make a phone contact with the subject on Day 15, Day 43, Day 102 and Day 144 to assess for any safety issues and possible new concomitant medications the subject may have started taking. In addition, subjects are to ask if they have had any new warts develop since the last in office visit.

[5] Subjects over the age of 18 are to apply the A-101 study medication on the following days: Day 1, Day 4, Day 8, Day11, Day 15, Day 18, Day 22, Day 25, Day 29, Day 32, Day 36, Day 39, Day 43, Day 46, Day50 and Day 53. A window of +1 day is allowed. Subject between the ages of 1-17 will have their A-101 study medication applied by a parent or 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.

[6] A-101 will only be dispensed to subjects who have not cleared all their warts, or who have developed new warts, and will be starting a new 8-week treatment cycle.

Table 3 Safety Observation Assessments for Subjects that are Clear at Visit 1 and Remain Clear

Visit	V1	V2	V3	V4	EOS
Treatment Day	Day 1	Week 6 (Day 42)	Week 12 (Day 84)	Week 18 (Day 126)	Week 26 (Day 182)
Window		+7 Days	+ 7 Days	+ 7 Days	+ 2 Days
In Office Visit	▲[1]				▲

Visit	V1	V2	V3	V4	EOS
Phone Call		▲[2]	▲[2]	▲[2]	
Informed Consent	▲				
Inclusion Criteria/Exclusion Criteria	▲				
Concomitant therapies		▲	▲	▲	▲
Adverse Events	▲	▲	▲	▲	▲

[1]Visit 1 of A-101-WART 303 may occur on the same day as Visit 13 of A-101-WART 301 or A-101-WART 302.

[2] Investigational site staff will contact via a documented phone call on Visit 2 Day 42, Visit 3 Day 84, Visit 4 Day 126 and Visit 5 Day 182. During the phone calls sites are to ask the subject if they have had any new warts develop or if a wart that was previously treated has recurred. If a subject has had a new wart develop or a previously treated wart has recurred, then the subject is to be scheduled for an in -office visit to start an 8-week treatment course with A-101 study medication. Subjects are to be instructed to contact the investigational site as soon as they think a new wart (or a recurrence) has developed. The 8-week treatment period can start no later than Day 122. Refer to Table 2 for the 8- week treatment schedule.

9. STUDY ASSESSMENTS

9.1. Identification of Common Warts

Subjects who have completed participation in the A-101-WART 301 or A-101-WART-302 study are eligible to enroll into the A-101-WART -303 study. Subjects that were previously treated on the double- blind phase 3 study whose warts have recurred, were not treated or who develop new warts during the observation period of A-101-WART -303 are also eligible to receive treatment with A-101 Topical Solution 45% twice a week for 8 weeks. An 8-week treatment period may begin anytime between Day 1 and Day 122.

Warts that are identified by the treating investigator must meet the following criteria:

- Subject may have 1 wart and up to 6 common warts treated during an 8-week treatment period
- Identified warts must have a longest axis of ≤8 mm.
- Be a discrete lesion, i.e. each wart meeting the entry criteria must be clearly separated from other warts
- 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).

Each identified wart will be identified on the body charts in the subject's eCRF.

9.2. Common Wart Dimensions and Physician's Wart Assessment (PWA)

Each identified wart that will be treated with A-101 study medication will be measured using the Aclaris supplied ruler. The longest axis of each identified wart will be documented on the subject's eCRF.

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.

During an 8-week treatment period, subjects will have their identified warts assessed using the PWA at the following time-points: Day 1, Day 29, Day 60 and Day 182.

The Investigator will assess each identified common wart and report the one integer that best describes the common wart severity using the following scale.

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.

Common warts that are assessed by the investigator as having cleared (PWA =0) will be instructed not to continue to apply the A-101 study medication.

Refer to Appendix 2 for the PWA Site Manual.

9.3. Phone Call Visits

Subjects that are enrolled to the study that do not have any identified warts to be treated will complete the Visit 1 (can be the same day as V13 of A-101-WART-301 or A-101-WART-302) assessment in the office and then will have telephone contact visits on Day 42, Day 84, and Day 126. During these calls site staff will ask the subject if they have any adverse events that they feel are related to their previous treatment with A-101 Topical Solution and if they have had a new wart develop or if they have had a recurrence of a wart that was previously treated on the A-101-WART 301 or A-101-WART 302 study. If a subject has a new wart or a recurrence they can be scheduled for an in-office visit and initiate treatment on another 8-week treatment period with A-101 study medication. If an 8-week treatment period is started then all assessments outlined in Table 2 must be followed. A subject cannot start an 8-week treatment period after study Day 122.

10. STUDY TREATMENT

10.1. Investigational Study Medication

The study medication for this study is open label A-101 45%. All study medications are clear, colorless solutions which are indistinguishable in physical appearance.

Table 4: Study Medication Information

Study Medication Name	A-101 45%
Manufacturer	James Alexander Corporation, Blairstown NJ
A-101 concentration (%)	45
Pharmaceutical Form	Solution
Storage Conditions	59ºF to 77ºF (15ºC to 25ºC) protected from excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area*
Route	Topical
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)

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

10.2. Subject Randomization

This is an open label study.

10.3. Study medication packaging, storage, and dispensing

A-101 Topical Solution 45% 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.

Open label subject kits will contain 20 A-101 Topical Solution 45% applicators. The subject kits will remain at the investigational site and the site staff will dispense study medication applicators 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 A-101 study medication applicators that are to be used at home.

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 destroyed after accountability has been completed.

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.

Subjects who have warts identified for treatment with A-101 Topical Solution, 45% will be instructed to treat each wart according to the technique outlined in Section 10.7. Subjects that are 18 years of age and older will apply their own study medication and subjects age 1 to 17 will have their study medication applied by a parent or legal guardian.

Identified warts are to be treated twice a week for up to 8 weeks (maximum 16 applications) or until the wart has cleared. Subjects are to be instructed to apply the A-101 study medication on the following days: Day 1, Day 4, Day 8, Day11, Day 15, Day 18, Day 22, Day 25, Day 29, Day 32, Day 36, Day 39, Day 43, Day 46, Day 50 and Day 53. A window of +1 day is allowed.

Subjects (or parents/legal guardians) are to apply the A-101 study medication in the office on the following days: Day 1 and Day 29.

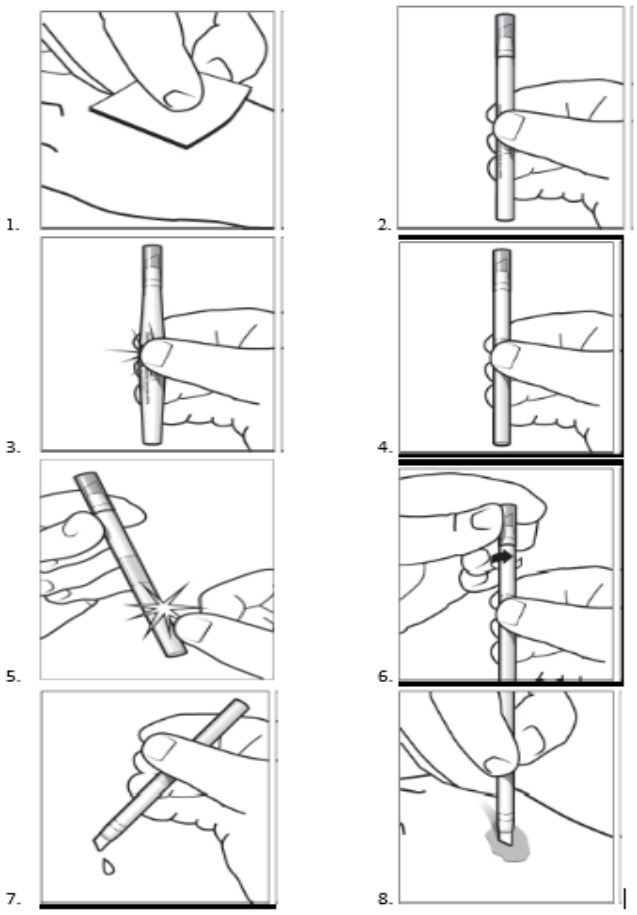
10.6. Preparing the Study Medication for Application

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 instruct the subject/parent or guardian to:
    - Washing their hands prior to applying the study medication.
    - 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 2.

Figure 2: 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.

Subjects 18 years of age and older will apply their A-101 study medication to his/her identified common warts. Study medication will be applied in the office on Day 1 and Day 29 prior to the PWA being performed.

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
- 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. 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 and document all at home treatment applications on the subject diary.

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)
- 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**.
    - 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.

10.9. Other Study Supplies

Aclaris Therapeutics, Inc. will provide:

- An appropriate ruler, or other instrument, for measuring of all common wart dimensions;
- Nitrile gloves
- Zip top plastic bags
- Supplies and instructions for collecting, labeling, shipping and result reporting for the clinical laboratory tests from ACM Laboratories;

10.10. 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.

10.11. Breaking the Blind

Not applicable as this is an open label study.

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.

For subjects starting an 8-week treatment schedule for an identified wart, topical products (*e.g.*, moisturizers, sunscreens, etc.) must not be applied to any of their identified common warts within **12 hours prior** to any treatment application (Note: routine cleansing products are allowed).

After the completion of a treatment application, 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. 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.

12.1. 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 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)

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

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.

Subjects are to remain in the clinic for 20 minutes after the application of their study medication. Any local skin reactions or other adverse experiences that occur during this time period must be

documented as an adverse event.

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 OR No signs or symptoms present.
1	Asymptomatic or mild symptoms OR clinical or diagnostic observations only OR intervention not indicated.
2	Moderate OR minimal, local or noninvasive intervention indicated.
3	Severe or medically significant but not immediately life threatening OR disabling OR limiting self-care of activities of daily living.

12.2. Clinical Laboratory Sampling

Subjects that do not have their Visit 1 the same day as Visit 13 of either A-101-WART 301 or A-101-WART 302 will have to have a clinical chemistry and CBC performed. Non-fasting blood samples for clinical laboratory analysis will be collected by a qualified staff member on Day 182 for all subjects. 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	Hemoglobin
Alanine aminotransferase (ALT)	Platelet count
Aspartate aminotransferase (AST)	Red blood cell morphology
Blood urea nitrogen (BUN)	Red blood cell count
Bicarbonate	White blood cell count
Calcium	White blood cell differential
Chloride	% & absolute
Creatinine	Basophils
Glucose	Eosinophils

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

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

The investigator must 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. ADVERSE EVENTS

13.1. Definitions

13.1.1. 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.

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.

13.1.2. 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.

13.1.3. Adverse Event Reporting Period

The investigator must start reporting non-serious AEs starting with the subject's first study medication treatment continuing until the subject's last study visit. 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 the subject's last study visit (regardless of relationship to study medication). If a subject experiences a SAE after the subject's last study visit, 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.

13.1.4. 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.

13.1.5. 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.

13.2. Reporting Procedures

13.2.1. 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.

13.2.2. 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 the Aclaris of the SAE by entering the event in to the Axiom database. If the Axiom database is unavailable, the site must fax a provided paper SAE form to Aclaris at the number below:

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 entered in to the Axiom database.
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 entered in to the Axiom database.

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).

13.2.3. 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.

14. STATISTICAL CONSIDERATIONS

Details of all statistical summaries and analyses will be provided in the study specific Statistical Analysis Plan (SAP).

14.1. Sample Size and Power Considerations

The sample size is based on an estimate of how many patients will be required to provide at least 100 subjects requiring repeated treatment for a wart over the course of the study.

- By recruiting 400 subjects, we estimate 200 subjects will have received active treatment in the A101-WART 301/302 studies.
- We expected approximately 26% of warts treated in A-101-WART-301/302 studies to be clear at the end of the A101-WART 301/302 studies.
- Based on the assumption that 26% of warts will be clear, at least 148 subjects will require exposure to active treatment.
- We anticipate that some subjects originally randomized to vehicle will be exposed to active treatment.

As a result, the study should exceed the target of exposing more than 100 subjects to repeated treatments over the course of the study.

14.2. Analysis Populations

The Intent-to-Treat (ITT) population will consist of all subjects consented in the study.

14.3. Statistical Analysis of Efficacy

Unless otherwise stated, all efficacy summaries and analyses will be conducted using the ITT population. All efficacy summaries and analyses will be produced for the following groups:

- Subjects treated in the study that were randomized to active treatment during the previous A101-WART 301/302 study.
- Subjects treated in the study that were randomized to vehicle during the previous A101-WART 301/302 study.
- Subjects treated in the study overall.
- Subjects not requiring treatment during the study that were randomized to active treatment during the previous A101-WART 301/302 study.
- Subjects not requiring treatment during the study that were randomized to vehicle during the previous A101-WART 301/302 study.
- Subjects not requiring treatment in the study overall.
- All subjects combined

The primary efficacy analysis will be the effectiveness of A-101 45% based on the proportion of subjects who achieve complete clearance (PWA=0) of all identified common warts at any scheduled visit. Any identified common wart for a subject that has missing PWA data will be treated as not clear for the purpose of the primary efficacy analysis.

Four secondary efficacy analyses will be performed:

- Durability of response: for warts achieving a status of Clear (PWA=0), the number of weeks the wart remains clear will be tabulated and these results will be summarized using descriptive statistics. The proportion of these warts that remain clear at the end of the study will also be presented.
- Mean per-subject percent of treated warts that are Clear (PWA=0) at each visit will be summarized using descriptive statistics.
- Proportion of subjects with a single wart at baseline whose wart is Clear (PWA=0) will be summarized using descriptive statistics by visit.
- Median time to achieve onset of Clearance (PWA=0) for all treated warts.

Efficacy summaries will be supported by listings of PWA data.

14.4. Statistical Analysis of Safety Data

Unless otherwise stated, all safety summaries will be conducted using the ITT population. All safety summaries will be produced for the following groups:

- Subjects treated in the study that were randomized to active treatment during the previous A101-WART 301/302 study.
- Subjects treated in the study that were randomized to vehicle during the previous A101-WART 301/302 study.
- Subjects treated in the study overall.
- Subjects not requiring treatment during the study that were randomized to active treatment during the previous A101-WART 301/302 study.
- Subjects not requiring treatment during the study that were randomized to vehicle during the previous A101-WART 301/302 study.
- Subjects receiving active treatment during the study or the previous A101-WART 301/302 study.

The proportion of subjects with treatment emergent adverse events will be tabulated and presented by System Organ Class and Preferred Term from the Medical Dictionary for Regulatory Activities (MedDRA). Likewise, the proportion of subjects with serious AEs will be summarized. Adverse event summaries will be presented 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 SAP.

Local skin reaction (LSR) scores and clinically relevant abnormal laboratory results will be tabulated and presented at the subject level. For each LSR sign and at each in-house visit, the proportion of subjects who had at least one treated wart with LSR severity >= 1 will be summarized.

Safety summaries will be supported by listings of all adverse events, laboratory results, and LSR data.

14.5. Interim Analysis

No formal interim analysis will be conducted for this study.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. 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.

15.2. 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.

15.3. 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.

15.4. 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.

15.5. 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.

15.6. 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.

15.7. 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.

16. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

16.1. 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.

16.2. 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.

16.3. Regulatory Documents

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

16.4. Contractual Requirements

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

17. REFERENCES

1. Chan HP, Maibach HI, 2008. "Hydrogen Peroxide, Blanching, and Skin: an Overview". Cutaneous and Ocular Toxicology, 307-309.
2. Richardson. 1866. "On the Introduction of Peroxide of Hydrogen as a Medicine." The Lancet 87 (2220):300.
3. 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.
4. 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
5. Schumb WC, Satterfield CN, and Wentworth RL. 1955. Hydrogen Peroxide. New York: Reinhold Publishing Comp.
6. Watt BE, Proudfoot AT, Vale JA. 2004 . "Hydrogen Peroxide Poisoning (Review)." Toxicological Reviews 51-57.
7. Zonios. 2007. "Probing Skin Interaction with Hydrogen Peroxide Using Diffuse Reflectance Spectroscopy." Physicis in Medicine and Biology 269-278.

APPENDIX 1. A-101-WART-303 SUBJECT INSTRUCTION SHEET FOR IDENTIFIED WARTS TO BE TREATED

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 1:

- 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 application of A-101 study medication.
- Do not wash/submerge the treated common warts for at least 6 hours after the application of A-101study medication.
- Do not apply any topical products to the treated common warts for at least 6 hours after the application of A-101 study medication.
- Do not occlude, bandage or otherwise cover the common wart treatment area (loose-fitting clothing is permissible) for at least 6 hours after the application of A-101 study medication.
- 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:

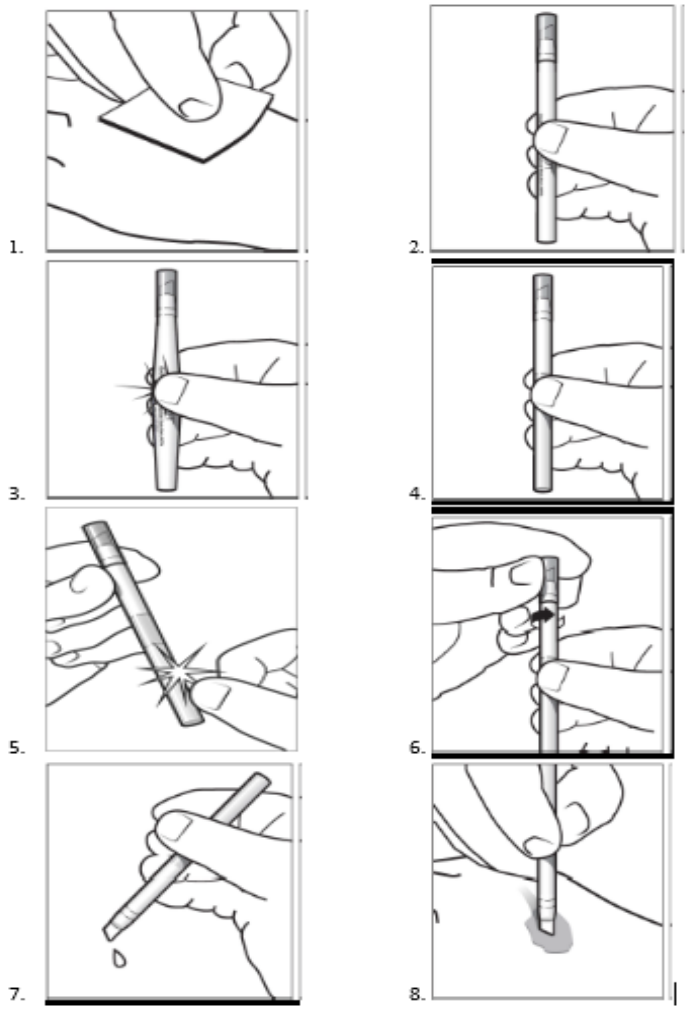
VISIT 2: Day 15 (Phone Call Visit) Date: Time:	VISIT 3: Day 29 (In Office Visit) Date: Time:
VISIT 4 Day 43 (Phone Call visit) Date: Time:	VISIT 5 Day 60 (In Office Visit): Date: Time:
VISIT 6 Day 102 (Phone Call Visit) Date: Time:	VISIT 7 Day 144 (Phone Call Visit): Date: Time:
VISIT 8: Day 182 (In Office Visit) Date: Time:	

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.
- Wear nitrile examination gloves during the treatment that were provided to you by your doctor. Latex gloves are prohibited
- Do not apply the study medications to eyes, nose, mouth, mucous membranes, or open wounds.
- 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 the provided plastic bag and placed in your trash can.

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

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.

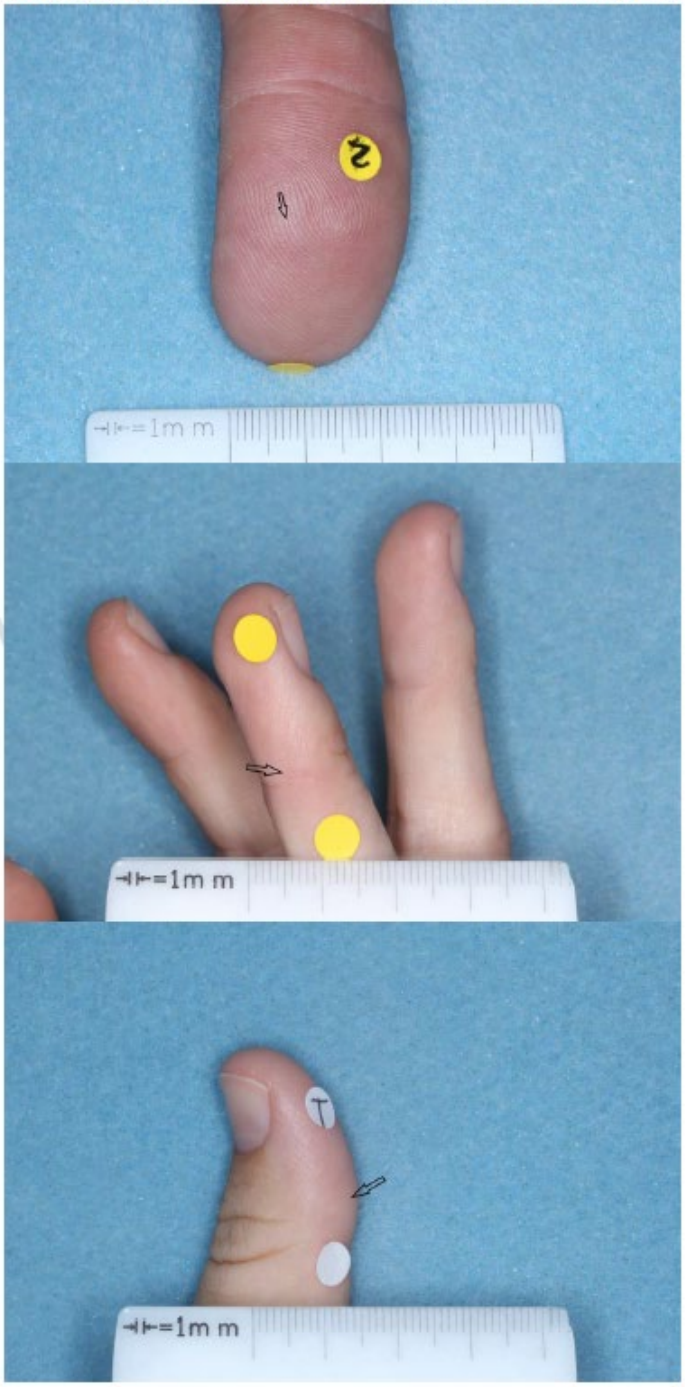
Grade	Descriptor
0	Clear: No visible wart. No further treatment is indicated.
1	Near Clear: A visible wart <3mm in maximal diameter (or length).
2	A visible wart ≥3mm and <6mm in maximal diameter (or length).
3	A visible wart ≥6mm in maximal diameter (or length).

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.

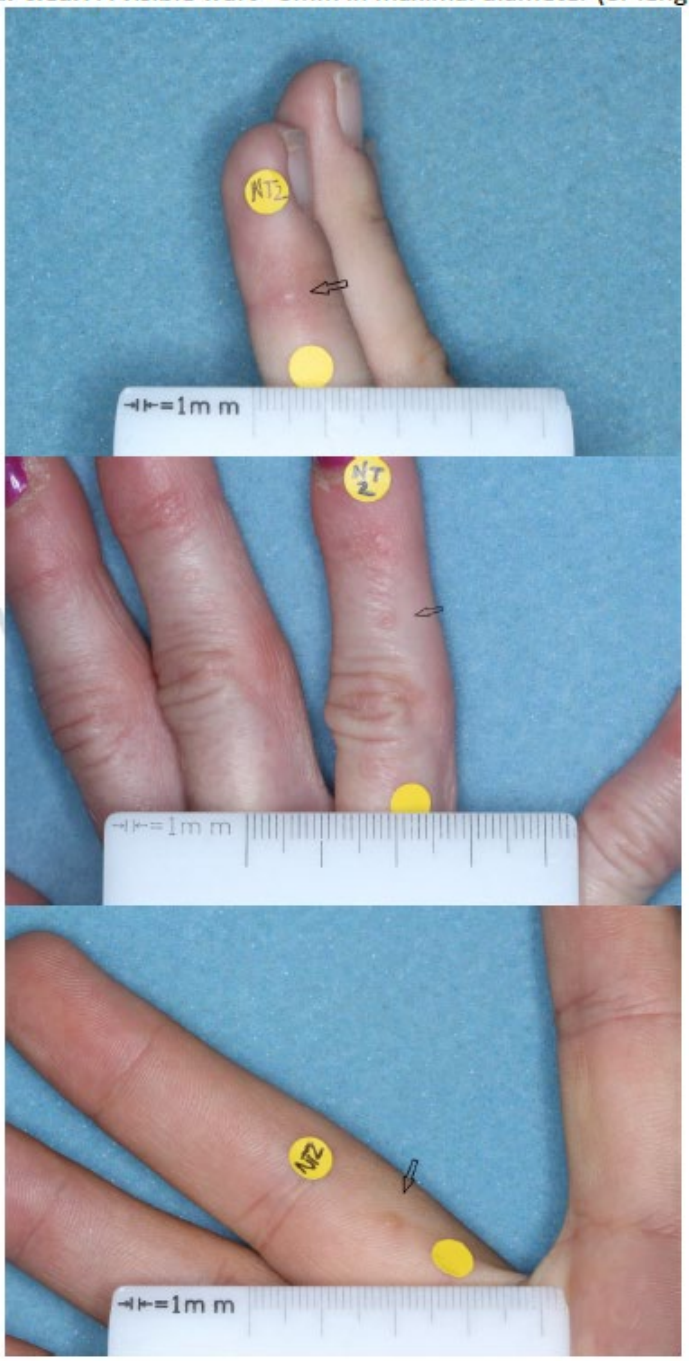
GRADE 0

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



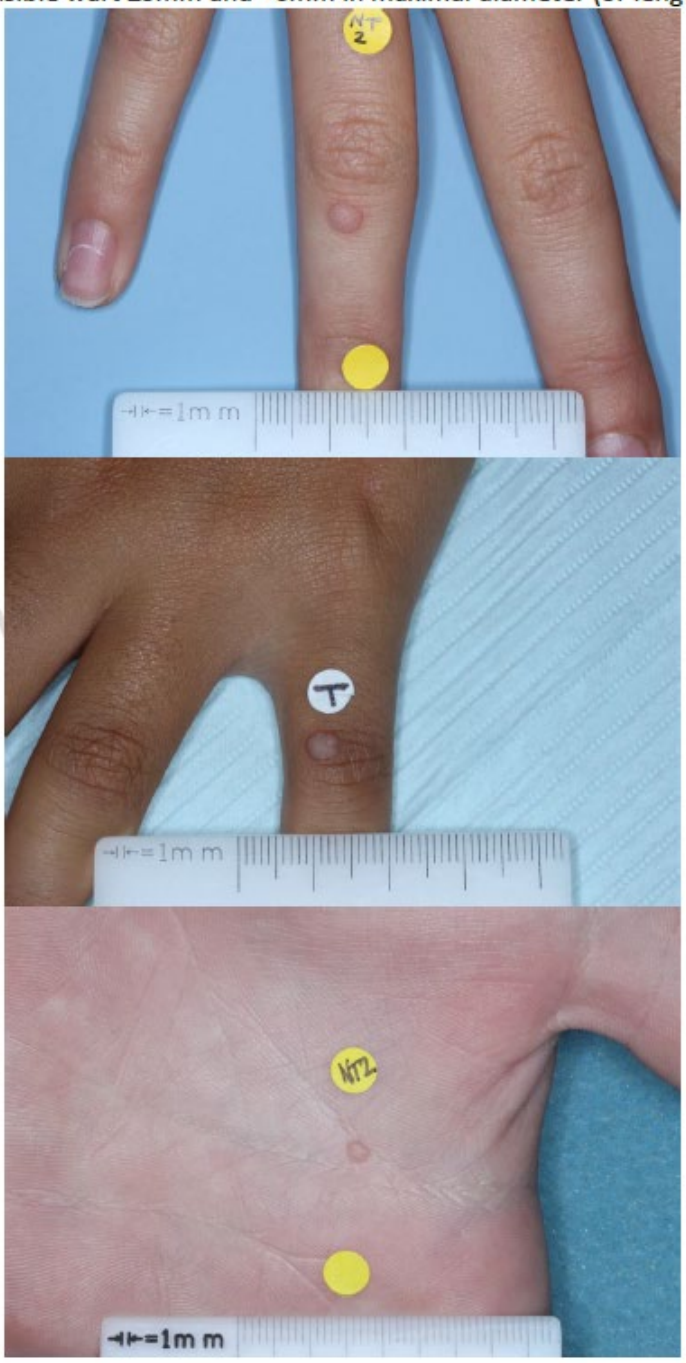
GRADE 1

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).