PROTOCOL NUMBER CLS006-CO-PR-002

Title:

A Phase 3, Randomized, Double-Blind, Vehicle-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of CLS006 versus Vehicle in Subjects 2 years of age or older with Cutaneous Common Warts

Test Product: Furosemide Topical Gel 0.125% w/w (CLS006)

Sponsor: Cutanea Life Sciences, Inc.
[redacted]
[redacted]

Sponsor Signature: _____

Print Name: [redacted]

Title: [redacted]

Date: May 23, 2017

GCP Statement:

This study will be conducted in accordance with United States Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) guidelines on current Good Clinical Practice (GCP).

Confidentiality Statement

1. SYNOPSIS

Title of Study: A Phase 3, Randomized, Double-Blind, Vehicle-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of CLS006 versus Vehicle in Subjects 2 years of age or older with Cutaneous Common Warts
Phase of Development: Phase 3
Objective: To evaluate the efficacy and safety of six (6) weeks of once daily application of Furosemide Topical Gel 0.125% (CLS006) compared to vehicle in subjects ≥ 2 years of age with nongenital cutaneous common warts (verruca vulgaris).
Methodology: Randomized, double-blind, vehicle-controlled, parallel group, multicenter study
Number of Subjects Enrolled (planned): Approximately 480 (~240 per treatment group) of which approximately 160 of subjects enrolled will be pediatric subjects (~80 will be ≥2 to <12 years of age and ~80 will be ≥12 to <18 years of age). Subjects will be randomized and stratified by age (≥2 to <12, ≥12 to <18 or ≥18) and investigative site to one of two treatment groups in a 1:1 ratio (CLS006 or vehicle gel).
Number of Sites (planned): Approximately 40
Diagnosis and Main Criteria for Inclusion: • Male or female subjects 2 years of age or older with 1 to 6 clearly identifiable common warts (verruca vulgaris) located on hands (dorsal, periungual, or palmar), feet (dorsal), limbs, and/or trunk.
Total Duration of Subject Participation (Possible): up to 34 weeks • Screening: up to four (4) weeks • Treatment Period: six (6) weeks • Post-treatment Efficacy Evaluation Period: twelve (12) weeks • Follow-up Period: additional twelve (12) weeks following Post-treatment Efficacy Evaluation Period (only for subjects who achieved clearance of at least one treated wart at Week 18/End of Post-treatment Efficacy Evaluation period
Investigational Product: Furosemide Topical Gel 0.125% w/w (CLS006) **Comparator Product:** Vehicle Topical Gel **Mode of Administration:** Topical application to each wart **Dose:** Apply a small amount of gel to cover each Baseline Treatment wart once daily

Criteria for Evaluation: **Efficacy:** Wart identification/counts, characteristics, location/mapping, and size. Clinical photography will be performed at selected centers (optional for subjects <12 years of age) **Safety:** Adverse Events (AE), vital signs, physical examinations, and clinical safety laboratory evaluations as collected throughout the study.
Statistical Methods: **Efficacy (Primary):** Difference in the proportion of subjects with complete clearance of all treated warts between the active and vehicle at Week 18/End of Post-treatment Efficacy Evaluation will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by age group ≥2 to <12, ≥12 to <18 or ≥18) and investigative site. **Safety:** AEs will be coded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by body system and preferred term. Incidence of AEs will be presented overall, by body system and preferred term. Severity and relationship to study drug of the incidence of AEs will also be presented. AEs causing study drug withdrawal and/or early study discontinuation and incidence of SAEs will be summarized. Descriptive statistics and frequency tables will be prepared as appropriate for vital signs and safety laboratory measurements.

2. STUDY CONTACTS

Company representatives' individual contact information will be maintained on a clinical study team contact list

3. LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis Of Covariance
AST	Aspartate Aminotransferase
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CLS	Cutanea Life Sciences, Inc.
CLS003	[redacted]
CLS006	Furosemide Topical Gel 0.125% w/w
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
DBT	Double-blind Treatment
DNA	Deoxyribonucleic Acid
DNCB	Dinitrochlorobenzene
DPCP	Diphenylcyclopropenone (or diphencyprone)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EOT	End of Treatment
ET	Early Termination
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HDL	High-Density Lipoproteins
HPV	Human Papillomavirus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICVT	Ionic Contra-Viral Therapy
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoproteins
LOCF	Last Observation Carried Forward
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
mL	Milliliter
MI	Multiple Imputation
NDA	New Drug Application
PI	Principal investigator
PP	Per Protocol
PTEE	Post-treatment Efficacy Evaluation
qPCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cell
RDW	Red Cell Distribution
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
Sub-I	Sub-Investigator
TEAE	Treatment Emergent Adverse Event
µg	Microgram
WBC	White Blood Cell
w/w	Weight for Weight

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5. INTRODUCTION

5.1. BACKGROUND

Human papillomavirus (HPV) refers to a group of DNA tumor viruses that can induce neoplastic proliferation of human epithelial cells; this proliferation of cells is commonly known as warts. Cutaneous wart diagnosis is generally based on clinical examination, but can be determined by histological appearances. Some warts persist for many years and untreated warts represent a pool of HPV infection within the community. Many people find warts either unsightly or painful and there is considerable social stigma with visible warts. Current clinical treatments for cutaneous HPV infections mainly involve lesion destruction. The usual first line treatments are wart paints containing salicylic acid and/or cryotherapy, usually with liquid nitrogen. However, current available treatments are considered unsatisfactory and there is an unmet need to develop treatments with greater efficacy (Kwok, Gibbs, Bennett, Holland, & Abbott, 2012).

In 2006, Hartley et al. (2006), conducted an *in vitro* study where the cardiac glycoside, digoxin, and loop diuretic, furosemide, known inhibitors of the coupled, cotransports NKATPase and NKCC1, inhibited replication of several DNA viruses in various cell types. This novel approach to treating DNA viruses by the inhibition of coupled contransporters in the host cell is referred to as Ionic Contra-Viral Therapy (ICVT) and is believed to target viral DNA synthesis through inhibition of the transport of sodium and potassium across cellular membranes. The disturbances in the intracellular environment created by this inhibition are believed to compromise the ability of viruses to proliferate, as intracellular K+ is necessary for viral DNA synthesis. This controlled depletion of cellular K+ has the potential to provide a novel approach to antiviral therapy (Hartley, Hartley, Pardoe, & Knight, 2006).

Initially, Cutanea Life Sciences, Inc. (CLS) evaluated a combination formulation of [redacted] Topical Gel (CLS003) as well as single-agent formulations, Furosemide Topical Gel 0.125% w/w (CLS006) and [redacted] Topical Gel 0.125% w/w for the treatment of HPV-associated cutaneous lesions. Subsequently, it was determined that the development would focus on the Furosemide Topical Gel 0.125% w/w (CLS006) product.

CLS is developing Furosemide Topical Gel 0.125% w/w (CLS006) as a treatment for various conditions associated with HPV. For the purposes of product development in support of a New Drug Application for the treatment indication of nongenital cutaneous warts, common and plantar warts (verruca vulgaris and verruca plantaris, respectively) will be studied separately. Initial investigations will focus on nongenital cutaneous common warts (verruca vulgaris).

Data on topical administration of furosemide is limited. However, orally administered furosemide is a frequently prescribed medication worldwide with a well-established safety profile.

5.2. RATIONALE

An initial phase I/IIA study [redacted] of the [redacted] Topical Gel (CLS003) was conducted in [redacted]. Subjects with cutaneous warts applied the study product once daily during a 7-day treatment period with a 7-day follow-up period to evaluate the pharmacodynamic response (wart size and morphology assessment by standardized clinical photography, and HPV viral load assessment of target lesions by quantitative PCR as an exploratory biomarker) and systemic exposure of after repeated topical applications of the combination product. Twelve healthy subjects with multiple cutaneous warts on the hands were enrolled in the study. This study showed that doses of 1000 mg CLS003 (equivalent to 1250 µg [redacted] and 1250 µg [redacted]) were well tolerated by the subjects and did not result in any clinically significant changes in any safety laboratory parameters, vital sign measures or electrocardiogram (ECG) recordings. All pharmacokinetic measurements, except for one furosemide measurement (Day 7, 2 hours post-dose of 91.1 pg/mL), were below the limit of quantification (50 pg/mL). No treatment related study discontinuations occurred. The most frequent occurring adverse events (AEs) were headache, application site erythema and application site pruritus observed in 3/12 (25%), 2/12 (16.7%) and 2/12 (16.7%) respectively, of the treated subjects; all were mild in severity.

A follow-up phase II study [redacted] was also conducted in [redacted] to explore the efficacy and safety of the [redacted] Topical Gel (CLS003) as well as single-agents Furosemide Topical Gel 0.125% w/w (CLS006) and [redacted] Topical Gel 0.125% w/w for treatment of cutaneous warts. This was a randomized, double-blind, vehicle-controlled study in 80 subjects who were treated with study product daily for 42 days with an 8-week follow-up period. All active treatment groups (combination and single-agent) showed effects on wart size including statistically significant reductions in dimensions of all treated warts, and substantial effects on wart clearance. No serious adverse events (SAEs), discontinuations due to AEs, or deaths occurred during the study. All AEs were of mild (n=53) or moderate severity (n=2) and self-limiting without therapeutic intervention. The AE profile was similar for all subjects across treatment groups. Most treatment-emergent adverse events (TEAEs) were considered as unlikely related or unrelated (n=47) to treatment. Common TEAEs in the single-agent furosemide treated group included influenza-like illness and upper respiratory tract infections which occurred in 2 / 20 (10%) subjects. No clinically significant changes were attributable to treatment in any of the three investigational products for hematology, clinical chemistry, urinalysis, vital signs, or ECG parameters. Overall, the safety profile of the investigational products containing single-agent furosemide or [redacted] applied for 42 days supports the use of Furosemide Topical Gel 0.125% w/w (CLS006) for the treatment of nongenital cutaneous warts.

Based upon the favorable risk/benefit outcomes to date, two larger Phase 3 studies of Furosemide Topical Gel 0.125% w/w (CLS006) will be conducted to validate the Phase 2 results of the single-agent furosemide product for the treatment of nongenital cutaneous common warts (verruca vulgaris) and to support a new drug application (NDA) submission.

6. STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and safety of six (6) weeks of once daily application of Furosemide Topical Gel 0.125% w/w (CLS006) compared to vehicle in subjects ≥2 years of age with nongenital cutaneous common warts (verruca vulgaris).

7. INVESTIGATIONAL PLAN

7.1. OVERALL STUDY DESIGN

This study will be conducted in accordance with the FDA and ICH guidelines on current GCP, following the ethical principles originating from the Declaration of Helsinki. Additionally, the study will be conducted in accordance with any applicable laws or regulations of the country in which the clinical research is conducted.

The study will be conducted as a randomized, double-blind, vehicle-controlled, parallel group, multicenter study at approximately 40 sites involving approximately 480 subjects (~240 per treatment group) with nongenital cutaneous common warts. Approximately 160 of subjects enrolled will be pediatric subjects, (~80 will be ≥2 to <12 years of age and ~80 will be ≥12 to <18 years of age).

After giving informed consent, subjects will be screened for study eligibility according to the specified inclusion/exclusion criteria. Subjects must be male or female ≥2 years of age with 1 to 6 clearly identifiable common warts (verruca vulgaris) located on hands (dorsal, periungual, or palmar), feet (dorsal), limbs, and/or trunk. Eligible subjects will be randomized and stratified by age ≥2 to <12, ≥12 to <18 or ≥18) and investigative site to one of two treatment groups in a 1:1 ratio (CLS006 or vehicle gel).

Subjects or their caregiver(s) will apply the first application of study drug under supervision at the study site to ensure understanding of the treatment application instructions. Thereafter, subjects or their caregiver will apply study drug at home to all common warts treated at baseline once daily for 6 weeks. The 6-week treatment period will be followed by a 12-week post-treatment efficacy evaluation period. After completion of the 12-week post-treatment efficacy evaluation period, subjects who achieved clearance of at least one treated wart at week 18 will continue into the 12-week follow-up period for evaluation of recurrence and durability of response.

Other than the study drug, no other treatment, product or therapy (prescription or over-the-counter) intended for the treatment of warts is permitted during the course of the study including the follow-up period in accordance with the excluded medications/treatments listed in Section 7.6.10.1.

7.2. SELECTION OF STUDY POPULATION

Subjects must meet all of the inclusion criteria and none of the exclusion criteria at the baseline visit prior to randomization to be considered eligible for enrollment into the study.

7.2.1. Inclusion Criteria

1. Subjects, and/or their legal guardians for subjects under the legal age of consent, who provide written informed consent to participate in the study. Subjects who are under the legal age of consent are to provide written informed assent to participate in the study as required, according to IRB guidelines for obtaining assent.
2. Male or female subjects 2 years of age or older.
3. Females of childbearing potential who are using a highly effective form of birth control or females of non-childbearing potential (as specified below).
    - Non-childbearing potential females are defined as females who are premenarchal, or postmenopausal (12 months with no menstrual period without an alternative medical cause), or who have undergone a hysterectomy, bilateral oophorectomy, tubal ligation, or bilateral occlusion of the fallopian tubes (e.g., Essure®) with post-placement confirmation of complete blockage.
    - Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.
        - Forms of birth control include: Oral (e.g., birth control pills), Intravaginal (e.g., NuvaRing®), Implantable (e.g., Norplant®), Injectable (e.g., Depo-Provera®) or Transdermal (e.g., Ortho Evra®) contraception; Intrauterine device (IUD); double-barrier (e.g., diaphragm or condom with spermicidal gel or foam); a vasectomized partner or abstinence from heterosexual intercourse when in line with preferred and usual lifestyle of subject (periodic abstinence e.g., calendar, ovulation, sympto-thermal, post-ovulation methods and withdrawal are not acceptable methods of contraception).
            - If an abstinent subject of childbearing potential becomes sexually active during the study, the subject must be willing to use effective birth control as described.
        - For subjects using an acceptable hormonal based form of birth control (e.g., oral birth control, Norplant), she must have been doing so for at least three (3) months prior to the Baseline Visit and be willing to continue stable birth control methods throughout the study.
4. Females of childbearing potential with a negative in-office urine pregnancy test at Screening and Baseline (prior to being randomized to receive study drug).

5. Subjects must have 1 to 6 clearly identifiable common warts (verruca vulgaris). For clarity, subjects must not have > 6 cutaneous common warts at Baseline. All of the common warts must meet the following criteria at Baseline:
   - Warts must be located on hands (dorsal, periungual, or palmar), feet (dorsal), limbs, and/or trunk,
   - Each wart must measure 3 to 10 mm in their longest dimension (diameter) on the epidermal plane of the skin at the baseline visit,
   - Each wart must be present for at least 4 weeks at the baseline visit,
   - Plantar, facial, subungual, and other warts (e.g., flat, genital) are excluded from treatment (i.e., these wart types are excluded from treatment, however the subject is not excluded).
6. Subjects free of any clinically significant dermatologic disorder in the treatment area (e.g., eczema, psoriasis, atopic dermatitis, etc.).
7. Subjects free of any clinically significant systemic condition which, in the opinion of the investigator, will interfere with the study assessments or increase the risk of AEs.
8. Subjects willing to refrain from using other topical products in the treatment area, or prohibited medications for the duration of the study (refer to Section 7.6.10.1).
9. Subjects able and willing to comply with all study procedures, restrictions and visit requirements.

7.2.2. Exclusion Criteria

1. Female subjects who are pregnant, nursing/breastfeeding, or plan to become pregnant within the study period including the follow-up period.
2. Subjects who are immunocompromised.
3. Subjects who have used any wart treatments/therapies, prescription or over-the-counter, as follows:
   - Salicylic acid, cantharidin, sinecatechins (Veregen™), simple occlusion (e.g., duct tape), and/or any other over-the-counter wart-removing products in the treatment area within 4 weeks of the Baseline Visit.
   - Cryotherapy (e.g., treatment with liquid nitrogen), carbon dioxide, electrodessication, laser, surgery, or other forms of mechanical destruction (e.g., emery boards, clippers, debriders, etc.) in the treatment area within 8 weeks of the Baseline Visit.
   - Treatment with immunotherapy (DPCP, DNCB or other), imiquimod, 5-fluorouracil, bleomycin, podophyllin or any other wart immunotherapy or treatment (e.g., Candida antigen) designed to stimulate immune response within 12 weeks of the Baseline Visit.

4. Subjects who have taken, within 30 days prior to the Baseline visit, or require treatment with systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) during the course of the study.
    - Routine use of inhaled or intranasal corticosteroids is allowed.
5. Subjects who require ongoing treatment with oral or injectable furosemide.
6. Subjects who have used an investigational drug/device within 30 days of the Baseline visit or who are currently participating in an investigational drug/device study. Use of an investigational drug/device and/or participation in another investigational study is prohibited during this study.
7. Subjects with known sensitivities to any of the investigational product ingredients including furosemide (or other sulfonamides).
8. Subjects who have a clinically significant abnormality of the cardiovascular, hepatic or renal systems that, based on the Investigator's opinion, would compromise subject safety.
9. Subjects with clinically relevant/significant abnormal laboratory results, vital signs, ECG, and/or physical findings at Screening and/or Baseline that, based on the Investigator's opinion, would interfere with the study objectives or compromise subject safety (e.g. subjects who have common warts in a region of pre-existing inflammatory condition).
10. Subjects with a chronic medical condition or clinically significant abnormal physical or laboratory finding(s) that may require the use of a prohibited medication/treatment.
11. Subjects who currently abuse alcohol or drugs or who have a history of chronic alcohol or drug abuse within the past year.

7.2.3. Discontinuation and Withdrawal from Treatment or Study

A subject is free to discontinue treatment or withdraw from the study at any time and for any reason, specified or unspecified, without prejudice to his/her medical care by the physician.

Reasons for discontinuation from Treatment or the Study include, but are not limited to, the following:

- Adverse Event
- Lack of Efficacy
- Pregnancy
- Withdrawal By Subject
- Subject Lost To Follow-Up
    - The Investigator will attempt to reach the subject twice by telephone and once by certified letter before considering the subject lost to follow-up. Lost to follow-up discontinuation and actions taken should be appropriately documented and a copy of the follow-up letter maintained in the Investigator's file.
- Physician Decision

- Non-Compliance with Study
- Study Terminated by Sponsor
- Other

All premature discontinuations from treatment or the study must be appropriately documented in the source documents.

All efforts should be made to evaluate subjects not completing the study (e.g., Early Termination Visit procedures performed).

Subjects who withdraw from treatment or the study will not be replaced.

7.3. CONDUCT OF STUDY

7.3.1. Schedule of Visits and Study Assessments

Study Period	Screening	Double-Blind Treatment (DBT)				Post-treatment Efficacy Evaluation (PTEE)		Follow-up[1]	
Visit	Screening	Baseline	Week 2	Week 4	Week 6 / End of Treatment (or Early Term during DBT Period)	Week 12	Week 18 / End of Post-tx Efficacy Evaluation (or Early Term during PTEE Period)	Follow-up #1	Follow-up #2 (Final)
Time	Day -28 to -1	Day 1	Day 14	Day 28	Day 42	Day 84	Day 126 (3 mo post-treatment)	Week 24	Week 30 (6 mo post-treatment)
Procedures (Visit Window)			(± 3 days)			(± 5 days)		(± 7 days)	
Informed Consent	X								
Demographics & Medical/Surgical History	X	X[2]							
Prior & Concomitant Medication/Treatment	X								
Limited Physical Exam[3]	X				X				
Vital Signs (BP, HR)	X	X	X	X	X	X	X		
ECG	X								
Urine Pregnancy Test[4]	X	X			X				
Clinical Safety Lab Testing (Hematology, Chemistry)	X				X				
Wart Assessments	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Clinical Photography (select sites only)[6]		x			x		x		
Inclusion/Exclusion Criteria	X	X							
Enroll/Randomization		X							
Dispense Study Drug & Diary		X	X	X					
Treatment Compliance / Collect and Review Study Drug & Diary			X	X	X				
Apply Study Drug (Once Daily)		X[7] ◆	———	———	◆				
Concomitant Medication/Treatment Review		X	X	X	X	X	X	X[8]	X[8]
Adverse Events		X[2]	X	X	X	X	X		

1 Only required for subjects who achieved clearance of at least one treated wart as determined by the PI or an appropriately qualified Sub-I at week 18 / End of Post-tx Efficacy Evaluation.
2 Adverse event assessment will be performed following the first study drug application (any changes in subject's health before first study drug application should be recorded as medical history).
3 A limited physical exam (refer to Section 7.5.2) including height & weight measurements at Screening and weight measurement only at the Week 6/EOT (or Early Termination during DBT Visit).
4 Urine pregnancy test for women of childbearing potential only. Urine pregnancy testing should also be conducted at any visit for any female who is suspected of being pregnant.
5 New common warts that appear after the Baseline visit will be identified, characterized and location recorded/mapped **only**, but not treated.
6 Clinical photography will be optional for subjects < 12 years of age.
7 The first application of study drug will be performed under supervision at the study center.
8 Concomitant medication/treatment review at Follow-up visits will focus on review of restricted concomitant medication/treatment only (refer to Section 7.6.10.1).

7.3.2. Study Assessments by Visit

An unscheduled visit may occur at any time in the event that the investigator determines the subject should be seen for safety reasons.

7.3.2.1. Screening

Screening Visit procedures are to be conducted within 28 days prior to the subject's Baseline (Day 1) Visit.

The following procedures will be performed during Screening:

1. Obtain subject's and/or his/her legal guardian(s) for subjects under the legal age of consent, written informed consent prior to initiating any study procedures, including instructing the subject to discontinue excluded medications/treatments.
    a. Subjects who are under the legal age of consent are to provide written informed assent as required, according to IRB guidelines for obtaining assent;
    b. Provide subject and/or his/her legal guardian(s) with a copy of the signed and dated consent form (and assent form, if applicable);
    c. Document informed consent in the subject's medical record.
2. Obtain demographics including subject reported race and ethnicity.
3. Screen the potential subject according to the study inclusion/exclusion criteria (refer to Sections 7.2.1 & 7.2.2).
4. Perform an in-office urine pregnancy test on all females of childbearing potential.
5. Review and record medical/surgical history including:
    a. Wart history;
    b. Identification of any history of significant cardiovascular, hepatic or renal disease.
6. Review and record prior and concomitant medications/treatments (refer to Section 7.6.10) including:
    a. Wart medications/treatments used within one year;
    b. All non-wart medications/ treatments used within 1 month;
    c. Washout medications/treatments, if applicable.
7. Obtain vital signs.
8. Perform wart assessments (refer to Section 7.4.1).
9. Perform a limited Physical Exam including height and weight measurements (refer to Section 7.5.2).
10. Perform a 12-lead electrocardiograph (ECG) (refer to Section 7.5.5).
11. Collect blood samples for clinical safety laboratory testing (hematology, chemistry).
12. As appropriate, schedule the Baseline (Day 1) visit, to occur after the results of the clinical safety laboratory tests are received and any required washout period has been completed.

7.3.2.2. Baseline (Day 1)

The following procedures will be performed during the Baseline (Day 1) Visit:

Baseline Procedures:

1. Review study inclusion/exclusion criteria including review of the laboratory results for any clinically significant findings that would exclude the subject from the study.
2. Review and document any changes to the subject's health and concomitant medications/treatments since his/her Screening visit.
3. Perform an in-office urine pregnancy test on all females of childbearing potential.
4. Obtain vital signs.
5. Perform wart assessments (refer to Section 7.4.1).
6. Perform clinical photography, if applicable (select centers only).
7. Review study inclusion/exclusion criteria to confirm eligibility for inclusion in the study (refer to Sections 7.2.1 & 7.2.2).

Randomization/Dispense Study Drug:

If the subject fulfills eligibility requirements, enroll/randomize the subject to treatment (refer to Section 7.6).

First Treatment Application:

1. Give a copy of the treatment application instructions (refer to Appendix A) and study diary to subject and/or his/her legal guardian(s) for subjects under the legal age of consent and allow time to review.
2. Instruct subject and/or caregiver(s) on:
   - Study drug application and use (refer to Section 7.6 & Appendix A)
   - Study diary completion.
3. Provide study drug tube to subject and/or caregiver(s) for treatment application.
4. As a means of educating and confirming subject's understanding of the treatment application and diary completion instructions, under supervision of the study coordinator or designee the subject and/or caregiver(s) should:
   - Apply the first dose of study drug to each wart according to the treatment application instructions (refer to Section 7.6.2 & Appendix A).
   - Record the first application of study drug in the study diary.

After First Treatment Application:

1. Observe the subject for any immediate adverse events.
2. Remind subject and/or caregiver(s) about restricted medications/treatments (refer to Section 7.6.10.1)
3. Remind subject and/or caregiver(s) to contact the investigator if he/she experiences any severe or serious adverse events.

4. Remind subject and/or caregiver(s) to apply study drug once daily and follow treatment instructions, as directed.
5. Remind subject and/or caregiver(s) to record study drug application in the study diary each day during the treatment period and to return the study diary to the site at the next study visit.
6. Remind subject and/or caregiver(s) that the study drug tube is not to be discarded and that it must be returned to the site at the next study visit.
    - Instruct subject and/or caregiver(s) to immediately report a lost tube to the site.

7.3.2.3. Interim Visits: Week 2 (Day 14) and Week 4 (Day 28)

Interim Visits following the Baseline (Day 1) Visit are to occur at the end of weeks 2 (Day 14) and 4 (Day 28) (± 3 days). The following procedures will be performed:

1. Question the subject and/or caregiver(s) about any changes to his/her health.
2. Review and question subject and/or caregiver(s) about any changes to his/her concomitant medications/treatments.
3. Obtain vital signs.
4. Perform wart assessments (refer to Section 7.4.1).

Dispense and Return of Study Drug and Diary:

1. Collect study drug and review the returned study diary for any missed doses (refer to Section 7.6.8).
2. Perform Treatment Compliance Check (refer to Section 7.6.2.2).
    - Review compliance based on subject's reported number of treatment applications. If compliance is an issue, re-instruct subject on study drug application.
3. Provide study drug and diary to subject and/or caregiver(s).

7.3.2.4. Week 6 (Day 42) / End of Treatment (or Early Termination during Double-Blind Treatment Period)

The Week 6 / End of Treatment (EOT) Visit is to occur at the end of Week 6 (± 3 days) or if the subject discontinues the study prior to the Week 6 visit. The following procedures will be performed:

1. Question the subject and/or caregiver(s).about any changes to his/her health.
2. Review and question subject and/or caregiver(s).about any changes to his/her concomitant medications/treatments.
3. Obtain vital signs.
4. Perform a limited Physical Exam including weight measurement.
5. Collect blood samples for clinical safety laboratory testing (hematology, chemistry).
6. Perform an in-office urine pregnancy test on all females of childbearing potential.
7. Perform wart assessments (refer to Section 7.4.1).
8. Perform clinical photography, if applicable (select centers only).

Return of the Study Drug and Diary

1. Collect and review the returned study diary for any missed doses.
2. Collect the returned study drug.

7.3.2.5. Week 12 (Day 84)

The Week 12 visit is to occur at the end of Week 12 (± 5 days). The following procedures will be performed:

1. Question the subject and/or caregiver(s) about any changes to his/her health.
2. Review and question subject about any changes to his/her concomitant medications/treatments.
3. Obtain vital signs.
4. Perform wart assessments (refer to Section 7.4.1).

7.3.2.6. Week 18 (Day 126) / End of Post-Treatment Efficacy Evaluation (or Early Termination during Post-treatment Efficacy Evaluation Period

The Week 18 / End of Post-treatment Efficacy Evaluation Visit is to occur at the end of Week 18 (±5 days), or for any subject that discontinues the study after the Week 6 Visit and prior to Week 18. The following procedures will be performed:

1. Question the subject and/or caregiver(s) about any changes to his/her health.
2. Review and question subject about any changes to his/her concomitant medications/treatments.
3. Obtain vital signs.
4. Perform wart assessments (refer to Section 7.4.1).
5. Perform clinical photography, if applicable (select centers only).
6. If subject achieved clearance of at least one treated wart **as determined by the PI or an appropriately qualified Sub-I** at Week 18 / End of Post-treatment Efficacy Evaluation visit, schedule the Follow-up visits (#1/Week 24 and #2/Week 30).
   * Remind the subject and/or caregiver(s) about restricted medications/treatments (refer to Section 7.6.10.1).

7.3.2.7. Follow-up# 1 (Week 24) Visit

The Follow-up# 1 Visit is to occur at the end of Week 24 (±7 days). The following procedures will be performed during this visit:

1. Review and question subject and/or caregiver(s) about use of any restricted concomitant medications/treatments (refer to Section 7.6.10.1).
2. Perform wart assessments (refer to Section 7.4.1).
3. Confirm Follow-up #2 / Week 30 Visit.

* Remind the subject and/or caregiver(s) about restricted medications/treatments (refer to Section 7.6.10.1).

7.3.2.8. Follow-up# 2 (Week 30) Visit

The Follow-up Visit is to occur at the end of Week 30 (±7 days). The following procedures will be performed during this visit:

1. Review and question subject and/or caregiver(s) about use of any restricted concomitant medications/treatments (refer to Section 7.6.10.1).
2. Perform wart assessments (refer to Section 7.4.1).

7.4. EFFICACY ASSESSMENTS

Efficacy assessments will be performed at the time points indicated in the Schedule of Visits and Study Assessments (refer to Section 7.3.1).

7.4.1. Wart Assessments

Wart assessments, as specified, should be performed by the Principal Investigator (PI) or an appropriately qualified Sub-Investigator (Sub-I). Evaluator initials will be recorded on applicable wart assessments.

In order to reduce inter-evaluator variability, it is important that the same evaluator perform the wart assessments for the same subject at baseline and at <u>all</u> subsequent study visits, whenever feasible.

7.4.1.1. Wart Identification/Characteristics and Location/Mapping

The PI or an appropriately qualified Sub-I will assess each subject to document/review all clearly identifiable common warts (verruca vulgaris).

- **In order to reduce inter-evaluator variability, it is important that the same evaluator assess the same subject at baseline and at all subsequent study visits, whenever feasible.**

<u>All</u> clearly identifiable common warts will be identified, counted, characterized (solitary, cluster/splitting/satellite, or merging/confluent), location recorded (e.g., hands: dorsal, periungual, or palmar; feet: dorsal; limbs; trunk) and mapped, and numbered (e.g., 1 through 6) at the Screening Visit, reviewed and updated at the Baseline Visit (Day 1, pre-treatment) and reviewed at each subsequent visit. The warts confirmed at the Baseline Visit will be considered the "Baseline Treatment" warts. The number assigned to each Baseline Treatment wart will remain the same and will be used throughout the study to refer to the same wart or wart area. The objective of wart identification/characterization, location/mapping and numbering is to provide a systematic approach to identifying and assessing Baseline Treatment warts to promote accurate and consistent evaluations throughout the study.

Any new common warts that appear after baseline will be identified, characterized and location recorded/mapped, however they will **not** be treated.

7.4.1.2. Wart Size

The size of each Baseline Treatment Wart will be measured in millimeters (mm) using a standardized ruler. The longest dimension (diameter) on the epidermal plane of the skin will be recorded.

- **In order to prevent inter-evaluator variability, it is important that the same evaluator measure the subject's wart(s) at baseline and at all subsequent study visits, whenever feasible.**

Clinical Clearance:

Clinical clearance of a wart, **as determined by the PI or an appropriately qualified Sub-I**, should be recorded with a measurement of 0 mm.

7.4.1.3. Wart Identification/Characteristic and Measurement Guidance

Solitary Wart:

- Identification/Characteristic: a singular discrete and distinct wart
- Measurement: record the size of the longest dimension on the epidermal plane of the skin of the wart

Cluster/Satellite/Splitting Warts:

- Identification/Characteristic:
  - Two or more warts that are closely clustered together and not discrete/distinct from the other
  - A Baseline Treatment wart that changes to form 2 or more warts
  - Considered 1 "wart"
- Measurement: record the size of the longest dimension on the epidermal plane of the skin of the outermost wart considered part of the wart cluster/satellite

Merging/Confluent Warts:

- Identification/Characteristic:
  - 2 or more Baseline Treatment warts that grow together to form 1 wart
  - A Baseline Treatment cluster/satellite/splitting wart that changes to form 1 distinct wart
- Measurement: record the size of the longest dimension on the epidermal plane of the skin of the wart.

Clinical Clearance:

Clinical clearance of a wart, **as determined by the PI or an appropriately qualified Sub-I**, should be recorded with a size of 0 mm and the subject should be instructed to stop applying study drug to that specific wart (spot) only.

7.4.2. Clinical Photography

Clinical Photography will be conducted at approximately 5 selected centers for photo-documentation purposes only. Photography will be optional for subjects < 12 years of age.

At Baseline (pre-treatment), Week 6/EOT, and Week 18/End of Post-treatment Efficacy Evaluation, a standardized set of photographs will be taken of each wart identified at baseline. A Photography Manual will be provided by the vendor and will include further instructions and details for collecting the photographs.

7.5. SAFETY AND TOLERABILITY ASSESSMENTS

Safety assessments will be performed at the time points indicated in the Schedule of Visits and Study Assessments (refer to Section 7.3.1).

7.5.1. Demographics and Medical/Surgical History

Demographic information including the subject's date of birth, sex, and subject reported ethnicity and race will be collected at Screening.

A medical/surgical history including wart history and identification/review of any history of significant cardiovascular, hepatic, or renal diseases will be collected at Screening and reviewed/updated at baseline prior to study drug application.

7.5.2. Limited Physical Exam and Vital Signs

A limited physical exam will be performed at the Screening Visit, including height and weight measurements, and at the Week 6/EOT (or Early Termination during DBT Visit) with weight measurement only.

The limited Physical Exam should include an assessment of the following:

- General Appearance
- Head
- Eyes
- Ears
- Nose
- Throat
- Lungs
- Heart
- Skin

Vital signs (blood pressure [BP], heart rate [HR]) will be measured at each visit during Screening, Double-blind Treatment and Post-treatment Efficacy Evaluation Periods.

7.5.3. Clinical Safety Laboratory Testing

Blood samples will be collected at the Screening and Week 6/EOT visits (or, if the subject is terminated prior to the EOT visit). A central laboratory will perform the sample analysis for all study sites. It is anticipated that the minimum amount of blood required for analysis (approximately 3.5 mL to 5.5 mL) will be collected from each subject age ≥2, not to exceed more than 2% of estimated total blood volume in a 24 hour period. Instructions for sample collection, preparation, labeling, and shipping will be provided by the laboratory.

The clinical safety laboratory tests will include the following parameters:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) including mean corpuscular volume (MCV) and red cell distribution with (RDW), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.
- Chemistry/Lipids:
  - General: calcium, glucose, lactate dehydrogenase (LDH)
  - Electrolytes: carbon dioxide (bicarbonate), chloride, magnesium, sodium, potassium
  - Kidney/Liver: blood urea nitrogen (BUN), creatinine, uric acid, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin
  - Lipids: total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides

7.5.4. Urine Pregnancy Test

An in-office urine pregnancy test will be performed at the Screening, Baseline and Week 6/EOT visits (or, if the subject is terminated prior to the EOT visit). All female subjects of childbearing potential must have a negative urine pregnancy test at Baseline prior to randomization. Urine pregnancy testing should also be conducted at any visit for any female who is suspected of being pregnant.

Any female who becomes pregnant during the Double-blind Treatment Period should be withdrawn from the study and the Sponsor must be notified. This should be done by sending a copy of the Pregnancy Reporting Form (via fax or email pdf copy) plus other supporting documentation, as required, to the Safety Contact (refer to Section 7.5.6.4) within 24 hours (1 business day) of becoming aware of the event. The pregnancy should be followed until a final outcome is known and a final outcome report should be submitted as soon as possible.

7.5.5. Electrocardiogram

A resting (at least 5 minutes) 12-lead electrocardiogram (ECG) including ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QT interval corrected for heart rate (QTc interval) (msec) calculated using the Fridericia method, will be performed at Screening.

ECG equipment will be provided to sites by a central ECG vendor. A central reader may be used to interpret subject ECGs. User instructions for the ECG equipment will be provided by the central ECG vendor.

7.5.6. Adverse Events

7.5.6.1. Definition of Adverse Event

An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

Any condition, event and/or signs and symptoms occurring after signing the informed consent form and before starting study drug treatment should be recorded as medical history in the eCRF. Medical conditions/diseases are considered AEs only if they worsen after starting study drug treatment (first application of study drug). Any clinically significant change from baseline, based upon the opinion of the investigator, in physical examination findings, vital signs, and/or laboratory values should be recorded as an AE.

Study personnel should question and observe subjects for evidence of AEs paying particular attention to local application site reactions and any potential cardiovascular or hematologic AEs. At each visit during the double-blind treatment and post-treatment efficacy evaluation period, the study site personnel should assess for the presence of local application site reactions and question the subject about AEs using an open question taking care not to influence the subject's (or caregiver's) answer, e.g., "Have you (or your child for caregivers) had any changes in your (or your child's) health since your last visit?"

Any AE, whether or not it is related to the test products, will be recorded in the source documents and reported on the appropriate eCRF page along with the date of onset, the severity, the relationship to the test product and the outcome. Under certain circumstances, additional information may be requested.

When an AE persists at the end of the study, the Investigator will ensure a follow-up of the subject until the Investigator/ Sponsor agree that the event is satisfactorily resolved or that no further follow-up is required.

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study medication. Events which occur more than thirty days after the last dose of study medication will not be considered treatment emergent.

7.5.6.2. Relationship of Adverse Event to Study Drug

The relationship of an AE to study drug is to be assessed according to the following definitions:

- Not Related – no temporal association or the cause of the event has been identified, or the drug cannot be implicated based upon available information.
- Possibly Related – temporal association, but other etiologies are likely to be the cause. However, involvement of the drug cannot be excluded, based upon available information.
- Definitely Related – established temporal or other association (e.g., re-challenge) and event is not reasonably explained by the subject's known clinical state or any other factor, based on available information.

7.5.6.3. Severity of Adverse Event

The severity of an AE is to be scored according to the following scale:

- Mild - Awareness of sign or symptom, but easily tolerated
- Moderate - Moderate Discomfort enough to cause interference with usual activity
- Severe - Severe Incapacitation with inability to work or perform usual activity

7.5.6.4. Serious Adverse Event

An adverse event or adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE,
  - The term "life-threatening" in the definition of "serious" refers to an event or suspected adverse reaction in which in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the serious AE (SAE) definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The Investigator or designee must report any SAE occurring in a subject receiving study drug to the Safety Contact immediately (within 24 hours (1 business day) of becoming aware of the event), even if the SAE does not appear to be drug-related. This should be done by sending a copy (via email pdf copy or fax) of the Serious Adverse Event Report Form plus other supporting documentation, as required.

All additional follow-up evaluations must also be reported as soon as possible. All SAEs will be followed until the Sponsor agrees that the event is satisfactorily resolved or that no further follow-up is required.

Safety Contact Details (for SAE Reporting):

[redacted]

The Sponsor will be responsible for notifying the relevant authorities of any SAE according to applicable regulations. The CRO/Sponsor will also ensure that any central Institutional Review Board (IRB) /Independent Ethics Committee (IEC) and any other participating Investigators are notified of the SAE. The PI is responsible for ensuring that their local IRB/IEC, if applicable, is notified of the SAE, as per the IRB/IEC standard operating procedures.

7.6. TEST MATERIALS

7.6.1. Identity of Investigational Products

	TEST PRODUCT Furosemide Topical Gel 0.125% w/w (CLS006)	**Vehicle (Comparator Product)**
Active Ingredient	Furosemide	None
Concentration	0.125% w/w furosemide	NA
Inactive Components	[redacted]	
Dosing Schedule	Once daily	
Route of Administration	Topical	
Manufacturer	[redacted]	
Packaging	3 gram laminate tube	
Storage Requirements	Controlled Room Temperature (15°C – 30°C) [59°F - 86°F]	

7.6.2. Treatment Administration

Subjects will be instructed to apply a small amount of gel [approximately 20-30 mg CLS006 (equivalent to 0.025-0.0375 mg of furosemide)] to cover each wart identified at baseline once daily for 6 weeks (42 consecutive days). Subjects will be instructed to gently rub the gel into each wart for approximately 20 seconds or until the gel is fully absorbed.

Subjects (or caregivers) will apply study drug to **each** "Baseline Treatment" wart one time per day for the entire treatment period or until instructed to stop by study personnel.

- If clinical clearance of a wart is determined **by the PI or an appropriately qualified Sub-I**, subjects should be instructed to stop applying study drug to that specific "wart" (spot) only.
- Merging/Confluent warts should be treated with a small amount of study drug to cover the merged/confluent wart.
- Cluster/Satellite (Splitting) warts should be treated with a small amount of study drug to cover the area (to the outermost wart) considered part of the wart cluster/satellite.

7.6.2.1. Subject Dosing and Use Instructions

Prior to the first application of study drug, subjects and/or caregiver(s) will be given a copy of the study drug application instructions and study diary for review. The study coordinator or designee should instruct the subject and/or caregiver(s) on proper study drug application and diary completion.

The first application of study drug and documentation of treatment in the study diary will be performed by the subject and/or caregiver(s) under the supervision of the study coordinator or designee as a means of confirming proper study drug application technique and completion of the study diary (refer to Appendix A for detailed instructions).

Thereafter, subjects and/or caregiver(s) will apply at home the daily dose of study drug to the "Baseline Treatment" warts once daily for 6 weeks or until instructed to stop by study personnel. The subject and/or caregiver(s) will be asked to choose a similar time each day, based on convenience, to apply the study drug (e.g., in the morning after showering or in the evening prior to bedtime). Subjects and/or caregiver(s) will be instructed to record the date of each study drug application in the study diary provided.

The study drug should not be applied more than one time per day.

7.6.2.2. Treatment Compliance

Study drug treatment compliance will be assessed based on the subject's and/or caregiver(s) reported number of treatment applications. The subject and/or caregiver(s) should record the date of each study drug application in his/her study diary.

Site personnel should review and/or discuss treatment compliance with subject and/or caregiver(s) since last visit based on the completed study diary and/or verbally reported information. Any missed applications should be documented in the source documents (i.e., by subject in the study diary or by site personnel in subject chart). If compliance is an issue, site personnel should re-instruct subject and/or their caregiver(s) on study drug dosing, application and diary completion, as appropriate.

7.6.3. Treatment Assignment

Prior to the start of the study, a randomization list will be generated by the CRO responsible for biostatistics in the trial. Once it has been established that subjects are eligible to participate in this study, eligible subjects will be randomized within each age group strata (≥2 to <12, ≥12 to <18 or ≥18) for each study center and assigned a randomization number corresponding to one of two treatment groups in a 1:1 ratio.

7.6.4. Blinding

This study will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to the treatment until study closure. The investigational drug and its matching placebo are indistinguishable.

7.6.5. Packaging

Study drug will be provided in 3-gram tubes and packaged into individual subject kits for use by a subject for the duration of the treatment period. Each kit will be numbered with a unique number according to the randomization list generated. Each tube within the kit will be labeled with the matching kit number to correlate with the contents of the kit according to the randomization list generated.

Prior to the start of the study, a randomization list assigning kit numbers to one of two treatment groups in a 1:1 ratio will be generated by the study biostatistician. The drug packaging company will use this randomization list to package study drug into treatment kits.

7.6.6. Labeling

Study drug tubes and kits will be labeled in a blinded manner in accordance with applicable regulatory requirements of the country where the clinical trial will be conducted.

7.6.7. Unblinding a Subject

Study drug supplies will be packaged in a manner supporting the blinding of the study.

Unblinding a subject's treatment assignment should ONLY be performed in an emergency, when knowing the identity of a subject's assigned treatment is essential to their continuing medical care. If at all possible, every attempt should be made to contact the Medical Monitor/Safety Contact to discuss before unblinding. In the event of unblinding, the Medical Monitor/Safety Contact and/or Project Manager must be notified immediately (within 24 hours (1 business day)), and the circumstances under which the blind for a given subject was broken must be appropriately documented in the source documents.

7.6.8. Dispensing and Return of Study Drug

Each eligible subject will be assigned a kit from those available at the site according to the randomization schedule using the Interactive Web Response System (IWRS). When the kit is assigned, study personnel must record the required information on the kit and tube labels and attach the label(s) to the appropriate source document. The kit assignment must be recorded in the source document.

From the subject's assigned kit, one tube of study drug will be dispensed to the subject and/or caregiver(s) from his/her assigned study drug kit at Baseline, and again at his/her Week 2 and 4 visits. One extra tube will be in the kit in the event it is needed (e.g., tube is lost). Tube dispensation and return must be recorded in the source document.

The subject and/or caregiver(s) will be instructed to return the tube of study drug at each study visit. At the Week 2 and 4 Visit, the used tube will be exchanged and a new tube of study drug will be dispensed from the subject's kit.

7.6.9. Accountability

In accordance with federal regulations, the Investigator must agree to keep all clinical supplies in a secure location with restricted access.

Upon receipt of the clinical supplies, the Investigator or designee will conduct a complete inventory of all study drug and assume responsibility for storage and dispensing. Dispensation and return of study drug must be appropriately documented. Under no circumstance should any of the clinical supplies sent to the Investigator be used in any unauthorized manner.

All used and unused clinical supplies will be appropriately inventoried and returned to the designated facility as specified by the Sponsor.

7.6.10. Prior and Concomitant Medication/Treatment

Prior and concomitant medication/treatment history will be collected at Screening and reviewed/updated at the Baseline visit. Medications/Treatments used within 1 month prior to the Baseline visit and any washout medications/treatments specified (refer to Section 7.6.10.1) should be appropriately documented in the source documents. Wart treatments used within the last year should be recorded.

Any medication/treatment used by the subject either at or following the Baseline visit through study completion will be considered concomitant medication/treatment (e.g., aspirin, Tylenol, birth control pills, vitamins). Every attempt should be made to keep concomitant medication/treatment dosing constant during the study. Any change to concomitant medication/treatment should be appropriately documented in the source documents.

An AE should be recorded for any subject starting a concomitant medication/treatment (except medications/treatments used as prophylaxis) to treat any health condition/event not identified in the subject's medical history.

7.6.10.1. Excluded Concomitant Medication/Treatment

Other than the study drug, no other treatment, product, or therapy (prescription or over-the-counter) intended for the treatment of warts is permitted during the course of the study including the follow-up period, according to the instructions listed below.

The following treatments/medications are prohibited <u>in the treatment area</u> during the study including:

- Use of any wart treatments/therapies, prescription or over-the-counter products as follows:
  - Salicylic acid, cantharidin, simple occlusion (e.g., duct tape), and/or any other over-the-counter wart-removing products in the treatment area.
  - Cryotherapy (e.g., treatment with liquid nitrogen), carbon dioxide, electrodessication, laser, surgery, or other forms of mechanical destruction (e.g., emery boards, clippers, debriders, etc.) in the treatment area.

The following treatments/medications are prohibited in the treatment area and/or outside the treatment area during the study, including the follow-up period:

- Use of systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) during the course of the study.
  - Routine use of inhaled or intranasal corticosteroids during the study is allowed;
- Treatment with immunotherapy (DPCP, DNCB or other), imiquimod, 5-fluorouracil, bleomycin, podophyllin or any other wart immunotherapy or treatment designed to stimulate immune response.
- Use of sinecatechins (Veregen™)
- Use of topical and/or systemic Isotretinoin (e.g. Accutane).
- Ongoing treatment with cimetidine or other H2 receptor antagonists.
- Ongoing use of oral or injectable furosemide during the course of the study.
- Use of an investigational drug/device and/or participation in another investigational study.

7.7. STATISTICAL METHODS PLANNED

7.7.1. General Considerations

A Statistical Analysis Plan (SAP) will be developed and finalized prior to unblinding of the study. The SAP will include detailed methods of analysis, algorithms for handling data, any deviations from the protocol methods, and mock data displays.

7.7.2. Sample Size Determination

The sample size estimates for the current study are based upon the rates of clearance of warts in the previous Phase 2 study [redacted]. This was a randomized, double-blind, vehicle-controlled, Phase II study in 80 subjects who were treated with topical [redacted], furosemide, [redacted], or vehicle for 42 days daily with an 8-week follow-up period. For the furosemide treatment group, the proportion of subjects with all cleared warts was 0.1 (10%) versus 0 in the vehicle.

The difference in the proportion of subjects with all treated warts cleared (complete clearance) at the Week 18/End of Post-treatment Efficacy Evaluation period (is the primary endpoint of the current study. For conservative purposes, assuming 10% and 2% complete clearance rates in the furosemide and vehicle treated groups respectively 200 subjects randomized per treatment group will provide for 92% power at a two-sided α of 0.05 to detect a difference between active and placebo.

With the inclusion of an additional 80 subjects in the ≥ 2 to < 12 cohort, the total sample size of 480 will provide 96% power with the assumption unchanged.

7.7.3. Randomization

Subjects that meet all inclusion and exclusion criteria will be randomized to one of two treatment groups in a 1:1 ratio for each study center according to a predetermined computer-generated randomization code.

Subjects will be randomized to treatment using an IWRS. The randomization scheme will include age stratum at 3 levels (≥2 to <12, ≥12 to <18 or ≥18) and investigative site.

7.7.4. Analysis Populations

The 'Intent-to-Treat' (ITT) analysis population will include all randomized subjects. The ITT population will be the primary population for all efficacy analyses.

The "All-treated" analysis population will consist of all subjects receiving at least one application of study drug. All safety analyses will be performed on the all-treated population.

The Per-Protocol (PP) population will include all subjects in the ITT population who complete 6 weeks of treatment and 12 weeks of post-treatment efficacy evaluation without any major deviations from the protocol. The subjects to be included in the PP analysis population will be determined by the Sponsor prior to the unblinding of the study. The PP population will be secondary for the primary endpoint only.

7.7.5. Handling of Missing Data

The primary method of dealing with missing data is multiple imputations (MI). Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) will be used as sensitivity analyses.

For the multiple imputations, twenty sets of imputed data will be generated. These will be imputed using SAS Proc MI as shown below.

```
Proc MI NIMPUTE=20 SEED=861879112 ROUND=. . . . 1 1 1 1 1 1
        MINIMUM=. . . . 1 0 0 0 0 0 MAXIMUM=. . . .  6 6 6 6 6 6;
 class treat site sex agegrp;
 var treat site sex agegrp w0 w2 w4 w6 w12 w18;
 fcs logstic(treat) logistic(site) logistic(sex) logistic(agegrp) reg(w0) reg(w2)
     reg(w4) reg(w6) reg(w12) reg(w18);
run;
```

Where:

treat = study treatment (CLS006, Vehicle)
site = investigative site
sex =sex (male, female)

agegrp = age group (≥2 to <12, ≥12 to <18 or ≥18)

w0 = number of warts at baseline (total number to be treated during the study)

w2 = number of remaining treated warts at Week 2

w4 = number of remaining treated warts at Week 4

w6 = number of remaining treated warts at Week 6

w12 = number of remaining treated warts at Week 12
w18 = number of remaining treated warts at Week 18

Note: Variable names may differ from those used in the actual programs, but the methodology will be the same.

If an imputed value is not within the appropriate range after the default of 100 tries, the SAS Proc MI option MINMAXITER may be increased in order to impute appropriate values.

In general, data will not be imputed for safety analysis.

7.7.6. Efficacy Endpoints

7.7.6.1. Primary Endpoint

The primary analysis of efficacy will be made on the difference in the proportion of subjects with complete clearance of all treated warts (i.e., Baseline/Treated warts) between the active and vehicle at Week 18 /End of Post-treatment Efficacy Evaluation. This comparison will be made using a CMH test stratified by age group (≥2 to <12, ≥12 to <18 or ≥18) and investigative site.

7.7.6.2. Secondary Endpoints

Secondary efficacy analyses will be conducted sequentially as follows:

- The ratio of cleared warts to all treated warts at Week 18/End of Post-treatment Efficacy Evaluation.
- Difference in the proportion of subjects with complete clearance of all treated warts at Week 12, then Week 6/EOT.
- The ratio of cleared warts to all treated warts at Week 12, then Week 6/EOT.
- Comparisons of reduction from baseline in wart size of treated warts at Week 18/End of Post-treatment Efficacy Evaluation.

To control type-1 error, the statistical testing will stop if non-significant superiority of active to vehicle ($p>0.025$ one-sided) is observed for any of the primary or secondary endpoints.

7.7.6.3. Tertiary Endpoints

- All endpoints will be compared at all other time-points.

- Evaluation of durability of response (clearance and/or wart size reduction) and incidence of recurrence of treated warts from Week 18/End of Post-treatment Efficacy Evaluation period to the end of the follow-up period (week 30).

These data are considered tertiary and exploratory to gain insight regarding the pharmacodynamic nature of the treatment response. No formal hypothesis testing is planned. Therefore, any statistical testing done will be considered to be descriptive and not inferential.

7.7.7. Efficacy Analysis

Comparisons of proportions of subjects with all treated warts cleared will be made using Cochran-Mantel-Haenszel (CMH) test for treatment stratified by age group (≥2 to <12, ≥12 to <18 or ≥18) and investigative site at $\alpha = 0.05$. Because of the low complete clearance rate, sites will be pooled in a manner ensuring that each pooled site will have sufficient number of subjects cleared for a stratified CMH analysis. The algorithm for pooling sites will be described in the SAP and finalized prior to unblinding. Comparisons of clearance rates of treated warts (number of cleared warts/number of treated warts) will be made using two-sided Wilcoxon rank sum testing at $\alpha = 0.05$.

For the continuous variables of wart size (diameter), analysis of covariance (ANCOVA) will be used to test CLS006 versus vehicle at Week 6/EOT, Week 18/End of Post-treatment Efficacy Evaluation and each week of the Post-treatment Efficacy Evaluation period and Follow-up period using a mixed effects model with site, age group (≥2 to <12, ≥12 to <18 or ≥18) and Baseline Treatment Wart size (i.e., diameter) as covariates (baseline wart size will be used as a covariate for comparison of wart size).

Data listings and averages will be presented for safety measures.

7.7.8. Safety Endpoints

Safety variables including AEs, vital signs, and laboratory parameters will be collected according to the Schedule of Visits and Study Assessments (refer to Section 7.3.1).

7.7.9. Safety Analysis

Safety variables will be tabulated and presented for all patients in the Safety population. AEs will be categorized by system organ class and Preferred Term from the current version of MedDRA. AEs will be summarized overall, by seriousness, severity, and relationship to treatment. Incidence of AEs will be presented overall, by system organ class and preferred term. Severity and relationship to study drug of the incidence of AEs will also be presented. AEs causing study drug withdrawal and/or early study discontinuation and incidence of SAEs will be summarized.

Changes from baseline in vital signs and laboratory parameters, and shifts from baseline in laboratory parameters will be summarized by treatment. Descriptive statistics and frequency tables will be prepared as appropriate for laboratory measurements.

7.7.10. Multicenter Pooling

Approximately 40 centers are planned in this study; whenever possible, approximately at least 12 subjects will be enrolled per center. In the event a center has a low number of subjects enrolled or an insufficient number of subjects with complete clearance for the stratified CMH analysis, pooling of centers will be performed based on geographical center location. The algorithm for pooling of centers will be described in the Statistical Analysis Plan. Descriptive summary statistics will be generated including center and pooled-center (when appropriate) by primary and secondary efficacy endpoints.

8. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

8.1. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the FDA and ICH guidelines on current GCP following the ethical principles originating from Declaration of Helsinki. Additionally, the study will be conducted in accordance with any applicable laws or regulations of the country in which the clinical research is conducted.

8.2. PROTOCOL ADHERENCE

The Investigator must read the protocol thoroughly and must follow the instructions exactly. Any change should be agreed upon by prior discussion between the Sponsor and the Investigator, with appropriate written protocol amendments made prior to implementation of the agreed-upon changes.

8.2.1. Changes in Study Conduct/Statistical Analyses/Amendments

No change in the conduct of the study should be instituted without written approval from the Sponsor. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will require written approval from the Sponsor and IRB/IEC before it may be implemented.

8.3. INSTITUTIONAL REVIEW BOARD /INDEPENDENT ETHICS COMMITTEE

This study, all appropriate amendments, all advertising, and written materials given to the subjects will be reviewed and approved by an IRB/IEC, prior to use.

8.4. SUBJECT INFORMATION AND CONSENT

The study personnel will inform all subjects in this study in accordance with GCPs, about the study. The study personnel will review the informed consent form (ICF) with each subject and give the subject an opportunity to read the consent and have all questions answered before proceeding. A current written consent form, approved by an IRB, is to be supplied by the Investigator and willingly signed by each subject, or their legal guardian, prior to initiating any study procedures, including instructing the subject to discontinue the use of medications requiring wash-out. A written assent form, approved by

an IRB, is to be supplied by the Investigator and willingly signed by each subject who is legally not able to sign an informed consent form, as required, in accordance with IRB guidelines for providing assent. The Investigator is responsible for maintaining each subject's consent form and assent form, if applicable, in the study file and providing each subject with a copy of the signed form(s).

8.5. RECORD KEEPING

8.5.1. Data Collection

The Investigator must maintain detailed records on all study subjects. Data for this study will be appropriately documented in the source documents and entered into eCRFs through the eDC system provided by the Sponsor's designated data management group. Applicable data from the subject's source documents should be recorded in the eCRFs completely, promptly, taking time to correct any mistakes as prompted by the eCRF system.

Throughout the study, representative(s) of the Sponsor (e.g., CRO's Monitor) will review the appropriate eCRF pages. eCRFs should be completed and ready for review by the Sponsor/CRO's Monitor, within one (1) week of each study visit for a given subject.

8.5.2. Data Corrections

Corrections of data entered into the eCRF must be made in the system for electronic case report forms and supported by source documents, as appropriate.

- The Sponsor's Monitor will review the eCRFs, evaluate them for completeness and accuracy, and ensure that all appropriate information is entered.
- No changes will be made to the data on the eCRF pages after the data are determined to be final by the Sponsor's Monitor and data management group. Corrections to the eCRF through queries and comments will be tracked by the eCRF internal audit trail as outlined in the eDC system.

8.5.3. Source Documentation

Investigators must keep accurate separate records (other than the eCRF) of all subjects' visits, which include all pertinent study-related information including the original signed/dated informed consent and assent forms, and drug accountability records. As a minimum, a statement should be made in the subject's record indicating that the subject (or caregiver) has signed an informed consent form and has been enrolled in Protocol CLS006-CO-PR-002.

Any AEs must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Relevant telephone conversations with the subject and/or the Sponsor/CRO concerning the study must also be recorded.

8.5.4. Monitoring/Auditing

Representatives of the Sponsor, following GCP guidelines, will monitor the conduct of the study. In addition, inspections or on-site audits may be carried out by the FDA, local regulatory authority or by the Sponsor's independent Quality Assurance Department. The Investigator will allow the Sponsor's representatives and any regulatory agency to examine all study records, eCRFs, corresponding subject medical records, clinical drug dispensing records, drug storage area, and any other documents considered source documentation.

8.5.5. Archives

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and study drug inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents no longer need to be retained. The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records.

The Investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during the study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities. If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility and the Sponsor must be notified in writing of the name and address of the new custodian.

8.6. CONTRACTUAL REQUIREMENTS

A contractual agreement will be signed between the Sponsor/CRO and the Investigator. This document will contain complementary information, i.e. financial agreement, confidentiality, study payment schedule, and publication of study results.

8.7. PUBLICATION POLICY

All data generated from this study are the property of the Cutanea Life Sciences, Inc. Publication of data will be done in accordance with the contractual agreement between the Sponsor/CRO and Investigator/clinical site.

9. REFERENCES

Hartley, C., Hartley, M., Pardoe, I., & Knight, A. (2006). Ionic Contra-Viral Therapy (ICVT); a new approach to the treatment of DNA virus infections. *Archives of Virology*, 151(12):2495-501.

Kwok, C. S., Gibbs, C., Bennett, C., Holland, R., & Abbott, R. (2012). Topical treatments for cutaneous warts. *Cochrane Database of Systematic Reviews*.

10. INVESTIGATOR AGREEMENT

I have read the protocol entitled "A Phase 3, Randomized, Double-Blind, Vehicle-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of CLS006 versus Vehicle in Subjects 12 years of age or older with Cutaneous Common Warts".

I agree that the Protocol CLS006-CO-PR-002 contains all of the information necessary to conduct the study. I agree to conduct the study as described herein.

Principal Investigator Name (Printed)	Principal Investigator Signature	Date

APPENDIX A: STUDY DRUG APPLICATION INSTRUCTIONS

For this research, it's important to standardize the way study drug is applied to each wart. Please read these instructions carefully.

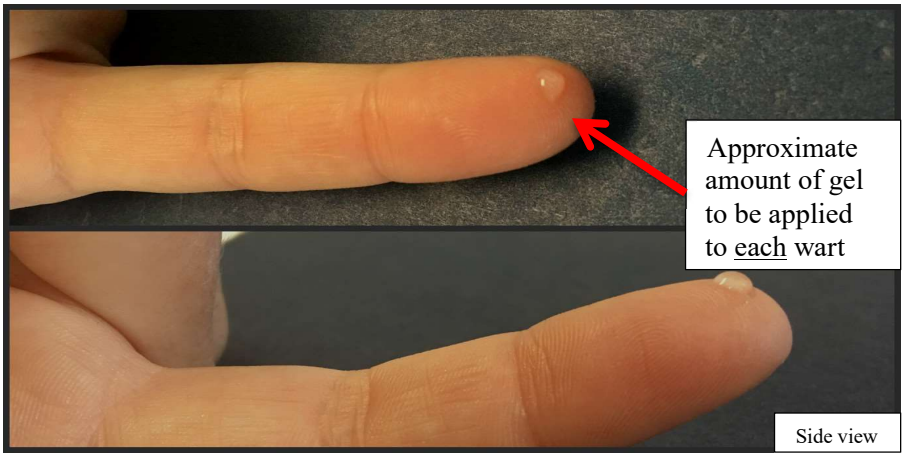
APPLY STUDY DRUG ONCE DAILY, AS DIRECTED.

- Study drug must be used to treat the wart(s) **ONLY** as directed by study personnel.
- For children under the age of 12, an adult caregiver (a parent/guardian) should apply the study drug.
- Each wart needs to be treated daily (one time per day) **or until advised to stop by study personnel**.
  - Choose a regular time each day, based on convenience, to apply the study drug (e.g., in the morning after showering or in the evening prior to bedtime). If you/your child are not able to apply the study drug at the regular time, you/your child should still apply but be careful, you/your child should not apply the gel on the wart more than 1x per day.

Applying study drug:

1. Wash, rinse and thoroughly dry your (or your child's) hands before applying study drug.
2. Remove the cap from the study drug tube and squeeze a **small amount** of the study drug gel (see photo) to cover **each** wart as directed by study personnel.
3. Gently rub the gel into the wart for approximately **20 seconds** or until the gel is fully absorbed.

- Avoid contact with your (or your child's) eyes, mouth, and inside the nose. If study drug comes in contact with eyes, flush the area with water.
- Avoid contact with others while the gel dries.



After applying study drug:

1. Return the cap to the study drug tube and store the study drug tube at room temperature.
2. Record each study drug application in the study diary provided.
3. Keep the skin dry as long as possible, **at least for an hour!**
   - ***Unless hands are being treated***, wash hands after application.
   - DO NOT apply bandages or dressings to the treated wart(s).
4. If the study drug is applied by an adult caregiver (a parent/guardian), they will need to wash their hands after application.

- **Reminder:** Bring the study drug tube and study diary to the clinic at EVERY visit; **do NOT discard the study drug tube (even if it's empty)!** Please call the clinic immediately if you have lost the tube.