A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED STUDY OF HYLORIS DEVELOPMENT'S PODOFILOX TOPICAL GEL 0.5% COMPARED TO ALLERGAN'S CONDYLOX® GEL 0.5%, AND BOTH ACTIVE TREATMENTS TO A VEHICLE CONTROL IN MALE AND FEMALE PATIENTS WITH EXTERNAL ANOGENITAL WARTS

Protocol Number:	016-POD-001
Development Phase:	Phase 3
Sponsor:	Hyloris Developments SA Bâtiment GIGA EE1 Avenue Hippocrate n° 5 4000 Liège (Sart-Tilman) Belgium
Protocol Version:	2.0

Hyloris

SIGNATURE PAGE

Protocol number:	016-POD-001
Study title:	A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study of Hyloris Development's Podofilox Topical Gel 0.5% compared to Allergan's Condylox® Gel 0.5%, and Both Active Treatments to a Vehicle Control in male and female patients with external anogenital warts

Signatures of the noted individuals ensure that all designated persons have agreed this version is final.

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INVESTIGATOR SIGNATURE PAGE

I have read and agree to the protocol 016-POD-001, entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study of Hyloris Development's Podofilox Topical Gel 0.5% compared to Allergan's Condylox® Gel 0.5%, and Both Active Treatments to a Vehicle Control in male and female patients with external anogenital warts" (Version 2.0, dated 15 January 2018). I am aware of my responsibilities as an Investigator under the guidelines of GCP, FDA regulations, local regulations (as applicable) and the study protocol. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with applicable local and FDA regulations.

Clinical Site: _____

Clinical Site Address _____

Site Principal Investigator:

_____	_____
Print Name	Title
_____	_____
Signature	Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCA	Bichloroacetic Acid
BE	Bioequivalence
CDC	Center of Disease Control
CO_2	Carbon Dioxide
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRF	Case Report Form
CV	Coefficient of Variation
DD	Drug Dictionary
DNA	Deoxyribonucleic Acid
EAW	External Anogenital Warts
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
H	Hours
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSIL	High-Grade Squamous Intraepithelial Lesions
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product

IRB	Institutional Review Board
ITT	Intent-To-Treat
IRT	Interactive Response System
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified Intent-To-Treat
OGD	Office of Generic Drugs
OTC	Over-the-counter
PD	Protocol Deviation
PMH	Past medical history
PI	Principal Investigator
PP	Per-Protocol
PRN	Pro Re Nata (As Needed)
QA	Quality Assurance
QC	Quality Control
RLD	Referenced Listed Drug
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedures
STI	Sexually Transmitted Infection
Sub-I	Sub-Investigator
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCA	Trichloroacetic Acid
TEAE	Treatment Emergent Adverse Event
UPT	Urine Pregnancy Test
WHO	World Health Organization

PROTOCOL SYNOPSIS

Study Title	A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Study of Hyloris Developments's Podofilox Topical Gel 0.5% compared to Allergan's Condylox® Gel 0.5% in male and female patients with external anogenital warts
Protocol Number	016-POD-001
Development Phase	3
Type of Study	Bioequivalence (BE) with Clinical Endpoints
Study Medication:	1) Podofilox Topical Gel 0.5% (Test formulation), manufactured by Hyloris Developments 2) Condylox® Gel 0.5% (Reference Product), manufactured by Allergan Pharmaceuticals 3) Vehicle of test product, manufactured by Hyloris Developments SA
Name of Active Ingredient	Podofilox
Route of administration	Topical application
Sponsor	Hyloris Developments SA Bâtiment GIGA EE1 Avenue Hippocrate n° 5 4000 Liège (Sart-Tilman) Belgium
Study Objectives	**PRIMARY** • To compare the clinical efficacy among patients with anogenital warts when treated with Podofilox Topical Gel 0.5% or Condylox® Gel 0.5% or placebo. **SECONDARY** • To demonstrate safety of Podofilox Topical Gel 0.5% compared to Condylox® Gel 0.5% or placebo assessed by the frequency and severity of adverse events, and application site reaction scores (erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding).

Study Design	This is a multicenter, parallel group, randomized, double-blind, placebo-controlled, trial with clinical endpoint comparing Podofilox Topical Gel 0.5% to Condylox® Gel 0.5% and a matching placebo. The study will be conducted among adult male and female patients with external anogenital warts. All study related procedures will be conducted only after written informed consent is obtained at the Screening visit, which will occur up to 14 days prior to the Baseline (Days -14 to -1). During the Screening visit, the Investigator will record subject's demographics, medical history, review concomitant medication, identifying any prohibited therapies that subject is currently taking. The Investigator will assess vital signs and perform physical examination identifying any clinically significant abnormalities. Laboratory samples will be collected, including HIV, Hepatitis B&C and urine pregnancy tests (UPT) for women of childbearing potential. The Investigator will confirm the diagnosis of External Anogenital Warts (EAW) and the absence of contraindications specified in the exclusion criterion 4 during the visual examination. The biopsy of skin lesions will be performed per the discretion of the Investigator for microscopic verification of the diagnosis of EAWs if any doubts of the diagnosis. Once the results of Screening assessments are obtained, suggesting that the subject is eligible for entering the study, the Baseline visit (Day 0) will take place. During this visit, the Investigator will identify any AEs that occurred from the last visit, review concomitant and prohibited therapies, perform vital signs and physical examination. Those subjects who qualify for entering the study will be randomized to one of the following arms in a ratio of 3:3:1: • **Arm 1** (Test product): Subjects in this arm will receive test formulation of Podofilox Topical Gel 0.5% (Hyloris Developments SA) • **Arm 2** (Reference Listed Drug [RLD]): Subjects in this arm will receive RLD Condylox® Gel 0.5% (Allergan Pharmaceuticals) • **Arm 3** (Placebo): Subjects in this arm will receive a vehicle that matches the test product, except for the inclusion of the active ingredient (Hyloris Developments SA) Randomization and study medication number assignment will be performed using an Interactive Response Technology (IRT) system that is fully integrated with the Electronic Data Collection (EDC) system. EAWs will be inspected and the count of EAWs will be captured in the source worksheet and electronic Case Report Form (eCRF). The Investigator will assess the baseline level of Local Application Site Reactions, recording the scores based on the Local Application Site Reactions Scale. During the inspection of EAWs, study physician (Principal Investigator (PI),

	or Sub-Investigator) will train the subject on proper application of the study drug using the properly labeled demonstration tube (contains vehicle of the study drug) and applicator. The subject will be trained to apply the study drug to the surface of the warts at a proper amount (not to exceed 0.5 g per day or 0.25 g per application), avoiding unaffected and wounded skin areas, and to let the gel dry completely before allowing the return of opposing skin surfaces to their normal positions. Mirrors are to be used in order to facilitate process of application. Subjects will be instructed to not use the study drug in the vagina or in the rectum, and remove medication from any areas that experience stinging or burning immediately upon application. Site staff will also visually show the subjects what the correct amount of drug to be used per application looks like. The subject will also be trained on Subject Diary Card Completion and Contraception Methods. The subject will be given a study drug, mirror and a Subject Diary Card to capture application details, and acknowledge any changes in skin reactions, other AEs and concomitant medications during the intervening time between the site visits. On the following day after the Baseline visit (Day 1) the subject will apply the study drug on EAWs following the recommendations given during training at the clinic site. The treatment phase will consist of four weekly treatment cycles at a maximum, during which the drug will be applied twice a day (in the morning and at the bedtime) for 3 consecutive days, then discontinuing for 4 consecutive days. Study drug will thus be applied only on Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23 and 24. Study visits will occur on the seventh (7) day of each treatment cycle: on Day 7 (Week 1), Day 14 (Week 2), Day 21 (Week 3), and Day 28 (Week 4). Primary endpoint (total disappearance of all treated warts) will be evaluated during each of these visits. In case the primary endpoint is reached at any of the visits prior to the Day 28 visit, it will be considered as End of Study (EOS) visit – the Investigator will perform physical examination and repeat urine pregnancy test, and subject's participation will be considered complete. If total disappearance of warts is not achieved, a new treatment cycle will be initiated for a maximum of four cycles in total for the subject. During each study visit, the Investigator will collect vital signs, evaluate EAWs for absence or present, capturing the count of EAWs, record Local Application Site Reactions and adverse events (AEs), assess Subject Diary Card completion and subject's compliance with the study drug application, review concomitant medication and confirm that there were no prohibited therapies applied from the last visit. In the event the primary endpoint (total disappearance of all warts within all

	treated areas) has been achieved prior to the Day 28 visit, this visit will be considered End of Study (EOS) visit. In case a subject discontinues prematurely, the Investigator will conduct an Early Termination (ET) visit, capturing the reason for discontinuation and performing assessments of EOS visit.
Number of Subjects and Sites	The planned overall sample size for this clinical trial is approximately 413 adult male and female subjects with external anogenital warts, who will be randomized at a 3:3:1 ratio (test: RLD: placebo) at about 16 clinical research centers in the United States, Russia and Ukraine. mITT and PP population size will be approximately 392 and 350 correspondingly.
Eligibility Criteria	Subjects who satisfy **ALL** the following **inclusion** and have **NONE** of the following **exclusion** criteria may be enrolled in the study: **INCLUSION CRITERIA** 1. Willing and able to provide written informed consent prior to participating in this study. 2. Male or female subjects, aged 18-65 inclusive, with a clinical diagnosis of external anogenital warts (i.e., perianal warts and/or external genital warts), including two or more distinct external genital warts, and wart area that is equal or less than 10 cm^2. Histological confirmation should be obtained if there is any doubt of the diagnosis. 3. Females of childbearing potential may be enrolled if they practice a method of birth control with a reliability of at least 90%. 4. Sexually active study participants must agree to abstain from sexual activity of any kind throughout the treatment period to prevent cross- and reinfection by HPV. 5. Any female subject with childbearing potential has a negative urine pregnancy test at Baseline. 6. Negative HIV test within 4 weeks before Baseline. **EXCLUSION CRITERIA** 7. Female subjects who are pregnant or lactating or planning to become pregnant during the study period. 8. Hypersensitivity or intolerance to Podofilox or any component of the formulation. 9. History of previous unsuccessful treatment with any formulation of Podofilox. 10. Wart area that is greater than 10 cm^2. 11. Patients with internal anogenital and mucous membrane warts, Bowenoid papulosis, squamous cell carcinoma, active herpes lesion, or other skin abnormalities of treatment area, such as eczema, or skin that had not healed following surgery (cryosurgery, laser ablation or similar). 12. Primary or secondary immunodeficiency.

	13. Known presence of diabetes type I or II. 14. Local irritation in any treatment area that would interfere with treatment. 15. Use within 4 weeks prior to baseline of any: 1) treatment for anogenital warts, 2) systemic corticosteroids, or 3) systemic immunosuppressive drug. 16. Any medical or surgical condition in the judgment of the Investigator that may interfere with the assessment of efficacy or safety, or pose a risk to the subject. 17. Patients known to abuse alcohol and/or drugs, or with a history of chronic alcohol or drug abuse that may result in protocol non-compliance. 18. Received another investigational drug, device or biologic within 90 days prior to the start of Screening or has planned to participate in another clinical trial while enrolled in this study. 19. Subjects who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study 20. Employee (or employee's family member) of the research center or private practice, CRO or Sponsor, or subjects who have a conflict of interest. 21. Subjects living (e.g., siblings, spouses, relatives, roommates) in the same household cannot be enrolled in the study at the same time. 22. Previous enrollment in this study, current enrollment in this study at another participating site or current enrollment in another study (in parallel to this study) at another clinical research site.
Withdrawal and Early Discontinuation	Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of external anogenital warts during the study should be discontinued, and the Early Termination visit must be performed.
Prohibited Concomitant Medication	Use of following therapies is prohibited during study participation: • Any other topical products applied to the treatment area(s). • Systemic corticosteroid or immunosuppressive drugs. • Antipruritic, including antihistamines, in the 24 hours prior to study visits. • Immunomodulators. • Immunostimulatory drugs. • Interferons. • Another Investigational Drug.
Study Drug	Study drug includes Test, Reference and Placebo drug products. The Sponsor will supply study drug as matching 3.5 g of clear gel in aluminum tubes with an applicator tip, labeled for a blinded study. • Test Drug: Podofilox Topical Gel 0.5% (Hyloris Developments SA)

	• RLD: Condylox® Gel 0.5% (Allergan Pharmaceuticals) • Placebo: Vehicle of the test drug (Hyloris Developments SA) Storage temperature is 20-25°C (68-77°F).
Duration of Patient Study Participation	Up to 50 Days
Study Endpoints	**PRIMARY** • The primary endpoint is the proportion of subjects in the per protocol (PP) population with "treatment success" defined as "total disappearance of all warts within all treated areas". **SECONDARY (Safety Endpoints)** • Local application site reactions scores (erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding) in each group during the study drug application period. • Other adverse events including serious adverse events throughout the study participation.
Statistical Analysis	**EFFICACY ANALYSIS** The difference in the proportion of subjects in the test and reference treatment groups who achieve "treatment success" defined as "total disappearance of all warts within all treated areas" at four days (± 5 days) after the last day of the last cycle of treatment will be evaluated using a two-sided, continuity-corrected 90% confidence interval. The therapeutic equivalence of the test and reference products will be established if the confidence bounds of the 90% confidence interval are contained within the limits of -0.20 to +0.20. The results in the per-protocol (PP) population will be considered definitive for therapeutic equivalence with those in the modified Intent-To-Treat (mITT) population considered supportive. Superiority will be assessed through continuity-corrected Z-tests comparing each active treatment to placebo. If both the test and RLD success proportions are statistically significantly greater than the placebo proportion ($p<0.05$, two-sided) then they will be considered superior to the placebo. The results in the mITT population will be considered definitive for superiority with those in the PP population considered supportive. Subjects discontinuing due to "treatment failure", defined as worsening of condition and requiring alternate or supplemental therapy for the treatment of external anogenital warts during the study, will be included in the PP population analysis as treatment failures, and provided with effective

	treatment. Subjects discontinued prematurely from the study for any other reason (i.e., noncompliance, or withdrawal of consent, etc.) will be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF). **SAFETY ANALYSIS** Safety data analysis will include local application site reaction scores (erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding), reported adverse events, vital signs and concomitant medication assessments summarized by treatment group and time point of collection, when appropriate. Descriptive statistics (arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, when appropriate. Adverse events will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA®) noted in the Statistical Analysis Plan. A subject AE listing by MedDRA® system organ class and by preferred term within system organ class, including verbatim term, dose level, severity, and relationship to treatment, will be provided. This listing will include all AEs and serious adverse events (SAEs). Adverse events will also be presented in summary tables. Concomitant medications will be listed by treatment and coded using the most recent version of the World Health Organization (WHO) Drug Dictionary.

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1 BACKGROUND AND RATIONALE

1.1 Background to the Disease

External anogenital warts (EAWs), also known as *Condylomata acuminate,* or anogenital human papillomavirus (HPV) infection, is one of the most common sexually transmitted infection (STI), in 86% caused by HPV types 6 or 11.[1] HPV types 16, 18, 31, 33, and 35 are also occasionally found in anogenital warts (usually as co-infections with HPV 6 or 11) and can be associated with foci of high-grade squamous intraepithelial lesions (HSIL), particularly in persons who have HIV infection.

Diagnosis of anogenital warts is usually made by visual inspection and can be confirmed by biopsy, which is indicated if lesions are atypical (e.g., pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated lesions). Biopsy might also be indicated in the following circumstances, particularly if the patient is immunocompromised (including those infected with HIV): 1) the diagnosis is uncertain; 2) the lesions do not respond to standard therapy; or 3) the disease worsens during therapy. HPV testing is not recommended for anogenital wart diagnosis, because test results are not confirmatory and do not guide genital wart management.

The aim of treatment is removal of the wart and amelioration of symptoms, if present. The appearance of warts also can result in significant psychosocial distress, and removal can relieve cosmetic concerns. In most patients, treatment results in resolution of the wart(s). If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. Because warts might spontaneously resolve within 1 year, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. Available therapies for anogenital warts might reduce, but probably do not eradicate, HPV infectivity. Whether the reduction in HPV viral deoxyribonucleic acid (DNA) resulting from treatment reduces future transmission remains unknown.

Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. No definitive evidence suggests that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts. The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes and should be encouraged. Because all available treatments have shortcomings, some clinicians employ combination therapy (e.g., provider-administered cryotherapy with patient-applied topical therapy between visits to the provider). However, limited data exist regarding the efficacy or risk for complications associated with combination therapy. Treatment regimens are classified as either patient-applied or provider-administered modalities. Patient-applied modalities are preferred by some persons because they can be administered in the privacy of their home. To ensure that patient-applied modalities are effective, instructions should be provided to patients while in the clinic, and all anogenital warts should be accessible and identified during the clinic visit. Follow-up visits after several weeks of therapy enable providers to answer any questions about the use of the medication and address any side effects experienced; follow-up visits also facilitate the assessment of the response to treatment. Following treatment alternatives are recommended by Center of Disease Control (CDC) for clinical management of EAWs (Table 1).

Table 1. Recommended Regimens for External Anogenital Warts (i.e., penis, groin, scrotum,

vulva, perineum, external anus, and perianal*)

Patient-Applied	Podofilox 0.5% solution or gel, OR
	Imiquimod 3.75% or 5% cream†, OR
	Sinecatechins 15% ointment†
Provider-Administered	Cryotherapy with liquid nitrogen or cryoprobe, OR
	Surgical removal either by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery, OR
	Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% solution

* Many persons with external anal warts also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy

† Might weaken condoms and vaginal diaphragms

Podofilox (podophyllotoxin) is a patient-applied antimitotic drug that causes wart necrosis. Podofilox solution (using a cotton swab) or Podofilox gel (using an applicator tip or a finger) should be applied to anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2, and the total volume of Podofilox should be limited to 0.5 mg of the gel per day. Health-care provider should describe proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. Podofilox is contraindicated in pregnancy.[2]

Imiquimod is a patient-applied, topically active immune enhancer that stimulates production of interferon and other cytokines. Imiquimod 5% cream should be applied once at bedtime, three times a week for up to 16 weeks.[3] Similarly, Imiquimod 3.75% cream should be applied once at bedtime, but is applied every night.[4] With either formulation, the treatment area should be washed with soap and water 6–10 hours after the application. Local inflammatory reactions, including redness, irritation, induration, ulceration/erosions, and vesicles might occur with the use of Imiquimod, and hypopigmentation has also been described.[5] A small number of case reports demonstrate an association between treatment with Imiquimod cream and worsened inflammatory or autoimmune skin diseases (e.g., psoriasis, vitiligo, and lichenoid dermatoses).[6–8] Data from studies of human subjects are limited regarding use of Imiquimod in pregnancy, but animal data suggest that this therapy poses low risk.[2]

Sinecatechins is a patient-applied, green-tea extract with an active product (catechins). Sinecatechins 15% ointment should be applied three times daily (0.5 cm strand of ointment to each wart) using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for longer than 16 weeks.[9–11] The medication should not be washed off after use. Genital, anal, and oral sexual contact should be avoided while the ointment is on the skin. The most common side effects of Sinecatechins are erythema, pruritus/burning, pain, ulceration, edema, induration, and

vesicular rash. The medication is not recommended for persons with HIV infection, other immunocompromised conditions, or with genital herpes because the safety and efficacy of therapy has not been evaluated. The safety of Sinecatechins during pregnancy is unknown.

Cryotherapy is a provider-applied therapy that destroys warts by thermal-induced cytolysis. Health-care providers must be trained on the proper use of this therapy because over- and under-treatment can result in complications or low efficacy. Pain during and after application of the liquid nitrogen, followed by necrosis and sometimes blistering, is common. Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large.

Surgical therapy has the advantage of eliminating most warts at a single visit, although recurrence can occur. Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit. After local anesthesia is applied, anogenital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Care must be taken to control the depth of electrocautery to prevent scarring. Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by carbon dioxide (CO_2) laser, or by curettage. Because most warts are exophytic, this procedure can be accomplished with a resulting wound that only extends into the upper dermis. Hemostasis can be achieved with an electrocautery unit or, in cases of very minor bleeding, a chemical styptic (e.g., an aluminum chloride solution). Suturing is neither required nor indicated in most cases. In patients with large or extensive warts, surgical therapy, including CO_2 laser, might be most beneficial; such therapy might also be useful for intraurethral warts, particularly for those persons who have not responded to other treatments.

Trichloroacetic acid (TCA) and Bichloroacetic acid (BCA) are provider-applied caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA solution has a low viscosity comparable with that of water and can spread rapidly and damage adjacent tissues if applied excessively. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA/BCA treatment can be repeated weekly if necessary.

1.2 Background to the Study Drug

Podofilox is an antimitotic drug which can be chemically synthesized or purified from the plant families *Coniferae* and *Berberidaceae* (e.g. species of *Juniperus* and *Podophyllum).*

RLD Condylox® Gel 0.5% is formulated for topical administration and supplied in 3.5 g aluminum tubes with an applicator tip. Each gram of drug substance contains 5 mg of Podofilox in a buffered alcoholic gel containing alcohol, glycerin, lactic acid, hydroxypropyl cellulose, sodium lactate, and butylated hydroxytoluene.

Podofilox Gel 0.5% must be applied to the warts surface with the applicator tip or finger. The Podofilox Gel 0.5% may cause skin irritation, and hence must not be applied to the unaffected skin areas. Treatment cycle consists of twice daily applications (morning and evening) for three consecutive days followed by a four day "rest" period. This one-week cycle may be repeated until there is no visible wart tissue or for a maximum of four cycles in total. Treatment should be limited to 10 cm^2 or less of wart tissue and to no more than 0.5 g of the gel per day.

1.2.1 Clinical Pharmacology

1.2.1.1 Mechanism of Action

Treatment of anogenital warts with Podofilox results in necrosis of visible wart tissue. The exact mechanism of action is unknown.

1.2.1.2 Pharmacokinetics

In systemic absorption study in 52 patients, topical application of 0.05 mL of an ethanolic solution containing 0.5% Podofilox to external genitalia did not result in detectable serum levels.[12] Applications of 0.1 to 1.5 mL resulted in peak serum levels of 1 to 17 ng/mL one to two hours after application. The elimination half-life ranged from 1.0 to 4.5 hours. The drug was not found to accumulate after multiple treatments.[12]

1.2.2 Clinical Experience

Following data is available for RLD Condylox® Gel 0.5% clinical trials.

In the first multicenter clinical study in 326 patients with anogenital warts, Condylox® Gel 0.5% and its vehicle were applied in a double-blind fashion to comparable patient groups.[13] Of the 260 patients with efficacy data, 176 were treated with Condylox® Gel 0.5%. Patients applied Condylox® Gel 0.5% twice daily for three consecutive days followed by a 4 day "rest" period. At the end of 4 weeks, 38.4% of the patients had complete clearing of the wart tissue when treated with Condylox® Gel 0.5%.

In the second multicenter clinical trial in 108 evaluable patients with anogenital warts, Condylox® (podofilox) Topical Solution 0.5% was compared with Condylox® Gel 0.5% for efficacy. As in the first clinical trial, patients applied Condylox® Gel 0.5% twice daily for three consecutive days followed by a four day "rest" period. Similar clearance rates were observed. At the end of 4 weeks, 25.6% of the patients had complete clearing of the wart tissue when treated with Condylox® Gel 0.5%.[14]

1.2.3 Safety Profile

In clinical trials with Condylox® Gel 0.5%, the following local adverse reactions were reported during the treatment of anogenital warts:

Table 2. Local adverse reactions reported in Condylox® Gel 0.5% clinical trials

Adverse Reaction	Mild	Moderate	Severe
Inflammation	32.2%	30.4%	9.3%
Burning	37.1%	25.9%	11.5%
Erosion	27.0%	20.8%	8.9%
Pain	23.7%	20.4%	11.5%
Itching	32.2%	16.0%	7.8%
Bleeding	19.2%	3.0%	0.7%

The severity of local adverse reactions was predominantly mild or moderate and did not increase during the treatment period. Severe reactions were most frequent within the first 2 weeks of treatment.

Other local adverse reactions reported included stinging (7%), and erythema (5%); less commonly reported local adverse events included desquamation, scabbing, discoloration, tenderness, dryness, crusting, fissures, soreness, ulceration, swelling/edema, tingling, rash, and blisters. The most common systemic adverse event reported during the clinical studies was headache (7%).[14]

Further details are provided in the Investigator's Brochure [IB][15].

1.3 Rationale of the Study

As stated in Section 1.2.1.2, topical application of 0.05 mL of an ethanolic solution containing 0.5% Podofilox to external genitalia did not result in detectable serum levels. In these settings, a conventional pharmacokinetic human study to demonstrate that Hyloris Developments SA Podofilox Gel 0.5% is bioequivalent to the Reference Listed Drug [RLD] Condylox® Gel 0.5% is not appropriate.

Hyloris Developments SA will initiate a clinical endpoint bioequivalence (BE) study for a Podofilox Gel 0.5% formulation for the treatment of external anogenital warts in comparison to Condylox® Gel 0.5% that follows the study design and recommendations according to Office of Generic Drugs (OGD) of U.S. Food and Drug Administration (FDA) Draft Guidance for Podofilox recommendations.[16]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

To compare the clinical efficacy among patients with anogenital warts when treated with Podofilox Topical Gel 0.5% versus Condylox® Gel 0.5% and placebo.

2.1.2 Secondary Objective

To demonstrate safety of Podofilox Topical Gel 0.5% compared to Condylox® Gel 0.5% and placebo assessed by the frequency and severity of adverse events, and application site reaction scores (erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding).

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint is the proportion of subjects in the per protocol (PP) population with "treatment success" defined as "total disappearance of all warts within all treated areas".

2.2.2 Secondary Endpoint (Safety Endpoints)

Local application site reactions scores (erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding) in each group during the study drug application period.

Other adverse events including serious adverse events throughout the study participation.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is a multicenter, parallel group, randomized, double-blind, placebo-controlled, trial with clinical endpoint comparing Podofilox Topical Gel 0.5% to Condylox® Gel 0.5% and a matching placebo. The study will be conducted among adult male and female patients with external anogenital warts.

All the study related procedures will be conducted only after written informed consent is obtained at the Screening visit, which will occur up to 14 days prior to the Baseline (Days -14 to -1). During the Screening visit, the Investigator will record subject's demographics, medical history, review concomitant medication, identifying any prohibited therapies that subject receives.

The Investigator will assess vital signs and perform physical examination identifying any clinically significant abnormalities that may prevent subject from participation in the study. Laboratory samples will be collected, including HIV, Hepatitis B&C, urine pregnancy tests (UPT) for women of childbearing potential and Syphilis (if required by applicable local regulations).

The Investigator will confirm the diagnosis of External Anogenital Warts (EAW) and the absence of contraindications specified in the exclusion criterion 5 during the visual examination. The biopsy of skin lesions will be performed per the discretion of the Investigator for microscopic verification of the diagnosis of EAWs.

Once the results of Screening assessments are obtained, suggesting that the subject is eligible for entering the study, the Baseline visit (Day 0) will take place. During this visit, the Investigator will identify any AEs that occurred from the last visit, review concomitant and prohibited therapies, perform vital signs and physical examination. Those subjects who qualify for entering the study will be randomized to one of the following arms in a ratio of 3:3:1:

- **Arm 1** (Test product): Subjects in this arm will receive test formulation of Podofilox Topical Gel 0.5% (Hyloris Developments SA)
- **Arm 2** (Reference Listed Drug [RLD]): Subjects in this arm will receive RLD Condylox® Gel 0.5%
- **Arm 3** (Placebo): Subjects in this arm will receive a matching vehicle

Randomization and study drug kit number assignment will be performed using an Interactive Response System (IRT).

EAWs will be inspected and the count will be captured in the source worksheet and electronic Case Report Form (eCRF). The Investigator will assess the baseline level of Local Application Site Reactions, recording the scores on the Local Application Site Reactions Scale.

During the inspection, study physician (Principal Investigator (PI), or Sub-Investigator) will train the subject on proper application of the study drug using the demonstration tube (contains vehicle of the study drug) and applicator. The subject will be trained to apply the study drug to the surface of the warts at a proper amount (not to exceed 0.5 g per day or 0.25 g per application), avoiding unaffected and wounded skin areas, and to let the gel dry completely before allowing the return of opposing skin surfaces to their

normal positions. Mirrors are to be used to facilitate the process of application. Subjects will be instructed to not use the study drug in the vagina or in the rectum, and remove medication from any areas that experience stinging or burning immediately upon application. A visual representation of this quantity will be showed to the subjects.

The subject will also be trained on Subject Diary Card completion and contraception methods. The subject will be given a kit of study drug, mirror and a Subject Diary Card to capture application details, and acknowledge any changes in skin reactions, other AEs and concomitant medications during the intervening time between the site visits.

On the following day after the Baseline visit (Day 1) the subject will apply the study drug on EAWs following the recommendations given at the training. The treatment phase will consist of four weekly treatment cycles at a maximum, during which the drug will be applied twice a day (in the morning and at the bedtime) for 3 consecutive days, then discontinuing for 4 consecutive days. Study drug will thus be applied only on Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23 and 24.

Study visits will occur on the seventh (7) day of each treatment cycle: on Day 7 (Week 1), Day 14 (Week 2), Day 21 (Week 3), and Day 28 (Week 4). Primary endpoint (total disappearance of all warts within all treated areas) will be evaluated during each of these visits. In case the primary endpoint is reached at any of the visits following Baseline, it will be considered as End of Study (EOS) visit – the Investigator will perform physical examination and repeat urine pregnancy test, and subject's participation will be considered completed. If reduction of warts is absent or incomplete, a new treatment cycle will be initiated for a maximum of four cycles in total for the subject.

During each study visit, the Investigator will collect vital signs, evaluate EAWs for healing, capturing the count, record Local Application Site Reactions and adverse events (AEs), assess Subject Diary Card completion and subject's compliance with the study drug application, review concomitant medication and confirm that there were no prohibited therapies applied from the last visit.

In the event the primary endpoint (total disappearance of all warts within all treated areas) has been achieved, this visit will be considered End of Study (EOS) visit. In case a subject discontinues prematurely, the Investigator will conduct an Early Termination (ET) visit, capturing the reason for discontinuation and performing assessments of EOS visit.

3.2 Number of Subjects and Sites

The planned overall sample size for this clinical trial is approximately 413 adult male and female patients with external anogenital warts, who will be randomized at a 3:3:1 ratio (test: RLD: placebo) at about 16 clinical sites in the United States, Russia and Ukraine.

4 SELECTION AND WITHDRAWAL OF STUDY POPULATION

4.1 Eligibility Criteria

Subjects who satisfy **ALL** of the following **inclusion** and have **NONE** of the following **exclusion** criteria may be enrolled in the study:

4.1.1 Inclusion Criteria

1. Willing and able to provide written informed consent prior to participating in this study.
2. Male or female subjects, aged 18-65 inclusive, with a clinical diagnosis of external anogenital warts (i.e., perianal warts and/or external genital warts), including two or more distinct external genital warts, and wart area that is equal or less than 10 cm^2. Histological confirmation should be obtained if there is any doubt of the diagnosis.
3. Females of childbearing potential may be enrolled if they practice a method of birth control with a reliability of at least 90%.
4. Sexually active study participants must agree to abstain from sexual activity of any kind throughout the treatment period to prevent cross- and reinfection by HPV.
5. Any female subject with childbearing potential has a negative urine pregnancy test at Baseline.
6. Negative HIV test within 4 weeks before Baseline.

4.1.2 Exclusion Criteria

1. Female subjects who are pregnant or lactating or planning to become pregnant during the study period.
2. Hypersensitivity or intolerance to Podofilox or any component of the formulation.
3. History of previous unsuccessful treatment with any formulation of Podofilox.
4. Wart area that is greater than 10 cm^2.
5. Patients with internal anogenital and mucous membrane warts, Bowenoid papulosis, squamous cell carcinoma, active herpes lesion, or other skin abnormalities of treatment area, such as eczema, or skin that had not healed following surgery (cryosurgery, laser ablation or similar).
6. Primary or secondary immunodeficiency.
7. Patients with diabetes type I or II.
8. Local irritation in any treatment area that would interfere with treatment.
9. Use within 4 weeks prior to baseline of any: 1) treatment for anogenital warts, 2) systemic corticosteroids, or 3) systemic immunosuppressive drug.
10. Any medical or surgical condition in the judgment of the Investigator that may interfere with the assessment of efficacy or safety, or pose a risk to the subject.
11. Patients known to abuse alcohol and/or drugs, or with a history of chronic alcohol or drug abuse that may result in protocol non-compliance.
12. Received another investigational drug, device, or biologic within 90 days prior to the start of Screening or has planned to participate in another clinical trial while enrolled in this study.
13. Subjects who in the opinion of the investigator, are unlikely to be able to follow treatment instructions, protocol requirements and complete the study
14. Employee (or employee's family member) of the research center or private practice, CRO or Sponsor, or subjects who have a conflict of interest.

15. Subjects living (e.g., siblings, spouses, relatives, roommates) in the same household cannot be enrolled in the study at the same time.
16. Previous enrollment in this study, current enrollment in this study at another participating site or current enrollment in another study (in parallel to this study) at another clinical research site.

4.2 Withdrawal and Early Discontinuation

A subject may voluntary withdraw from the study at any time and for any reason without prejudice to his or her future medical care. The Investigator, Sponsor, or Medical Monitor may also withdraw the subject at any time if it is medically necessary or in the interest of subject safety. Additional reasons for premature discontinuation of study drug may include adverse events and major non-compliance with study procedures as described below. The withdrawal of a patient from study drug by the Investigator should be discussed with the Medical Monitor before the patient stops study drug, whenever possible.

A subject will be discontinued from this study if any of the following criteria are met:

- Withdrawal of consent by the subject is received.
- In the opinion of the Investigator, it is not in the subject's best interests to continue in the study.
- Occurrence of an Adverse Event (AE) or Serious Adverse Event (SAE), which, in the opinion of the Investigator, warrants discontinuation of the subject from the study.
- Pregnancy (refer to Section 7.6).
- Significant non-compliance with study procedures that would interfere with the study results or increase the subject's risks in the study.
- If subject is deemed to be a treatment failure, which is defined as worsening of condition (increase in the number of warts, in the size of the warts, or other clinical signs as determined by the Investigator) and requiring alternate or supplemental therapy for the treatment of external anogenital warts during the study.
- The subject's medication code is unblinded.
- Subject did not meet, or no longer meets, the entry criteria.
- The subject is lost to follow-up. The investigator will document efforts to attempt to reach the subject twice by telephone and will send a certified follow-up letter before considering that subject lost to follow-up. All attempts must be thoroughly recorded.
- Investigator discretion.

Subjects discontinuing due to "treatment failure" will be included in the PP population analysis as treatment failures, and will have alternative treatment recommended by the Investigator. Subjects discontinued prematurely from the study for any other reason (i.e., noncompliance, or withdrawal of consent, etc.) will be excluded from the PP population, but included in the ITT population, using Last Observation Carried Forward (LOCF).

In the case if subject discontinues prematurely, the Investigator will perform Early Termination (ET) visit, capturing the reason for discontinuation and performing assessments of EOS visit (Section 6.3.4).

If a subject does not return for a scheduled visit, every effort will be made to contact the subject and document the End of Study (EOS) visit assessments. The patient should at least be contacted twice by phone and, if no answer, by registered letter within a week. The Investigator must document the primary reason

for discontinuation of a study subject in the source document and on the appropriate electronic case report form (eCRF).

Randomized subjects who discontinue due to an adverse event will have all events documented and followed to satisfactory resolution, as detailed in Section 7.4.

After a subject has been discontinued, he/she will not be allowed to re-enroll in the study at any facility.

4.3 Contraception and Pregnancy Avoidance Measures

The study will require that all female subjects of childbearing potential practice a method of birth control with a reliability of at least 90% defined as follows:

- Female subjects must be surgically sterile, postmenopausal (for at least one year).
- Female subjects not surgically sterile or postmenopausal (for at least one year), and non-vasectomized male subjects, must practice at least one of the following methods of birth control:
    - Total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to Screening visit, throughout the study).
    - A vasectomized partner.
    - Hormonal contraceptives (oral, parenteral, or transdermal) for at least three months prior to study drug administration or intrauterine contraception/device double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap *together with* spermicidal foam/gel/film/suppository).

Sexually active study participants must agree to abstain from sexual activity of any kind throughout the treatment period to prevent cross- and reinfection by HPV.

If a subject becomes pregnant during the participation in the study, the Investigator will immediately discontinue the patient from the study and contact the Medical Monitor, Biorasi Safety Team, or Sponsor. Diligent efforts will be made to determine the outcome for all pregnancy exposures in the clinical trial. Information on the status of the mother and the child will be forwarded to the Biorasi Safety Team using the Pregnancy Data Collection Form. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

5 STUDY DRUG ADMINISTRATION

5.1 Identity of Study Drug(s)

The term *study drug* is used to refer to the Test, Reference and Placebo drug products.

5.1.1 Formulation of Study Drug

Study drug in this study will be supplied as matching 3.5 g of clear gel in aluminum tubes with an applicator tip, labeled for a blinded study.

- **Test Drug:** Podofilox Topical Gel 0.5%, manufactured for Hyloris Developments SA by Perrigo Company Ltd.
- **RLD:** Condylox® Gel 0.5%, manufactured for Allergan Pharmaceuticals, by DPT Laboratories, Ltd., distributed by Actavis Pharma, Inc.
- **Placebo:** Vehicle of the test drug, manufactured for Hyloris Developments SA by Perrigo Company Ltd.

5.2 Packaging and Labeling

The study drug tubes to be dispensed to the subject will be packaged and labeled in accordance with Good Manufacturing Practice. Each individual tube of the study drug will be diaper-labelled and look identical.

5.3 Storage of the Study Drug

Storage temperature for study drug is 20-25°C (68-77°F). All study medication supplies must be kept in a secure cabinet or room. Only the designated study personnel will have access to study medication supplies.

The Investigator will maintain temperature continued monitoring of the study drug with temperature readings. All temperature excursions must be reported to Biorasi using Temperature Excursion Form. The study drug that experienced excursions must be quarantined until the Medical Monitor / Sponsor's approval on future use.

5.4 Reserve Sample Retention

When a site receives a shipment of the study drug, study pharmacist, or designated study personnel will separate one randomly selected set of study drug for retention. The retention samples will be marked accordingly, stored securely along with sealed randomization codes for FDA use (according to Guidance for Industry - Handling and Retention of BA and BE Testing Samples.; 2004, and CRF 320.38 and 320.63). For all subsequent shipments, the same procedure is to be followed.[17] Retention samples will be stored under the same temperature conditions as the study drug for use in the study by subjects.

The Investigator will store the retention samples of the study drug until such time or until notification is received from the Sponsor that the samples are no longer required and proper instruction of what to do with the sample is given by the Sponsor.

5.5 Treatment Assignment (Randomization)

Randomization will be performed using an Interactive Response Technology (IRT) system that is fully integrated with the Electronic Data Collection (EDC) system. Randomization and treatment assignment will be determined at the time the subject has met all eligibility criteria and is ready for enrollment. Subjects will be randomized in a 3:3:1 ratio to receive the test product, RLD, or placebo.

Subjects will be stratified by gender. A balanced distribution amongst male and female subjects across the study in all three study groups will be maintained by the IRT system which will assign subjects to the treatment arm and specify the kit number to be dispensed.

The randomization scheme will be held by the independent third party throughout the conduct of the study (through database lock) and will not be available to the Hyloris Developments SA, Biorasi, Investigator, or study staff, or to clinical staff who could have an impact on the outcome of the study.

5.6 Blinding

This is a double-blind study, thus Sponsor, Biorasi, Investigator, site staff, study monitors, and subjects will be blinded to the randomization scheme. The packaging of the test, RLD products and placebo will be similar in appearance to make no difference in treatment to the subjects and study staff.

The blinding code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Investigator to complete a serious adverse event report. In such situations, the Medical Monitor or the Investigator will use the IRT system to unblind the treatment for the individual subject. Unblinded information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded.

As the study is blinded, the Investigator should promptly document and report to the Sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

5.7 Treatment Administration

5.7.1 Study Drug Dispensation and Application

Subjects will receive the randomized treatment along at the Baseline Visit (Day 0) with a Subject Diary Card, written instructions and precautions. Prior to dispensation Investigator will measure the weight of the study medication using electronic scales. Each subject will be instructed by the Investigator on proper application technique. The Investigator will identify which warts should be treated during the application training session at the Baseline visit.

Following application instructions will be provided to the subject:

1. This medication is for topical use only. Apply it on the warts pointed out by your doctor. It should be applied once in the morning and again in the evening (at bedtime) for 3 days followed by a 4-day rest period. If the warts do not go away, your study doctor will decide if another cycle of

treatment is necessary. This cycle may be repeated up to 4 times. If the warts do not go away after 4 weeks of treatment, your study doctor will advise you on the alternative treatment methods.
2. To apply the study drug, use an applicator tip or your finger. Apply a small amount of medication to the wart to cover it. Application on the surrounding normal tissue should be minimized. If the genital wart is in a skin fold, spread the skin apart and apply the medicine. Allow the treated skin to dry before releasing the skin fold. Wash your hands thoroughly with soap and water before and after each application.
3. This medication should be used only as directed by study doctor. You should wash your hands thoroughly before and after each application. It is for external use only. Avoid contact with the eyes. If contact occurs, immediately wash with plenty of water and contact your study doctor.
4. Do NOT use large amounts. Maximum amount that can be applied is 0.5 gram per day (or 0.25 gram per one application). Do NOT apply more often or use for a longer period than directed. Your condition will not clear faster, and the chance for side effects may be increased.
5. Do NOT use this medication for any disorder other than for External Anogenital Warts. The medication should NOT be used in the vagina or in the rectum or on any open wounds. You should not wash the medication off the wart area unless you experience excessive pain, burning, or itching.
6. Report any signs of adverse reactions to your study doctor. If the area you are putting study medication on is bleeding or swollen, or if there is excessive pain, burning or itching, stop applying it and contact your doctor.
7. Do not have sexual contact of any kind during the treatment period.
8. The study drug is flammable and must be kept away from open flames.

The subject will return used tubes of the study drug at the next visit along with completed Subject Diary Card. The Investigator will measure the weight of returned study medication using electronic scales. Measured weight of the study medication will be documented in a Study Drug Accountability Log.

If an additional treatment cycle is required, the Investigator will dispense the returned tube. If the remaining amount of the study drug in the used tube is not sufficient for another treatment cycle, study site will dispense a new tube of the study drug using the IRT system. The Investigator will measure the weight of study medication using electronic scales prior to providing to subject.

5.8 Treatment Compliance

Treatment compliance will be assessed by the Investigator based on Subject Diary Card completion at each study visit following the Baseline. Compliant subjects are defined as those who have completed at least 75% and no more than 125% of study drug applications until treatment success or for a maximum of four cycles of treatment.

5.9 Accountability, Destruction and Return of Study Supplies

The Sponsor will supply sufficient quantities of the study drug for the following:

1. Completion of this study
2. Samples retention, as per applicable regulations described in Section 5.4.

The study pharmacist or designated study personnel will maintain a Study Drug Accountability Log itemizing all study drug received, dispensed to and returned from each subject during the study. All

dispensed tubes must be accounted for, and any discrepancies explained. Study site should contact site Clinical Research Associate (CRA) in the case if any dispensing errors or discrepancies are discovered.

Prior to site closure and at appropriate intervals during the study, site CRA will perform study drug accountability and reconciliation. At the end of the study, the Investigator will retain all the original documentation regarding study drug accountability, return, and/or destruction, and copies will be sent to the Biorasi/Sponsor.

All unused and used Study Drug tubes will be returned to the Sponsor or its designee for destruction at the end of the study except for the Retention Samples.

5.10 Prior, Concomitant and Prohibited Therapy

Current medications and any medications taken within the 30 days prior to the start of the study will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication, start and stop dates. The medications to be recorded include prescription and all over-the-counter (OTC) medications and all dietary supplements. All medications taken on a regular basis, including aspirin and acetaminophen, should be recorded prior to commencing the use of the investigational product. Any medications started during the study (including "as needed" medications) will be recorded in the concomitant medication list as soon as the Investigational Site will become aware of the medication being added.

Prohibited Therapies are those medicinal products and treatment methods that are not allowed in the current study within the timeframes specified in the Table 3.

Table 3. List of Prohibited Medication and Treatment Methods

Treatment	Timeframe the Therapy is Prohibited
Systemic corticosteroid or immunosuppressive drugs	4 weeks prior to the Baseline visit and until the EOS/ET visit
Treatment of EAWs, including surgical removal (cryosurgery, laser ablation, electrocoagulation, shaving, etc.), over-the-counter (OTC) treatments, Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) solution, etc.	
Any other topical products applied to the treatment area(s)	From the Baseline visit and until the EOS/ET visit
Antipruritic (anti-itch medication), including antihistamines	within 24 hours of study visits
Immunomodulators	From the Baseline visit and until the EOS/ET visit
Immunostimulatory drugs	From the Baseline visit and until the EOS/ET visit
Interferon	From the Baseline visit and until the EOS/ET visit
Another Investigational Drug	90 days prior to the Screening visit and until the EOS/ET visit

If the Investigator becomes aware of a subject having taken a prohibited medication, they will report the incident to the Medical Monitor and Biorasi within 24 hours, and the Medical Monitor and/or Sponsor will provide written approval of the subject's continuation or discontinuation from the study.

6 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same Investigator or site personnel whenever possible.

6.1 Administrative Procedures

6.1.1 Subject Informed Consent

A signed and dated, study-specific, approved by Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and applicable regulatory authorities Informed Consent Form must be obtained from each subject prior to performing any study related procedures. No study related procedures or activities may be performed until each subject is fully informed and the consent form is signed and dated.

A copy of the signed consent (or a second original) will be given to every participant (or legally authorized representative) and the original will be maintained with the participant's records.

Subjects that require a wash-out of more than 30 days from their initial informed consent/ signing must be re-consented before any further study procedures can begin.

6.1.2 Documentation of Screen Failures

Investigators must account for all subjects who sign informed consent and will maintain an Enrollment log capturing subjects screened and indicating who was enrolled or excluded and the reason why. If the subject is found not to be eligible prior to enrollment, the reason(s) for ineligibility must be documented by the Investigator.

Subject Numbers assigned to subjects who fail Screening will not be re-used.

6.2 Study Procedures and Evaluations

6.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the study:

6.2.1.1 Subject Demographics

Basic demographic information, including date of birth, sex, ethnicity, and race will be recorded at the Screening visit.

6.2.1.2 Medical history

Medical history will be collected at the Screening visit. Relevant medical history, including any history of HPV infections and EAWs will be documented. Presence of immunodeficiency, or other clinically significant ongoing medical condition or disease will disqualify subject from participation.

6.2.1.3 Concomitant Medication Recording

All medications (both prescription and nonprescription, and including vitamins, herbals, topicals, inhaled, and intranasal) taken within 30 days prior to the start of the Study Treatment and through the final study visit will be recorded on the appropriate eCRF (using their generic and brand name, if known) with the corresponding indication, start and stop dates. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (pro re nata, as needed) medication use.

Previous treatment of HPV infection with any formulation of Podofilox must be recorded irrespectively of the term it was given. Corresponding condition shall be captured in the subject's Medical History.

6.2.1.4 Vital Signs

Vital signs will be collected at each study visit. Vital signs will include body temperature, pulse rate and blood pressure (systolic and diastolic). Blood pressure and pulse rate will be measured after the subject has been sitting restfully for at least 5 minutes.

Any abnormal characteristics will be evaluated by the Investigator from based on their significance. Abnormal vital signs will be considered AEs if they require therapeutic medical intervention, and/or if the Investigator considers them to be AEs due to the clinical judgement.

6.2.1.5 Physical examination

Physical examination, including height, weight, and evaluation of organs and systems (General Appearance, Heart/Cardiovascular, Lungs, Gastrointestinal, Ears / Nose / Throat, Extremities, and Skin) will be assessed at the Screening, Baseline and EOS/ET visits.

Clinically significant abnormalities other than presence of external anogenital warts will disqualify subject from participation. The following skin abnormalities are also considered disqualifying:

- Internal genital warts
- Mucous membrane warts
- Bowenoid papulosis
- Squamous cell carcinoma
- Active Herpes lesion within any treatment area
- Eczema
- Skin that had not healed following surgical procedure (cryosurgery, laser ablation, or similar).

6.2.1.6 Visual Examination of External Anogenital Warts

Visual examination at the Screening visit aims to confirm the clinical diagnosis of external anogenital warts based on positive identification of perianal warts and/or external genital warts. Two or more distinct external genital warts, and wart area that is equal to or less than 10 cm^2 are required for participation in the trial (refer to Section 4.1.1).

Histological confirmation should be obtained at the discretion of the PI if there is any doubt of the diagnosis and to rule-out skin lesions of different origin, such as mucous membrane wart, Bowenoid papulosis, Squamous cell carcinoma, or active Herpes lesions.

The Investigator will record total number of anogenital warts within treatment area(s), indicating:

(a) total number of external genital warts and

(b) perianal warts at each study visit.

A cluster of warts is to be counted as a single wart. As far as possible, the same physician will perform the record for the same subject throughout the study.

Visual examination of EAWs will be repeated at each study visit. Total disappearance of all warts within all treated areas will be considered a "treatment success".

6.2.1.7 Assessment of Local Application Site Reactions

Local skin reaction scores for erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding will be recorded by the Investigator for every study visit based on their intensity.

Table 4. Skin Reaction Scale

Reaction	Score, 0-3*
erythema	
dryness	
burning/stinging	
erosion	
edema	
pain	
itching	
bleeding	

* Scores are: 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

The Application Site Reaction Assessment must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated these tasks by the PI. The PI may delegate this task to Physicians, Physician Assistants, or Nurse Practitioners, Registered Nurses (RNs) or Licensed Practical Nurses (LPNs) who have documented training and past experience conducting this assessment.
Application site reactions (erythema, dryness, burning/stinging, erosion, edema, pain, itching, and bleeding) are to be recorded as adverse events of special interest.
All application site reactions must be recorded as adverse events in the source document and eCRFs.

6.2.1.8 Adverse Event Assessments

Beginning with the Screening visit and through the EOS/ET visit, the Investigator and study personnel will

review each subject's clinical evaluation findings and query the subject directly regarding AEs (see Section 7, Safety Data Collection, Recording and Reporting). Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.

6.2.2 Laboratory Evaluations

The following laboratory evaluations will be conducted during the study:

6.2.2.1 Serology test for HIV

During the Screening visit (Visit 1), the Investigator or designee will obtain serum test for HIV. Negative test is required to participate in the study.

6.2.2.2 Test for Hepatitis B&C

During the Screening visit (Visit 1), the Investigator or designee will obtain serum test for Hepatitis B&C. Negative test is required to participate in the study.

6.2.2.3 Pregnancy test

A urine pregnancy test will be performed at the Screening, Baseline and EOS/ET visits for females of childbearing potential (refer to Section 4.2 for definitions). The Baseline urine pregnancy test result must be available and must be negative before the subject applies the first application of study drug. An investigator may repeat the pregnancy test anytime during the study if there is any suspicion or possibility that the subject may be pregnant.

6.2.2.4 Test for Syphilis

The test for Syphilis will be performed if required by applicable local regulations. During the Screening visit (Visit 1), the Investigator or designee will obtain serum test for Syphilis. Negative test is required to participate in the study.

6.2.3 Subject Diary Card Review

The subject will be given a kit of study drug, mirror and a Subject Diary Card to capture application details, and acknowledge any changes in skin reactions, other AEs and concomitant medications during the intervening time between the site visits. Subjects will fill out their diary cards during each treatment cycle noting the following:

- Time and date of application
- Any changes in skin reactions, other AEs and concomitant medication

Subjects will return their completed diary cards to the clinical site at each of the post-baseline visits (visits 3-5 and EOS/ET) for review and filing with the subject's source documents. The Investigator will verify that the subject complied with the application requirements. The study staff will sign off on completed diary card. Any missed application notations will be clarified with the subject and documented. Refer to Section 5.8 for additional information regarding the treatment compliance.

6.3 Study Procedures

6.3.1 Visit 1: Screening (Day -14 up to -1)

Screening visit will occur at up to 14 days prior to the Baseline. During the screening, the following procedures will be performed:

- Informed Consent
- Collection of Subject Demographics and Medical History
- Concomitant and Prohibited Therapies Review
- Assessment of Vital Signs
- Physical Examination
- Serology test for HIV, Hepatitis B and C
- Urine pregnancy test
- Test for Syphilis (if required)
- Confirmation and documentation of the diagnosis of anogenital warts during the visual inspection (histological confirmation will be obtained if there is any doubt of the diagnosis)
- Eligibility Criteria Check
- Adverse Events Assessment
- Schedule next visit to occur within window

6.3.2 Visit 2: Baseline Visit (Day 0)

- Adverse Events Assessment
- Concomitant and Prohibited Therapies Review
- Assessment of Vital Signs
- Physical Examination
- Urine Pregnancy Test
- Visual Inspection of EAWs
- Assessment of Local Application Site Reactions
- Eligibility Criteria Check
- Randomization
- Study Drug Dispensation
- Subject Diary Card Dispensation
- Training on Study Drug Application
- Training on Subject Diary Card completion and contraception methods
- Schedule next visit to occur within window

6.3.3 Visits 3-6 (Day 7 [Week 1], Day 14 [Week 2], Day 21 [Week 3], and Day 28 [Week 4])

The following procedures will be performed:

- Subject Diary Card Return, Review and Dispensation
- Adverse Events Assessment
- Concomitant and Prohibited Therapies Review
- Assessment of Vital Signs

- Assessment of Local Application Site Reactions
- Visual Inspection of EAWs. *In the case there is a total disappearance of all warts within all treated areas at visits 2, 3, 4, or 5, this visit will be considered an End of Study (EOS) visit. In the case where reduction of warts is absent or incomplete, a new treatment cycle will be initiated for a maximum of four cycles in total for the subject.*
- Study Drug Return and Accountability
- Study Drug Dispensation

6.3.4 End of Study / Early Termination (EOS/ET) visit

The visit at which "treatment success" has been achieved will be considered EOS visit.

If "treatment success" has not been achieved through the EOS/ET visit (Day 28±5 [Week 4]), then the subject will be considered "treatment failure" and EOS activities will be performed. Similarly, if the Investigator assesses the subject's condition at any time and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as "treatment failure". ET visit procedures will be performed, and an alternative treatment will be advised at the Investigator's discretion.

Subjects discontinuing from the study sooner than the Day 28 visit will undergo the ET visit as soon as possible.

Following activities will be performed at EOS/ET visit:

- Subject Diary Card Return and Review
- Adverse Events Assessment
- Concomitant and Prohibited Therapies Review
- Assessment of Vital Signs
- Physical Examination
- Assessment of Local Application Site Reactions
- Visual Inspection of EAWs
- Study Drug Return and Accountability
- Urine Pregnancy Test
- For prematurely discontinuing subjects - record reason for discontinuation.

6.3.5 Unscheduled Visit

Subjects will be encouraged to report any complications or adverse effects during their participation. Investigator may evaluate the subject at an unscheduled visit, if subject's condition will be considered as worsening. If the investigator assesses the subject's condition and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure, an Early Termination Visit conducted, and a standard of care treatment may be advised at the investigator's discretion. The following procedures should be performed at the Unscheduled Visit if required.

- Subject Diary Card Return, Review and Dispensation
- Adverse Events assessment

- Concomitant and Prohibited Therapies review
- Collection of Vital Signs
- Physical examination
- Assessment of Local Application Site Reactions
- Visual Inspection of EAWs

7 SAFETY DATA COLLECTION, RECORDING AND REPORTING

The Investigator will monitor each subject for clinical evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "related" or "probably related" to study drug, final diagnosis, if known, and any action(s) taken. For AEs to be considered intermittent, the events must be of similar nature and severity and each intermittent AE will be reported separately. AEs and SAEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded, monitored and followed-up until the resolution (or until the Investigator deems the event to be stable/chronic).

7.1 Definitions

7.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether the event is considered causally related to the use of the investigational product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Clinically significant abnormalities are to be followed to resolution (i.e. become stable, return to normal, return to Baseline, or become explainable). Laboratory abnormalities and changes in vital signs are considered AEs only if they necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

7.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to the Biorasi Safety and Pharmacovigilance as a serious adverse event (SAE) using SAE report form within 24 hours of occurrence or notification to the study site:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an out-patient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital	An anomaly detected at or after birth or any anomaly that result in fetal loss.

Anomaly/birth defect	
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Other Important Medical Event	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life- threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such 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.

7.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE and SAE:

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

7.3 Causality of Adverse Events

The Investigator will use the following definitions to assess the relationship of the AE/SAE to the use of investigational product:

Related	The event occurred within a reasonable time after drug administration or drug concentration and body fluids demonstrated that the study drug was present: the event could not be reasonably explained by known characteristics including concomitant therapies; the adverse event abated after discontinuing the study drug.
Probably Related	The event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.
Possibly Related	The event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	The event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	The event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an Investigator's opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided by the Investigator for the AE.

7.4 Adverse Event Collection Period

Any AE/SAE prior to the Screening visit will be considered past medical history (PMH). The AE reporting period for this study begins with the signature of the Informed Consent Form and, for unresolved AEs, ends 30 days following the last study medication application. Those events that occur during the screening period and up to the day of the first application of the study drug will be considered Non-Treatment Emergent AEs.

Adverse events that occur during the treatment period (starting from the day of the first application of Study Drug and up to the final protocol required visit) will be considered Treatment Emergent AEs (TEAEs).

SAE(s) that are observed or spontaneously reported during the subject's participation in the trial will be captured and monitored until the Investigator deems the event to be chronic or not clinically significant or the subject to be stable.

7.5 Adverse Event Reporting

Information regarding AEs will be derived by questioning the participants in an unbiased, general query (e.g., "How do you feel?" or "How have you been feeling since your last clinic visit?"), by subjects' spontaneous reports, or by observation.

AEs will be recorded in the source documents. All AEs will then be transcribed into the CRF.

For each sign, symptom or adverse event, the following information will be recorded in the CRF:

• a brief descriptor of the adverse event

• severity (mild/ moderate/ severe)

• whether the AE was "serious" or not (as defined in the serious adverse event section)

• frequency (single occurrence/ intermittent/ continuous)

• outcome (resolved/ resolved with sequelae/ improving/still present and unchanging/ death

• whether any treatment was administered for the AE.

In the event of a SAE, whether related to study drug or not, the Investigator or representative must make an accurate and adequate report consisting of at least the minimum criteria (Site and Subject ID, Date site became aware of the event, SAE Term, Seriousness criteria, Study Drug information, Investigator/Reporter and site address) within 24 hours after the site became aware by email, fax, or telephone to Biorasi Safety and Pharmacovigilance team. Biorasi Safety and Pharmacovigilance team will complete the SAE report onto a MedWatch 3500A form for evaluation and convey for review by the Medical Monitor and Sponsor contact. Accurate Completion of the MedWatch 3500A form will consist of all data supplied such as Subject's demography, SAE narrative, concomitant medication, laboratory parameters and relevant medical history.

Copies of each report with the associated documentation (i.e., queries, medical records, lab records,

IRB/IEC communications and all source documents) will be kept in the site's study file.

A subject experiencing one or more SAEs will receive treatment and follow-up evaluations by the Investigator or may be referred to another appropriate physician for treatment and follow-up. The Investigational Site will be responsible for collection and forwarding follow-up SAE information to the Biorasi Safety and Pharmacovigilance.

MEDICAL MONITOR

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7.6 Reporting of Pregnancies

If a subject becomes pregnant during the participation in the study, the Investigator will immediately discontinue the patient from the study and contact the Medical Monitor, Biorasi Safety Team, and the Sponsor. Diligent efforts will be made to determine the outcome for all pregnancy exposures in the clinical trial. Information on the status of the mother and the child will be forwarded to the Biorasi Safety Team using the Pregnancy Data Collection Form. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Detailed guidance on the reporting of Pregnancies will be provided in the SAE and Pregnancy Reporting Guidance.

7.7 Unblinding due to SAE

Patients, Investigators, site staff, Hyloris Developments SA and Biorasi will be blinded to treatment assignment.

Reasons to unblind patient should be clearly documented in subject notes, and the monitoring site visit report. In the event of an emergency necessitating unblinding the PI/site staff will make every effort to contact and discuss the event with the Medical Monitor prior to unblinding.

Treatment assignment for an individual subject should be unblinded only in an emergency by the Investigator, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Treatment should be provided in accordance with the medical condition and according to the information provided in the Investigator's Brochure.

According to the FDA guidance *Safety Assessment for IND Safety Reporting* IND safety reports submitted should be unblinded. If the blind is broken and a subject with an adverse event that would meet the criteria for reporting as a single event was receiving placebo, the event will not be reported in an IND safety report because there is a reasonable possibility that the drug did not cause the adverse event. However, if the SAE is determined to be from drug exposure reporting to the FDA will take place.

The Investigator must document the breaking of the code, and the reasons for doing so on the CRF, in the site file, and in the medical notes.

The Investigator must notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break. Subject always to clinical need and where possible, all other members of the research team should remain blinded.

8 DATA ANALYSIS

The sections below summarize the intended statistical methods and analyses of data for the study. A more detailed statistical analysis plan will be written prior to finalization of the clinical trial database. Any changes to the planned methods and analyses will be described and justified in the protocol and/or in the final clinical study report, as appropriate.

Descriptive statistical methods will be used to summarize the data from this study, with confidence intervals calculated for the primary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and proportions for categorical data. The term "treatment group" refers to randomized treatment assignment: active-test and active-reference. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment assignment, subject number, and then by date within each subject number.

Unless specified otherwise, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.

All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

8.1 Subject Population/Data Sets to Be Evaluated

The subject populations are defined as follows:

1. **Safety Population:** The safety population includes all randomized subjects who received and used study product.
2. **Modified Intent-to-Treat (mITT) Population:** A modified intent-to-treat population includes all subjects who are randomized, applied at least one dose of assigned product, and returned for at least one post-baseline evaluation visit.
3. **Per Protocol (PP) Population:** all randomized subjects who met all inclusion/exclusion criteria, had no protocol violations that would affect the treatment evaluation, were compliant with applying study product, and returned to the study site for the primary endpoint evaluation at four days (± 5 days) after the last day of the last cycle of treatment. Compliant subjects are defined as those who used at least 75% and no more than 125% of study drug doses until treatment success or four cycles of treatment.

Subjects discontinuing due to "treatment failure" will be included in the PP population analysis as treatment failures, and will have alternative treatment recommended by the Investigator. Subjects discontinued prematurely from the study for any other reason (i.e., noncompliance, or withdrawal of consent, etc.) will be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

The results in the PP population will be considered definitive for therapeutic equivalence with those in the mITT population considered supportive. The results in the mITT population will be considered definitive

for superiority of each active treatment to placebo with those in the PP population considered supportive. Safety analyses will be performed using the Safety population.

8.2 Sample Size Determination

The difference in the proportion of subjects in the test and reference treatment groups who achieve "treatment success" defined as "total disappearance of all warts within all treated areas" at four days (± 5 days) after the last day of the last cycle of treatment will be evaluated using a two-sided 90% confidence interval. The therapeutic equivalence of the test and reference products will be established if the confidence bounds of the 90% confidence interval are contained within the limits of -0.20 to +0.20. The results in the PP population will be considered definitive for therapeutic equivalence with those in the mITT population considered supportive.

Table 5. Sample Size Rationale

Equivalency margin	Power (%)	CI (%)	Sample Size mITT* (test: RLD: placebo)	Sample Size PP* (test: RLD: placebo)
20%	85%	90%	392 (168:168:56)	350 (150:150:50)

* Sample sizes were calculated assuming: 40.0% success rate for active treatment, and 15.0% success rate for vehicle; 20% equivalency margin (EQ).

8.3 Statistical Analyses

8.3.1 Subject Disposition and Demography

Descriptive statistics will be generated by treatment group for selected continuous variables. The number and percentage of subjects in each class of categorical demographic and baseline variables (e.g., gender, ethnicity, and race) will be tabulated by treatment group. Individual subject demographic and baseline characteristic data will be listed.

8.3.2 Assessment of Bioequivalence as Primary Endpoint

Bioequivalence assessment will be evaluated by comparing proportions of patients with treatment success in the test and the reference treatment groups. Bioequivalence between the test and the reference product will be established if the 90% confidence interval for the difference in success proportions between test and reference treatments is contained within the equivalence limits [-0.20, +0.20].

In this case, the compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$ (meaning test product is not bioequivalent to the reference);

versus

H_A: $-.20 \leq p_T - p_R \leq .20$ (supporting bioequivalence);

where p_T = success proportion of test treatment, p_R = success proportion of reference treatment.

Let

1. n_T = sample size of test treatment group
2. c n_T = number of subjects with success in test treatment group
3. n_R = sample size of reference treatment group
4. c n_R = number of subjects with success in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}$.

The 90% confidence interval will be estimated as follows, using Yates correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

H_0 is rejected if $L \geq -0.20$ and $U \leq 0.20$ resulting in accepting H_A and concluding bioequivalence of the two products.

The primary endpoint is the evaluation of the proportion of subjects in each group with "treatment success" defined as "total disappearance of all warts within all treated areas". The primary endpoint will be evaluated at four days (± 5 days) after the last day of the last cycle of treatment. The results in the PP population will be considered definitive, with those in the mITT population as supportive.

8.3.3 Assessment of Superiority

Superiority will be assessed through continuity-corrected Z-tests comparing each active treatment to placebo. If both the test and RLD success proportions are statistically significantly greater than the placebo proportion ($p<0.05$) then they will be considered superior to the placebo. The results in the mITT population will be considered definitive for superiority with those in the PP population considered supportive.

8.3.4 Assessment of Safety

The reporting of safety data is descriptive, and will include all subjects who receive at least one dose of investigational product. The variables for safety endpoints are AEs, Local Application Site Reactions and vital signs measurements. AEs will be summarized based on the frequency of AEs and their severity for all treated subjects. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Data will be summarized using preferred term and primary system organ class.

If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to study drug will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study drug.

Summaries of treatment-emergent AEs will include any AEs reported beginning with the first dose of study drug on Day 1. The occurrence of treatment-emergent adverse events will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events, treatment-emergent adverse events related to study drug, and events leading to the discontinuation of study drug will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. These data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

Local Application Site Reactions will be recorded at each study visit and will be summarized by the type of reaction (erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding) and intensity score: 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense).

8.3.5 Comparability of Subjects at Baseline

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group differences will be discussed in the CSR.

9 STUDY CONDUCT

9.1 Ethical Conduct of the Study

The study will be conducted according to the protocol, GCP, as outlined in the ICH Guidelines and Code of Federal Regulations. Written informed consent for the study must be obtained from all subjects before protocol specific procedures are performed. Subjects must be informed of their right to withdraw from the study at any time.

9.2 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (e.g., recruitment advertisements, subject's diaries, if applicable) from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the Sponsor or its designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In case of such an event, the Investigator must notify the IRB/IEC and the Sponsor in writing immediately after the implementation.

9.3 Other Required Approvals

In addition to IRB/IEC approval, all other required approvals (e.g. approval from local Research and Development Board or Scientific Committee) required by the individual site for participating in this study will be obtained by the Investigator prior to recruitment of subjects into the study and shipment of the investigational product(s). It is the responsibility of the Investigator to notify the Sponsor and the CRO of the requirement of such approvals prior to participating in the study.

9.4 Informed Consent

It is the responsibility of the Investigator to give each subject (or the subject's acceptable representative), prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial at any time.

Furthermore, it is the responsibility of the Investigator, or a person designated by the Investigator, to obtain signed informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the trial. The Investigator will retain the original of each subject's signed consent form.

The informed consent form will be in compliance to the ICH GCP, local regulatory, and legal requirements. The informed consent form used in this study, and any changes made during the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use.

9.5 Subject Confidentiality

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to Hyloris, it is required that the investigator permit the study monitor, any Hyloris authorized representative, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process. As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by Hyloris or their authorized representative, or a representative of the competent authorities (e.g. FDA). Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's CRF).

9.6 Publication

The Investigator is obliged to provide the sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law and regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator.

Manuscript authorship for any peer-reviewed publication by Investigator will appropriately reflect contributions to the production and review of the document. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. The Sponsor keeps the right to delete prior to submission any information identified by the Sponsor as confidential. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

9.7 Protocol amendments

The Investigator will not make any changes to this protocol without prior written consent from Hyloris and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed between Biorasi and Hyloris. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days.

10 ADMINISTRATIVE OBLIGATIONS

10.1 Source Documentation Forms

The Investigator/institution will permit study-related monitoring, audits/inspections, IRB/IEC review and regulatory inspection providing direct access to source documents, including all medical records or pertinent data relevant to the audit/inspection. Source documents will represent a record of the raw data. Source document templates may be provided by either the clinical site or the Sponsor. If provided by the clinical site, the source document template must be provided to the Sponsor prior to subject recruitment. The source documents will become part of the subject's permanent medical record maintained by the clinical site. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidances (ex. 21 CFR Part 11 and 312).

ECRFs will be used in this study. ECRFs are required and should be completed for each subject participating in the study. ECRFs will contain data captured from subject source documents and results of laboratory tests. In most cases, the source documents are contained in the subject's chart at the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts. Data must be transcribed from the source documents (e.g. physical exam report, associated medical records, date and version of informed consent form) onto the CRF by clinical site personnel prior to data monitoring.

Any corrections to entries made in the source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms.

Investigator will sign eCRFs electronically after completion of data entry, to attest that the data contained on the CRFs is complete and accurate. Completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

10.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).

The records will be retained by the Investigator according to the International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor will be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to

the Sponsor. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

10.3 Quality Control (QC) and Quality Assurance (QA)

10.3.1 Study Site Monitoring Visits

During study conduct, the Sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will follow study Monitoring Plan to review source documents to confirm that the data recorded on CRFs is accurate. The Investigator/institution will allow the Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to quality assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the IRB/IEC, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

10.3.2 Protocol Deviations

The protocol must be read thoroughly and the instructions must be followed. Investigator will not implement any protocol deviations or modification without prior approval of the Sponsor, IRB/IEC and regulatory authorities, as required. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the patient requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by email or telephone. This allows for an early joint decision to be made as to whether the patient should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision. In the event of a deviation, the Investigator will notify the Sponsor or its designee (and IRB or IEC, as required).

10.4 Trial Discontinuation/Investigative Site Termination

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects.

After such a decision, the Investigator must contact all participating subjects within a specified timeframe established by the Sponsor to inform them of the decision to discontinue the trial.

10.4.1 Criteria for Premature Termination or Suspension of the Study

The following criteria may result in either temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the Study Drug that indicates a change in the

known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The Sponsor reserves the right to discontinue the trial for other valid administrative reasons.

10.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

10.4.3 Procedures for Premature Termination or Suspension of the Study or Investigational Site(s)

Should the Sponsor elect to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by applicable investigational sites during the course of termination or study suspension.

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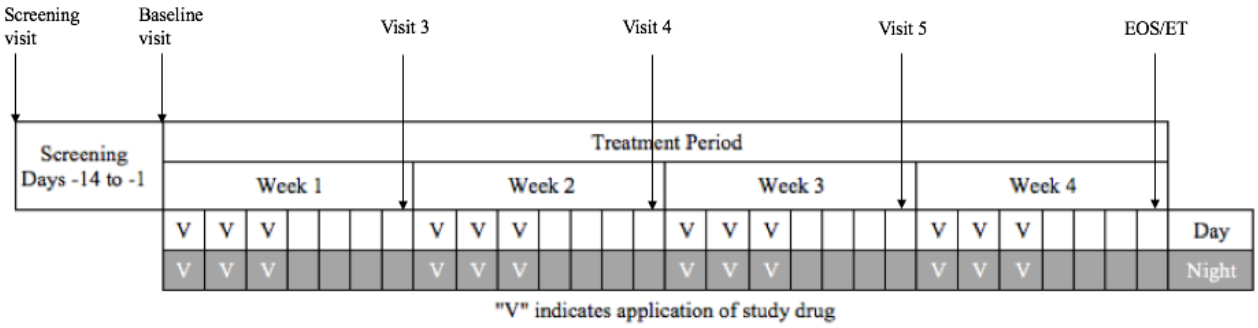
12 APPENDICES

12.1 Appendix A. Study Flowchart



12.2 Appendix B. Schedule of Events

Study Visit	Screening Visit 1	Baseline Visit 2	Treatment Period			
			Visit 3	Visit 4	Visit 5	EOS/ET Visit 6
Visit Day	**Day -14 to -1**	**Day 0**	**Day 7 (±1 day)**	**Day 14 (±1 day)**	**Day 21 (±1 day)**	**Day 28 (±5 day)**
Informed Consent	X					
Subject Demographics	X					
Medical History	X					
Concomitant and Prohibited Therapies Review	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Physical Examination	X	X				X
Visual Inspection of EAWs[1]	X	X	X	X	X	X
Serology test for HIV[2]	X					
Test for Hepatitis B, C	X					
Test for Syphilis[3]	X					
Urine Pregnancy Test	X	X				X
Eligibility Criteria Check	X	X				
Randomization		X				
Training on Study Drug Application		X				
Training on Subject Diary Card completion and contraception methods		X				
Study Drug Dispensation		X	X	X	X	
Assessment of Local Application Site Reactions		X	X	X	X	X
Adverse Events Assessment	X	X	X	X	X	X
Study Drug Return and Accountability			X	X	X	X
Subject Diary Card Return and Review			X	X	X	X
Subject Diary Card Dispensation		X	X	X	X	
Histological confirmation of diagnosis[4]	X					

[1] If total disappearance of all warts is achieved within all treated areas at visits 2, 3, 4, or 5, respective visit will be considered an End of Study (EOS) visit. In the case where reduction of warts is absent or incomplete, a new treatment cycle will be initiated for a maximum of four cycles in total for the subject.

[2] Test may not be repeated if the subject has negative HIV test results within 4 weeks before Baseline. Copy of the test result needs to be filed with the study records.

[3] If required by applicable local regulations.

[4] Histological confirmation will be obtained if there is any doubt of the diagnosis.