CLINICAL PROTOCOL

TITLE OF STUDY:

COVE-2: A Phase 3, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of VP-102 in Subjects with Common Warts (Verruca Vulgaris)

Protocol VP-102-106

Version Number/Date of Issue	(Version 2) 06 March 2020
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Date of Original Protocol:	10 February 2020
Sponsor	Verrica Pharmaceuticals Inc. 10 N. High Street, Suite 200 West Chester, PA 19380

PROTOCOL APPROVAL

Signatures of Approval of Protocol (Version 2)

This protocol was subject to critical review and has been approved by the following persons:

Affiliation	Name	Signature/Date:
Sponsor:	Cindy Willson, RN, BSN	DocuSigned by: Cindy Willson FBBB6025E10E483... 13-Mar-2020 | 12:51 PM EDT
Medical Monitor:	Devon Kuehn, MD, FAAP	DocuSigned by: Devon Kuehn 42D2262C15B14D7... 13-Mar-2020 | 9:57 AM PDT

Sponsor:

Verrica Pharmaceuticals Inc.
10 N. High Street; Suite 200
West Chester, PA 19380

Sponsor contact:

Cindy Willson, RN, BSN
Director Clinical Operations
10 N. High Street; Suite 200
West Chester, PA 19380
Phone: (415) 823-4449
Email : cwillson@verrica.com

Medical Monitor:

Devon R. Kuehn, MD, FAAP
Medical Monitor
Paidion Research, Inc.
240 Leigh Farm Road, Suite 175
Durham, NC 27707
Phone: (919) 885-1911
Email: Devon.Kuehn@Paidion.com

Acknowledgment of Responsibilities (Version 2)

This protocol is the property of Verrica Pharmaceuticals Inc. I understand that the information within it is confidential and is provided to me for review by myself, my staff, and applicable ethics committees. I understand that the protocol must be kept in a confidential manner and must be returned to the sponsor (Verrica Pharmaceuticals Inc.), or destroyed per Verrica Pharmaceuticals Inc. instructions, upon request. No part of this protocol may be reproduced in any form without permission from Verrica Pharmaceuticals Inc. By accepting this protocol, I agree that the information contained herein will not be disclosed to a third party without written authorization from Verrica Pharmaceuticals Inc.

I have read and understood the protocol and agree that it contains all of the necessary information to carry out the study.

I agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the following: Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki; Title 21 of the Code of Federal Regulations, Parts 50 (Protection of Human Subjects), and 56 (Institutional Review Boards), and 312 (Investigational New Drug Application); and International Council for Harmonisation E6 (Guideline for Good Clinical Practice).

I agree that I will not modify this protocol without obtaining the prior approval of the sponsor and of the institutional review board or independent ethics committee, except when necessary to protect the safety, rights, or welfare of subjects.

Institution Name	Investigator Name	Signature	Date

1.0 PROTOCOL SYNOPSIS

Name of sponsor company: Verrica Pharmaceuticals Inc.	
Name of finished product: VP-102	
Name(s) of active ingredient(s): Cantharidin	
Title of study: COVE-2: A Phase 3, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of VP-102 in Subjects with Common Warts (Verruca Vulgaris)	
Number of sites: Approximately 23 sites in the United States	
Study period: 147 days	**Phase of development**: Phase 3

Objectives:

Primary objective

- To evaluate the efficacy of dermal application of VP-102 relative to Placebo, when applied once every 21 days for up to four applications to common warts by assessing the proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84).

Key secondary objective

- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects achieving complete clearance of all treatable warts (Baseline and new) at the end of treatment (EOT) visit (Day 84).

Secondary objectives

- To assess the safety and tolerability of VP-102 relative to Placebo, by assessing physical examinations, concomitant medication use, and adverse events (AEs) including expected local skin reactions (LSRs).
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4.
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4.
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the change from Baseline in the number of treatable warts (Baseline and new) at the EOT visit (Day 84).

- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at EOT visit (Day 84).

- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts present at Baseline at the EOT Visit (Day 84).

Exploratory objectives

- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4.

- To evaluate the efficacy of VP-102 relative to Placebo with respect to the time to achieve onset of complete clearance of all treatable warts present at Baseline.

- To evaluate the efficacy of VP-102 by assessing the proportion of subjects who continue to exhibit complete clearance of all treatable warts (Baseline and new) at Follow-up Visits on Day 105 and Day 147.

- To evaluate the impact on quality of life (QOL) by assessing the change from Baseline of the composite score from the Children's Dermatology Life Quality Index (CDLQI) assessment (subjects 4 to 16 years of age) and Dermatology Life Quality Index (DLQI) (subjects 17 years of age and older) at the EOT Visit (Day 84).

- To assess endpoints other than complete clearance that may be indicative of treatment efficacy.

Methodology: This is a Phase 3, double-blind, randomized, placebo-controlled study (Study number VP-102-106; referred to as COVE-2 [Cantharidin and Occlusion in Verruca Epithelium]) to evaluate the efficacy, safety and tolerability of VP-102 treatment in subjects with common warts.

The study utilizes a treatment interval of 21 days between treatments. Approximately 606 subjects (2 years and older) will be enrolled. Approximately 23 sites will participate in the study.

Subject participation**:** Pre-study screening for eligibility (informed consent and assent [when applicable]), demographics, physical exam, prior and current concomitant medications and medical history can occur up to 30 days before, or on the same day as the first study drug application. To assess eligibility, a dermatologic exam and measurement of diameter and height of each wart (paring can be performed, if necessary, before assessing height) will be conducted by a qualified member of the research team before the first treatment. The dermatologic exam, measurements, location of all warts and evaluation of response to treatment (ERT) must be repeated if not conducted on the same day as treatment. Warts must have a longest axis that measures ≥ 3 and ≤ 8 mm.

Subjects who continue to meet criteria at Treatment Visit 1 will be randomized and treated per protocol. Those who do not will be considered Screen Failures, discontinued and treated at physician determination per standard of care.

Subjects who meet the enrollment criteria will be treated with application of VP-102 or Placebo at Treatment Visit 1. Treatment will continue every 21 (±4 days) until complete clearance or a maximum of four treatment

sessions during the 75-day treatment period. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. Subjects will be required to return for every treatment and follow-up visit whether or not their warts have cleared. Phone follow-ups will be conducted per protocol for those instances where the subject was treated.

Subjects will be given take home instructions describing what they might expect throughout the course of the study, as well as recommendations for wound care, when it is important to call their doctor, and instructions for who to contact in an emergency. In addition, an LSR guide will be provided and reviewed in detail at the clinic with the subject/guardian and used for reference by the subject/guardian during assessments conducted via phone call.

Treatments**:** Subjects will either receive study drug containing 0.7% cantharidin topical solution or Placebo (vehicle). Instructions for application of the study drug are outlined in the Instructions for Use included in the site regulatory packet and drug shipment. Treatment will be applied up to four times during a 75-day treatment period. The treatment interval is 21 days. It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing LSRs. At any visit where the investigator is unable to evaluate or treat some warts due to ongoing LSRs, an "Unscheduled" visit should be documented. The timing of the next visit will be determined by the resolution of the local skin reaction. The research team should be in contact with the patient until LSRs are resolved and Treatment Visit can be scheduled within 21 days (±4) when possible. A Treatment Visit should be documented at every visit in which study drug is applied. Treatment should only take place at a visit when all warts are evaluable (i.e., not obscured by an ongoing LSR) and all warts that are not completely clear, should undergo treatment with study drug. No partial treatment of warts is permitted unless a subject would be required to exceed the maximum number of two applicators per treatment session in order to complete treatment.

Study drug is to be applied to the wart site on any Treatment Visit in which a new clinical assessment of complete clearance is made for that wart (e.g., if a patient returns for Treatment Visit 2 and is clinically assessed to have no visible evidence of remaining wart, then study drug is to be applied to this wart site at Treatment Visit 2. However, if the patient remains completely clear at that wart site when returning for Treatment Visit 3, then no study drug would be applied at Treatment Visit 3).

In instances in which the clinician can adequately assess the treatment sites, but is uncertain if residual wart is remaining, treatment should be applied, and the subject should return for evaluation per protocol. Treatment visits are to take place in order (e.g., Treatment 1, Treatment 2, Treatment 3 and Treatment 4). Subjects who receive less than four treatments within the 75-day treatment period, due to the duration of post-treatment LSRs, will not be considered a protocol deviation. No treatment should be administered after the 75-day treatment period without sponsor's approval.

Subjects will be required to attend all visits regardless of whether they have achieved complete clearance of all warts at a previous visit. Once the investigator has determined a wart is clear, an additional treatment to the area should be applied. If the wart remains clear, additional treatments will not be required however the subject is to return for all subsequent visits as outlined in the protocol Subjects who have completed their Day 84 EOT Visit (- 0/+ 8 days) will be assessed at two additional Follow-up Visits on Day 105 and Day 147.

Subjects enrolled in this study will be eligible to enroll in a Long Term Extension (LTE) study to evaluate the safety and efficacy of VP-102 over 54 weeks. Subjects who have not achieved complete clearance of all warts at Day 84 and those that have new warts or recurrence of previously treated warts after Day 84 will be eligible to transition into the LTE study where they can receive VP-102 open-label every 21 days to all treatable warts are clear. At the EOS (Day147) visit, all subjects remaining in this study will be eligible to transition to the LTE for continued follow up and treatment.

All subjects will receive application of the study drug (VP-102 or Placebo) to common warts including a 1 to 2 mm margin of healthy, surrounding skin with an interval of every 21 days, until complete clearance of all treatable warts, or a maximum of four applications. Warts are to be treated and then covered with transparent surgical tape (e.g.; 3M™ Blenderm™ brand) that will remain on overnight and removed just before the 24-hour ERT phone call.

Subjects will undergo wart paring with a sharp surgical instrument (e.g., scalpel or flexible medical blade) to remove any adherent thick scale from a wart before application of study drug. Wart paring is required to be

performed at any Treatment Visit when adherent thick scale is present, and the investigator considers that it can be safely applied. Paring should be conducted by a trained practitioner and in compliance with any local regulations and should be discontinued when it results in punctate bleeding or significant pain. Not all warts may require paring and if adherent scale is not present, then study drug can be applied without paring.

Subjects should be retreated only after 17 days (i.e., 21 ±4 days) have elapsed, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. Subjects are to attend all visits regardless of whether they have achieved complete clearance before the EOT Day 84 (- 0/+ 8 days) assessment.

Removal of study drug**:** At 24 hours (±8 hours) after drug application, subjects are instructed to wet the treated area with water and then carefully and slowly remove the surgical tape from each wart, pulling the tape back over itself in a low and slow manner, trying not to unroof any intact blisters. Treated warts should be gently washed with soap and water after the tape is removed.

Note: The surgical tape and study drug may be gently removed from individual warts before 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. Subjects who remove study drug before 24 hours will be considered a protocol deviation if it does not meet the requirements for early removal as outlined in Section 9.2.2 of the protocol. Early removal is defined as removal before ≥ 16 hours have passed from study drug application.

The surgical tape and study drug should not be removed from any remaining unproblematic warts until the 24-hour (±8 hours) time point is reached. Washing of intact blisters should be gentle and without use of a washcloth. Washing and removal of surgical tape in a bath or shower is encouraged.

Assessments and procedures**:**

Assessments and procedures (Table 1) will include measurement of diameter and an ERT, before treatment application when applicable. All required study activities, including ERT evaluations, will be conducted per protocol. If new warts are identified during the course of the treatment period, they should be documented, evaluated and treated per protocol.

A Blinded Assessor is required to perform wart counts before the ERT assessment at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, End of Treatment Visit (EOT), and Follow-up Visits on Day 105 and 147. The Blinded Assessor is not required to be the same person for each assessment.

An in-person ERT will also be conducted at every visit, including at Treatment Visit 1, before study drug application. The ERT includes questions related to removal of the surgical tape and study drug, if applicable, and records the intensity of any LSRs, including AEs, and concomitant medications. The in-person ERT assessment prior to the first treatment is intended to be a Baseline assessment to capture the subject's pre-treatment local skin condition in order to help distinguish the subject's Baseline presentation from post-treatment LSRs following Treatments 1-4. The subject and/or guardian will have time to ask questions and review any concerns. In the event that any post-treatment LSR presents a safety concern (including but not limited to patient reports of severe blistering, ulceration, edema, or pain), an "Unscheduled" clinic visit must be scheduled, and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an "Unscheduled" visit.

For those visits where subjects have received treatment, additional ERT assessments will be conducted over the phone at 24 hours and 7 days after each Treatment Visit (not "Unscheduled" visits) to assess if there have been any AEs or if new warts have occurred. Phone calls conducted outside of the required 24-hour and 7-day study ERT assessments should be documented in the subject's source note but are not required to be entered into the electronic data capture unless an AE is reported by the subject.

All ERT safety assessments must be conducted by a qualified member of the research team. Any qualified team member may conduct the screening and Treatment Visit Day 1 study activities. Any subsequent ERT and phone calls must be conducted by a study team member who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation.

Subjects will participate in an in-person EOT evaluation at Day 84 (- 0/+ 8 days). A provider End of Study Treatment Questionnaire will be completed at the EOT Visit.

Subjects will continue in the study for two additional follow-up assessments at Day 105 and Day 147 (±4 days).

Photographic sub-study

At designated sites, subjects will be asked if they are interested in participating in a study sub-set where photos of their treated warts will be obtained at each treatment visit and in person follow-up study visit through Day 147. An additional 24 hour in-person visit will be conducted after Treatment Visit 1 to accommodate taking photos of the treatment site, including any LSRs that may have occurred. All subjects participating in this photographic sub-study will provide written informed consent and may withdraw from the sub-study at any time. The images may be used on handouts in future trials, for training purposes or future marketing materials. They will not be used for any portion of the efficacy or safety data. Photographs will be de-identified to those outside the research team and stored in a Health Insurance Portability and Accountability Act (HIPAA) compliant manner. Effort will be made to ensure that no photos with identifiable features are obtained.

Inclusion criteria:

To qualify for inclusion in this study, subjects must:

1. Be healthy, immunocompetent males or females ≥ 2 years of age.
2. Present with treatable common warts (*verruca vulgaris*):
    a) Common warts are considered treatable if they are located anywhere on the body except for the following prohibited areas: the eye area (including eyelids), lips, oral cavity, nasal cavity, inside of the ears, subungual (under the finger nails), soles of the feet, or the anogenital area *(Warts within 10 mm of a mucosal surface should not be treated).*
    b) Common warts located in prohibited areas and warts that are verruca plana, filiform, subungual, genital, or anal are excluded from treatment and evaluation in this study. A subject will not be excluded from the study if they have these types of warts, but the subject must also have warts that meet the inclusion criteria. If treatment of these excluded wart types is required during the study, it should be limited to cryosurgery, laser, and curettage.
    c) Subjects cannot have any warts present at Baseline in an allowed anatomic location that the subject, parent/guardian, or the investigator is unwilling to treat.
3. Have warts that measure at longest axis ≥ 3 and ≤ 8 mm; subjects with warts that exceed this size are not eligible for study participation. *Subjects with warts that are adjacent, touching or clustered may be included so long as the combined diameter at the longest axis does not exceed 8 mm and meets the minimal size of 3 mm. Individual lesions that are touching or clustered should be counted as one lesion for the purposes of tracking, inclusion and clearance.*
4. Have warts that have been present for ≥ 4 weeks at the time of the Baseline Visit.
5. Be free of any systemic or dermatologic disorder, which, in the opinion of the investigator, will interfere with the study results or increase the risk of AEs.
6. Refrain from swimming, bathing or prolonged immersion in water or any liquids until the study drug is removed after each treatment.
7. Have the ability, or have a guardian with the ability, to follow study instructions and be likely to complete all study requirements.
8. Agree to use no wart-removing product (prescription or over-the-counter) other than the study drug during the course of the study, with the exception of circumstances allowed under Inclusion Criterion 2b.
9. Provide written informed consent or assent in a manner approved by the Institutional Review Board (IRB) and/or have a parent/guardian provide written informed consent as evidenced by the signature on an IRB approved assent/consent form.
10. Provide written authorization for use and disclosure of protected health information.
11. If participating in the optional photographic sub-study, agree to allow photographs of warts to be taken at selected visits by the research team.

Exclusion criteria:

Candidates will be excluded from the study if they:

1. Are unable to cooperate with the requirements or visits of the study, as determined by the investigator.

2. Are systemically immunosuppressed or have required, systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days before enrollment or are planned to be required during the course of the study. (*Routine use of local [e.g., topical, inhaled, or intranasal] corticosteroids and episodic use of systemic medications to treat conditions arising during the course of the study is allowed*).
3. Have any chronic or acute medical condition that, in the opinion of the investigator, may interfere with the study results or place the subject at undue risk. *(e.g., human immunodeficiency virus, systemic lupus erythematosus, viral hepatitis, uncontrolled diabetes).*
4. Have previously been treated with VP-102 for common warts.
5. Have more common warts to be treated than can be adequately covered with the contents of 2 applicators, in the opinion of the investigator.
6. Have had human papilloma virus (HPV) immunization within the last 6 months before enrollment. NOTE that HPV immunization may NOT be administered during the course of the trial. Other immunizations (e.g., flu shots) may be administered throughout the study, but not within 5 days before or after treatment.
7. Have had any previous treatment (including an investigational agent in a clinical trial) of common warts, including but not limited to the use of imiquimod, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, iodine-based or nitric oxide-based therapies, curettage, or freezing of warts in the 30 days before treatment; in addition, no treatments, including over-the-counter wart treatment, should be implemented during the study. The wash out period for cantharidin, candida antigen, diphenylcyclopropenone, dinitrochlorobenzene, squaric acid dibutyl ester, and any other immunomodulating treatment not otherwise specified is 45 days before Treatment Visit 1.
8. Have received another investigational product as part of a clinical trial within 30 days before the first application of the study drug.
9. Currently have or have a history of epidermodysplasia verruciformis.
10. Have an active malignancy or are undergoing treatment for any malignancy.
11. Have a history or presence of clinically significant medical, psychiatric, or emotional condition or abnormality that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.
12. Have a history or presence of hypersensitivity or an idiosyncratic reaction to the study drug or related compounds, or drug product excipients (acetone, ethyl alcohol, nitrocellulose, hydroxypropyl cellulose, castor oil, camphor, gentian violet, and denatonium benzoate).
13. Have a condition or situation that may interfere significantly with the subject's participation in the study *(e.g., subjects who required hospitalization in the 2 months before screening for an acute or chronic condition including alcohol or drug abuse),* at the determination of the investigator.
14. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods. (e.g., combination of condoms and foam, birth control pills, intrauterine device, patch, shot and vaginal ring, etc.). Withdrawal is not an acceptable method of birth control. Females that have reached menarche must have a negative urine pregnancy test at each visit before treatment with study drug.
15. Are pregnant or breastfeeding.

Test product, dose, and mode of administration: Study drug (VP-102 or Placebo) is contained within a single-use applicator. Study drug will be applied in sufficient quantity to cover the entirety of each wart, including approximately a 1 to 2 mm margin of surrounding, healthy skin. No more than the contents of 2 applicators may be applied at each treatment visit. Each VP-102 applicator contains 0.45 mL of 0.7% w/v cantharidin. The Placebo applicator contains the same formulation as the VP-102 applicator but does not contain the active pharmaceutical ingredient cantharidin.

Duration of treatment: Study duration from Treatment Visit 1 through the final follow-up visit is approximately 147 days (21 weeks). The length of study participation is approximately 84 (–0/+8) days for the EOT assessment (primary endpoint) and Study Day 147 (±7 days) to complete the study, in addition to the screening visit of up

to 30 days before study drug administration. The study will consist of up to four applications of study drug at intervals of 21 ±4 days. All treatments will take place within a 75-day period. No treatment should be administered after Day 75 without the sponsor's approval. Post-treatment Follow-up Visits on Study Day 84 (–0/+8 days) (EOT), Study Day 105 (±7 days), and Study Day 147 (±7 days) are included for subjects to evaluate the durability of treatment response over time.

Criteria for Evaluation

Efficacy endpoints

Primary endpoint:

- Proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84)

Key Secondary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84)

Secondary endpoints:

- Proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4
- Proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4
- Mean change from Baseline in the number of treatable warts (Baseline and new) at the EOT Visit (Day 84)
- Proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at the EOT Visit (Day 84)

Exploratory endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4
- Time to achieve onset of complete clearance of all treatable warts present at Baseline
- Proportion of subjects who continue to exhibit complete clearance of all treatable warts (Baseline and new) at Follow-up Visits on Day 105 and Day 147
- Mean change from Baseline in the number of treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4
- Percent change from Baseline in the wart area based on treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and at the EOT Visit (Day 84)
- Proportion of subjects who respond to treatment, defined as a $\geq$ 50% reduction in total wart area at the EOT Visit (Day 84) as compared to Baseline
- Mean change from Baseline of the composite score from the CDLQI assessment (subjects 4 to 16 years of age) and DLQI (subjects 17 years of age and older) at the EOT visit to measure the QOL and impact of skin disease
- Proportion of subjects exhibiting reduction of at least one treatable wart from Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and at the EOT Visit (Day 84)
- Proportion of subjects who continue to exhibit complete clearance of all treatable warts (Baseline and new) at Follow-up Visits on Day 105 and Day 147
- Mean number of treatments needed to achieve complete clearance of all treatable warts present at Baseline (for subjects who achieve complete clearance only)
- Mean number of new treatable warts that develop post-Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and EOT Visit (Day 84)

- Proportion of subjects who develop at least one new treatable wart post-Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and EOT Visit (Day 84)

Safety parameters

Safety analyses will include AEs, LSRs, medical history (including relevant illnesses and previous HPV immunization), physical examinations, vital signs, and concomitant medication use.

- The incidence of AEs will be assessed throughout the study; AEs will include all LSRs, whether or not they are expected or related to the anticipated pharmacodynamic response of the skin to VP-102, a vesicant
- The incidence of LSRs of all previously treated areas at each treatment visit using the protocol specific ERT form
- Summary of physical examination findings as reported before the first treatment and at the Study Day 84 (EOT) and Day 147 (end of study [EOS]) Visit; additional physical examinations will be performed when clinically warranted (e.g., subject reports symptoms classified as an AE requiring further evaluation)
- Mean change from Baseline in the Vital signs (temperature, heart rate and blood pressure) at each treatment visit and at the start of the Study Day 84 (EOT) Visit
- The incidence of concomitant medication use as collected at each study visit and ERT telephone contact

Statistical methods:

The study is expected to enroll and randomize approximately 606 subjects with at least 550 subjects with up to 6 common warts to test for treatment differences in the rates of complete clearance (primary endpoint). Subjects will be randomized and treated in a double-blind manner with either VP-102 or Placebo in a 1:1 ratio (approximately 303 subjects on VP-102 to 303 subjects on Placebo).

Analysis populations

- The Intent to Treat (ITT) Population will include all randomized subjects
- The Safety Population will include all randomized subjects who receive ≥ 1 application of study drug (VP-102 or Placebo)
- The Per Protocol (PP) Population will include all subjects who receive all planned treatments of study drug (e.g., complete up to four treatments within the Day 75 treatment window or clear before Day 75), had no major protocol violations, and were assessed for clearance at the Study Day 84 (–0/+8 days) EOT Visit

Sample size calculation

Study assumptions include the following:

- a 10% drop out rate,
- a 10% clearance rate for subjects treated with Placebo, and
- a 30% clearance rate for subjects treated with VP-102.

Using these assumptions, a sample size of 550 subjects with 1:1 allocation of VP-102/Placebo in each protocol based on a Pearson Chi-Square test with a two-sided significance level of 0.05 will provide ≥ 95% power to detect treatment differences in clearance rates for subjects with up to 6 warts at Baseline (primary endpoint). It is assumed that an additional 10% of subjects enrolled in the study will have >6 warts, resulting in a total of 606 subjects to be enrolled. Subjects will be stratified by wart location (palmar/periungual versus all other locations) and by number of warts (≤6 versus >6 warts).

Efficacy analyses

Efficacy analyses will be conducted in the ITT and PP Populations.

The primary objective of this study is to determine the efficacy of VP-102-treated subjects relative to Placebo-treated subjects in the treatment of common warts. The primary endpoint of this study is the proportion of subjects with 6 or fewer warts at Baseline who achieve investigator-assessed complete clearance of all treatable warts (Baseline and new) at the Day 84 EOT visit. The primary analysis will be conducted in the ITT population.

The key secondary efficacy endpoint, the proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84), will also be analyzed using the ITT population.

A logistic regression model, adjusting for baseline number of warts and wart location, will be used to compare the treatment and Placebo groups for the primary endpoint. The key secondary efficacy endpoint and other binary endpoints also will be analyzed with this method.

Continuous endpoints will be analyzed with an analysis of variance (ANOVA) model with a factor for the site a subject is enrolled in or an analysis of covariance (ANCOVA) model with a factor for the site a subject is enrolled in, wart location (palmar/periungual versus all other locations), and a covariate for number of Baseline warts.

All statistical tests will be two-sided with a significance level of $\alpha = 0.05$, unless specified otherwise. To protect the overall Type I error, the efficacy endpoints will be tested using a sequential testing procedure in a pre-specified order as defined in the SAP. The primary efficacy endpoint will be tested at $\alpha = 0.05$, and if significant, the key secondary endpoint will be tested at $\alpha = 0.05$. The remaining secondary endpoints will be tested in order if the key secondary efficacy endpoint is significant. Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for discrete variables. Corresponding by-subject data listings will be tabulated. Further details of analyses of other endpoints will be provided in the Statistical Analysis Plan.

Safety analyses

Safety analyses will be conducted in the Safety Population.

Adverse events, including LSRs, will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of subjects having treatment-emergent AEs will be tabulated by system organ class and MedDRA preferred term with a breakdown by treatment group.

Table 1. Study Schedule of Assessments and Procedures

Period	**Screen**	**Treatment Period 1**			**Treatment Period 2**			**Treatment Period 3**			**Treatment Period 4**			**Follow-up and Unscheduled Visits**		
Task	Screen[a]	Tx	24 hr In-person or Phone Call[b]	Phone Call[b]	Tx	24 hr Phone Call[b]	Phone Call[b]	Tx	24 hr Phone Call[b]	Phone Call[b]	Tx	24 hr Phone Call[b]	Phone Call[b]	EOT[c]	Follow-up[d]	Unscheduled Visit[e]
Study Day Post-treatment time for each period	**–30 to 1**	**1[f]**	24±6 hours	7 days ±24 hours	21±4 days[f]	24±6 hours	7 days ±24 hours	21±4 days[f]	24±6 hours	7 days ±24 hours	21±4 days[f]	24±6 hours	7 days ±24 hours	**84** (-0/+8 days)	**105, 147** ±4 days	
Informed consent and authorization	X															
Inclusion/ Exclusion criteria	X	X														
Prior relevant medical history	X	X														
Wart history	X	X														
Physical Exam[g]	X													X	X[g]	
Height/Weight[h]	X	X												X	X	
Vital signs (T/P; BP)[i]	X	X			X			X			X			X	X	X
Demographics[j]	X															
Wart Count[k] (BA Only)	X	X			X			X			X			X	X	
Wart location[l]	X	X			X			X			X			X	X	
Wart height[l]	X	X														

Wart Measurement (Diameter)[l]	X	X			X			X			X			X	X	
Paring[m]		X			X			X			X					
Dermatologic exam; (includes Fitzpatrick at Screen only)[n]	X	X			X			X			X			X	X	X
Photos (Site & 24 hr in-person)[o]		X	X		X			X			X			X	X	
QOL *(CDLQI; DLQI)* questionnaire[p]		X												X	X	
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[q]		X			X			X			X			X	X	
ERT assessments[r] (No BA)		X[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug application[s]		X			X			X			X					
Apply surgical tape[s]		X			X			X			X					
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Take-home instructions, LSR guide/subject education[t]		X			X			X			X					

Provider questionnaire[u]														X		

BA = Blinded Assessor; BP = blood pressure; CDLQI = Children's Dermatology Life Quality Index; eCRF = electronic case report form; EOS = end of study; EOT=end of treatment; ERT= evaluation of response to treatment; HIPAA = Health Insurance Portability and Accountability Act; hr = hour; ICF = Informed Consent Form; IRB = Institutional Review Board; LSR = local skin reactions; QOL = quality of life; T/P= temperature, pulse

a. Screening can occur up to 30 days before study drug application on Day 1. Screening can occur on the same day as Treatment Visit 1/study drug application. If treatment is not applied on the same day as Screening, measurement (height and diameter), location of all warts and dermatologic exam must be repeated before study drug application. An IRB-approved ICF/Assent must be signed before any study specific procedures are performed.
b. Phone assessments for ERT will be conducted at 24 (±6) hours and at 7 days (±24 hours) after each Treatment Visits 1-4 where Study Drug is applied. Assessments will be recorded by the research team member on the ERT form. For those participating in the photo sub-study, an in-person clinic visit at 24 (±6) hours will be conducted to obtain photos as well as the required ERT information.
c. A final in person safety assessment, ERT, photos and study completion form will be completed at the Day 147 (EOS) Visit (±4 days) for all subjects. EOS conducted outside the Day 147 EOS visit window will be considered a protocol deviation. Treatments may be administered up to Day 75. Subjects are to attend all visits whether they have achieved complete clearance before and at the Day 84 (- 0/+ 8 days) EOT assessment.
d. Subjects will return for Follow-up Visits on Day 105 and 147 (EOS) (±4 days at each visit) for an assessment of warts to determine the durability of previous responses and/or local skin responses.
e. "Unscheduled" visits may be completed when clinically warranted. (e.g. if a subject reports signs or symptoms classified as a treatment emergent AE and requires further evaluation) "Unscheduled" visits should also be used for visits where treatment is unable to be applied to all warts due to ongoing LSRs.
f. Subjects are to be scheduled in 21-day intervals (±4 days) after each treatment. The next Treatment Visit is to be scheduled 21 (±4 days) after the last treatment, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. The research team should be in contact with the patient until LSRs are resolved and a treatment visit can be scheduled within 21 days (±4) when possible. The 24-hour phone contact may be conducted at ±6 hours. The 7-day phone contact may be conducted ±24 hours.
g. Directed physical examination will be conducted at screening, EOT Day 84 and Day 147. Symptom or AE-directed physical examination may be performed if warranted (see Source/eCRF for a more detailed description)
h. Height and weight will be collected at Screening/Day 1, with additional weights at EOT Day 84 (- 0/+ 8 days) and subsequent Follow up Visits on Day 105 and Day 147 (EOS) (±4 days).
i. Vital signs: (e.g., temperature, heart rate and blood pressure) will be obtained at screening, before application of study drug, and EOT Day 84 (- 0/+ 8 days) and subsequent Follow up Visits on Day 105 and 147 (EOS) (±4 days). Blood pressure is to be obtained only for subjects who are ≥ 12 years of age.
j. Demographics: date of birth, sex, race/ethnicity will be collected.
k. A Blinded Assessor is required to perform wart counts before the ERT assessment at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, End of Treatment Visit (EOT), and Follow-up Visits on Day 105 and 147. The Blinded Assessor is not required to be the same person for each assessment.
l. Wart measurement of height and diameter will be obtained before treatment on treatment visit day 1 (after paring if required), with wart diameter only obtained at all remaining visits. Measurements of warts should be recorded on Day 1 before treatment to confirm they meet inclusion criteria of warts measuring with longest axis ≥ 3 and ≤ 8 mm; subjects with warts that exceed this size are not eligible for study participation.
m. Paring by dermatologist or qualified designee identified at the site. Paring is required if significant hyperkeratosis is present at investigator's determination.
n. Dermatologic exam including Fitzpatrick Skin Type, location of each wart is identified and documented on the body map and source. Wart location, measurements, and assessments are to be completed before each treatment application and/or each in-person visit. New warts should be recorded in the corresponding Source/eCRF.

o. Subjects who agree to participate in the photographic portion of the study will have photos of warts taken before each treatment by the study team. If there are no warts remaining, the same areas will be photographed and repeated at the Day 84 (EOT), 105 and 147 (EOS) regardless of whether warts are present. Subjects will also be asked to return to the clinic at 24(±6) hours after the first treatment visit for their ERT assessment and photos to obtain any LSR's that may have occurred. These images may be used on handouts in future trials, for training purposes or future marketing materials. (Photographs will be de-identified to those outside the research team and stored in a HIPAA compliant manner. Effort will be made to ensure that no photos with identifiable features are obtained).

p. QOL questionnaire to be completed by each subject at Treatment Visit 1, EOT on Day 84, and Follow up Visit on Day 147 only. Subjects from 4 to 16 years of age will complete the CDLQI and subjects 17 years of age and older will complete the DLQI. Subjects less than 4 years of age will not complete a QOL questionnaire.

q. To be performed before study drug application and at follow-up visit Day 84 (EOT), 105 and 147 (EOS) in any females of childbearing potential (females that are capable of menstruating).

r. ERT assessments will be recorded by the research team member on the ERT form. All ERT safety assessments must be conducted by a qualified member of the research team. Any qualified team member may conduct the screening and Treatment Visit Day 1 study activities. Any subsequent ERT and phone calls must be conducted by a study team member who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation. Subjects must attend all visits regardless of whether complete clearance of all warts has been achieved at a previous visit.

s. Surgical tape and study drug may be gently removed from individual warts before 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. The tape and study drug should not be removed from the remaining unproblematic warts until the 24-hour time point is reached. Removal of the tape should be aided by soap and water. This will also help to prevent unroofing the blisters. Subjects who remove study drug before 24 hours will be considered a protocol deviation if it does not meet the requirements for early removal as outlined in Section 8.2.2 of the protocol. Early removal is defined by removal at < 16 hours after treatment is applied.

t. Subjects will be given take-home instructions describing how to remove the surgical tape, the possible LSRs and what to expect over the next 24 hours to several months. A 24-hour emergency number will also be provided. The next visit date/calls and time will be indicated on the form. An LSR Guide for subjects will be reviewed at the clinic with the subject /guardian by the research team with copies provided for home use in the required 24-hour post treatment follow-up phone calls. Both take home instructions and LSR Guide will be provided and reviewed after each treatment to ensure understanding and confirm the education materials are available.

u. Provider questionnaire to be completed at EOT by a clinician that applied treatment to the subject during the course of the study.

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ANOVA	analysis of variance
ANCOVA	analysis of covariance
CDLQI	Children's Dermatology Life Quality Index
cm	centimeter
COVE	Cantharidin and Occlusion in Verruca Epithelium
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
EDC	electronic data capture
ERT	evaluation of response to treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papilloma virus
IARC	Interim Analysis Review Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat population
LLOQ	lower limit of quantitation
LSR	local skin reaction
MC, Molluscum	Molluscum contagiosum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mm	millimeter
PK	pharmacokinetic
PP	per protocol population
QOL	quality of life
SAE	serious adverse event
SOP	Standard Operating Procedure

TCA	trichloroacetic acid
TEAE	treatment emergent adverse event
µL	microliters
UV	ultraviolet
VP-102	Verrica Pharmaceuticals-102 (0.7% w/v cantharidin)

4.0 BACKGROUND AND RATIONALE

4.1 INTRODUCTION

4.1.1 Verruca Vulgaris (common warts)

Cutaneous viral warts (verruca vulgaris) are caused by the human papilloma virus (HPV) and are a common problem with an estimated lifetime incidence of 79%.[1] There are over 100 known serotypes of HPV in humans. The majority of cutaneous warts are caused by HPV serotypes 1, 2, 3, 4, 7, and 10. HPV is a DNA virus which infects epithelial cells. Viral replication only takes place in fully differentiated epithelium and the subsequent proliferation results in a clinically evident warty papule or plaque.

The clinical appearance of warts is variable and depends to some extent on the serotype of HPV involved and the anatomical site. HPV has a histone-coiled, double-stranded DNA genome of approximately 8000 base pairs. This genetic material is surrounded by a 60-nanometer capsid composed of two interlocking proteins (L1 & L2), but no envelope.[2] This lack of an envelope gives the virus significant stability in the environment, allowing it to remain a viable infectious agent for weeks, or even months before coming in contact with a suitable host.[3] Any epithelial surface can be affected, and different types of HPV tend to favor particular anatomical sites, but the most common infections are with HPV type 2 on the hands and feet. Warts on the feet are referred to as plantar warts and comprise 30% of cutaneous wart cases.[4]

In general, viral warts are uncommon in infancy, increasingly common in childhood, reach a peak in the teenage years, and decline sharply in prevalence thereafter. Non-genital warts in immunocompetent people usually resolve spontaneously with time, but this can take several years.[5]

Although usually benign, there are numerous reasons why patients may desire treatment. Warts represent a significant reservoir of HPV that can be transmitted from person to person, or autoinoculated to multiple sites on the same individual. Verrucae can cause pain or discomfort, interfering with work or daily activities.[6] Warts are frequently considered cosmetically unsightly, and unacceptable to the patient, particularly if they occur on visually prominent areas like the face, neck, arms, or hands. Importantly, the possibility of squamous cell carcinoma of the skin is believed to be enhanced by the presence of HPV, especially on skin damaged by extensive ultraviolet (UV) exposure. This effect has been well documented in individuals with epidermodysplasia verruciformis, immunosuppressed individuals, and transplant recipients; however, it is also suspected to play a role in some cases of squamous cell carcinoma in immunocompetent individuals.[7-9]

4.1.2 Treatments

There are a wide variety of different treatments for warts, but most are of limited effectiveness. Ablative and surgical treatments are among the most commonly used, with their mode of action being

the destruction of the wart through physical means (e.g., cryotherapy, electrodessication with or without curettage, lasers, infrared photocoagulation); surgical modalities (e.g., blunt dissection, excision); and organic acids/keratolytics (e.g., salicylic acid, bi- or tri-chloracetic acid, urea).

Other published modalities attempt to modify the way the skin and immune system interact with the infection, such as immunomodulators (e.g., imiquimod, intralesional interferon, mumps vaccine, human α-lactalbuminoleic acid, cimetidine, levamisole) and allergens (e.g., diphenylcyclopropenone, Candida extract, squaric acid dibutylester). Some therapies attempt to directly interfere with infected cell proliferation, like cytotoxins (e.g., bleomycin, 5-fluorouracil, podophyllotoxin, aminolevulenic acid) and vesicants (e.g., cantharidin). Some studies have suggested the use of simple occlusion with impermeable tape, although the efficacy of this has subsequently been shown to be lacking.[10] The large number of treatment options reflects the lack of consensus among experts on what the best treatment for common warts is, despite the fact that common warts are seen so often in dermatology and primary care clinics. Expert reviews fail to find that any one treatment is considerably better than the others,[11] and most authors agree that adequate clinical studies are lacking for many of the treatments, including those considered first line[10] and newer modalities that are being used in an "off-label" approach to treatment.[12]

The two most commonly used treatments for cutaneous warts are salicylic acid and aggressive cryotherapy. A Cochrane meta-analysis of 6 randomized clinical trials with a combined 486 patients evaluating efficacy found topical salicylic acid showed a statistically significant result over Placebo (RR 1.56, 95% CI 1.20 to 2.03). For cryotherapy, a meta-analysis of 3 randomized clinical trials involving a total of 227 patients showed 'surprisingly, no advantage of cryotherapy over Placebo (RR 1.45, 95% CI 0.65 to 3.23) using a random-effects model.[10] Salicylic acid therapy, while effective, requires daily compliance and can cause a painful burning sensation. Cryotherapy has limited efficacy and is very painful, so much so that most physicians do not treat children with cryotherapy if they have other options. Both of these therapies have the potential to leave long-term scars. Unfortunately, in many cases patients are dissatisfied with their outcomes, with some studies showing this to be the case up to 91% of the time.[13] This is cause for concern, as the common wart is ranked among the most frequent reasons that individuals seek evaluation in a dermatology practice.[14]

4.1.3 Cantharidin

Cantharidin (1,2-Dimethyl-3,6-epoxyperhydrophthalic anhydride) is a lipophilic natural compound obtained from the body fluids of the blister beetle, primarily of the family Meloidae. Blister beetles are found in many parts of the world, including the Southern United States and Asia (*Mylabris cichorii L* and *Mylabris phalerata*).[15, 16] In all cases the structure of the cantharidin molecule is maintained with only variations in the quantity of compound that can be readily isolated. The Mylabris species of beetle contains a much greater concentration of cantharidin and is the primary type of beetle used in modern cantharidin preparations, including the cantharidin in VP-102.

Cantharidin functions as a vesicant causing the pharmacodynamic response of blistering when applied topically to the skin. The hypothesized mechanism of this response is thought to be through the weakening of desmosomal junctions in the epidermis due to the activation of neutral serine proteases resulting in the destruction of intercellular desmosomes.[17] Cantharidin has not been demonstrated to have direct antiviral effects.

Many physicians prefer cantharidin to other therapies for the treatment of common warts such as cryotherapy and curettage or topical therapies such as salicylic acid, because it is painless upon application, requires only limited treatment cycles for significant lesion reduction or complete resolution, and is well-tolerated by patients. Further, cantharidin's long history of use has provided strong evidence of its safety when applied topically.[18]

Although cantharidin has been used extensively for decades in the treatment of several dermatologic conditions including verruca vulgaris, specifications for the quality of active pharmaceutical ingredient or a standardized formulation have never been established. Most currently used cantharidin preparations are 0.7% w/v solutions in an acetone solvent with a flexible-collodion base packaged in a screw-top glass bottle at volumes intended for repeated use across multiple patients by the medical professional. This type of container closure system paired with highly volatile formulations presents multiple challenges. Current clinical practice, which often reuses the same bottle on multiple patients, increases the risk of cross-contamination and viral transmission. Furthermore, due to the presence of volatile solvents in the preparation, evaporation from multiple uses heightens the risk of increased concentration and viscosity of the cantharidin in solution and creates a scenario where highly concentrated material may be applied to the patient's skin. Many formulations also lack formal stability studies and medical professionals often will just use the material until it is "too thick" to apply. Further, the nature of the liquid product coupled with the traditional application strategy of using the wooden part of a cotton-tipped swab makes it difficult to apply the minimum amount of drug necessary to achieve the desired effect. These factors may lead to unnecessary variability in the amount of drug being applied to the skin and may impact safety and efficacy.

4.1.4 VP-102

Verrica Pharmaceuticals Inc. (Verrica) has developed VP-102, a 0.7% w/v cantharidin formulation, consistent with the predominant concentration of cantharidin used by physicians. VP-102 is manufactured in a single-use applicator configuration to minimize cross-contamination and the potential changes in concentration over repeated uses. Each applicator contains 450 µL VP-102 drug product. The highly volatile solvent diethyl ether (a major component of flexible collodion) is replaced with additional acetone. Gentian violet, a dye common in surgical markers has also been included to facilitate healthcare provider recognition of treated versus untreated lesions. Finally, to afford additional safety and deter potential oral ingestion of the drug by young patients, the oral deterrent denatonium benzoate has been included.

4.2 Nonclinical Studies with Cantharidin

A full summary of the nonclinical pharmacology, pharmacokinetics, and toxicology information related to cantharidin, including information available in the published literature, is provided in the VP-102 Investigator's Brochure. Verrica has completed the recommended Good Laboratory Practices (GLP) hERG (human ether-à-go-go-related gene) assay (Study 170922.WFU), in vitro genotoxicity test battery and the requested nonclinical testing, including the GLP-compliant bacterial reverse mutation assay (Study AE58BG.502ICH.BTL), and the GLP micronucleus assay with calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) staining in TK6 cells, a human lymphoblastoid cell line (Study AE58BG.361CRESTICH.BTL).

For the proposed indication of verruca vulgaris, there are no animal models for assessing efficacy because of the species specificity of the HPV that causes common warts. However, the efficacy of cantharidin against common warts has been suggested by previously conducted clinical studies (Section 6.1 of the Investigator's Brochure [IB]). The therapeutic hypothesis is that the pharmacodynamic response of blistering and acantholysis from the topical treatment of cantharidin directly onto the infected skin lesion results in exfoliation of the wart. Epidermal irritation producing a localized inflammatory response and stimulation of the immune system may also play a role in clearing common warts. The mechanism of action of cantharidin in the treatment of warts is not known.

Cantharidin has been suggested to be a potent inhibitor of protein phosphatases types I and II that are found in all tissues.[19] The inhibition of these phosphatases may be involved in cantharidin's systemic manifestations when delivered orally or via injection (Section 6.1.1 of the IB). The available nonclinical studies to assess the potential for untoward pharmacodynamic effects of cantharidin with systemic exposure have largely focused on the cardiovascular system. With acute systemic exposure of rats to oral dosing with 6.9 mg/kg (41.4 mg/m2) of cantharidin, cardiac waveform and function were adversely affected, likely related to its inhibitory effect on protein phosphatases.[20] Cantharidin is a vasoconstrictor and may also be responsible for decreases in urine volume with single oral dose administration.[20, 21] However, it is possible that cantharidin may have a direct effect on the renal vascular and tubular epithelium via its inhibitory action on protein phosphatases. Cantharidin may also have an effect on central nervous system function,[20] although it is unclear whether noted decreases in locomotion and reduced body temperature were secondary to the cardiovascular manifestations noted with the high doses.

Information available on the pharmacokinetics (PK) and metabolism of cantharidin showed that oral absorption of cantharidin in rats and dogs is rapid but incomplete with peak systemic exposures occurring by 2 hours in rats (Section 6.2 of the IB).[22] The apparent plasma elimination half-life of cantharidin was about 20 minutes in dogs.[23] Tissue distribution of cantharidin was ubiquitous, consistent with the widespread distribution of protein phosphatases.

Nonclinical toxicity information available on cantharidin is predominantly from single dose (acute) studies by the dermal, oral, intraperitoneal, and intravenous routes of administration (Section 6.3 of the IB). The only adverse findings associated with acute dermal exposure to cantharidin in animals were local irritation and skin blistering. No systemic toxicity was noted by this route in animals.

4.3 Clinical Experience

Cantharidin has been used by healthcare providers for decades to treat verruca vulgaris. A summary of VP-102 Phase 2 and Phase 3 clinical studies are presented in Table 2. In addition to the summary information in Table 2, additional results are provided for three of the VP-102 studies:

- Results from a Phase 2 study (VP-102-105) evaluating the safety and efficacy of VP-102 in subjects with common warts (verruca vulgaris) are presented in Section 4.3.1.
- Two Phase 3 and three Phase 2 studies have been conducted in in subjects with molluscum contagiosum and results are summarized in the VP-102 IB.
    - Results from Phase 2 study VP-102-103 are presented in Section 4.3.2 because this study provides relevant information on the systemic exposure in subjects with molluscum after treatment with VP-102.
    - Results from Phase 2 study 16-10-195 are presented in Section 4.3.3 because this study treated subjects with molluscum for 6 hours and 24 hours.

Table 2. Phase 2 and Phase 3 Clinical Studies with VP-102

Study	Study Design	Objectives	Number of Subjects	Drug/Device and Dosing Regimen	Results
VP-102-105	Phase 2, Open-label	Primary: • To evaluate efficacy of dermal application of VP-102 to common warts by assessing proportion of subjects achieving complete clearance of all treatable warts at Day 84. • To assess safety and tolerability of VP-102 by assessing AEs including expected LSR, physical examinations, and concomitant medications. Secondary: • To evaluate efficacy of VP-102 by assessing change from baseline in number of treatable warts (baseline and new) at Day 84 • To evaluate efficacy of VP-102 by assessing change from baseline in percent clearance of treatable warts (baseline and new) at Day 84 • To evaluate efficacy of VP-102 by assessing proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and Day 84	Cohort 1: 21 subjects (≥2 years of age) with common warts (Verruca Vulgaris) Cohort 2: 35 subjects (≥12 years of age) with common warts (Verruca Vulgaris)	Cohort 1: VP-102 applied once every 14 days for up to 4 applications; paring of lesions NOT allowed Cohort 2: VP-102 applied once every 21 days for up to 4 applications; paring of lesions allowed	Cohort 1: 19% subjects had complete clearance wart count decreased 44% at Week 12 Cohort 2: 51% subjects had complete clearance wart count decreased 51% at Week 12 Most subjects in Cohort 1 and Cohort 2 had mild TEAEs related to study drug and LSRs; no SAEs or study drug discontinuations due to AE
VP-102 -101 (CAMP-1)	Pivotal Phase 3, randomized, double-blind, placebo-controlled	Primary: To evaluate efficacy (proportion subjects achieving complete clearance of all treatable lesions) of VP-102 relative to Placebo at Day 84 Secondary: • To assess safety and tolerability (AEs, LSRs, physical examinations, and concomitant medications) of VP-102 compared to baseline at Day 84 • To assess efficacy (proportion of subjects achieving complete clearance of all treatable	N=266 subjects with molluscum contagiosum lesions n=161 VP-102 n=105 Placebo (3:2 VP-102: Placebo randomization)	VP-102 solution and applicator Single 24-hour treatment every 21 days for up to 4 applications	Statistically significant primary efficacy endpoint met ($p<.0001$) Secondary efficacy endpoints met at Visits 2, 3, and 4 Confirmed safety and efficacy with VP-102 in applicator

Study	Study Design	Objectives	Number of Subjects	Drug/Device and Dosing Regimen	Results
		lesions) of VP-102 relative to Placebo at Visit 2, Visit 3, and Visit 4			
VP-102 -102 (CAMP-2)	Pivotal Phase 3, randomized, double-blind, placebo-controlled	Primary: To evaluate efficacy (proportion subjects achieving complete clearance of all treatable lesions) of VP-102 relative to Placebo at Day 84 Secondary: • To assess safety and tolerability (AEs, LSRs, physical examinations, and concomitant medications) of VP-102 compared to baseline at Day 84 • To assess efficacy (proportion of subjects achieving complete clearance of all treatable lesions) of VP-102 relative to Placebo at Visit 2, Visit 3, and Visit 4	N=262 subjects with molluscum contagiosum lesions n=150 VP-102 n=112 Placebo (3:2 VP-102: Placebo randomization)	VP-102 solution and applicator Single 24-hour treatment every 21 days for up to 4 applications	Statistically significant primary efficacy endpoint met ($p<.0001$) Secondary efficacy endpoints met at Visits 3 and 4 Confirmed safety and efficacy with VP-102 in applicator

Study	Study Design	Objectives	Number of Subjects	Drug/Device and Dosing Regimen	Results
VP-102 -103	Phase 2 open-label	Primary: To determine presence or absence of systemic cantharidin exposure from single 24-hour dermal application of VP-102 applied to molluscum lesions. Secondary: • To assess safety (AEs, LSRs, physical examinations, concomitant medications) of VP-102 • To assess efficacy (clearance or reduction of treated lesions compared to baseline) of VP-102. • To assess impact of VP-102 treatment on QOL (assessed via CDLQI)	N=33 subjects (all exposed to VP-102) with molluscum contagiosum lesions	VP-102 solution and applicator Single 24-hour treatment every 21 days for up to 4 applications	Negligible systemic exposure under maximal use conditions. Confirmed safety and efficacy with VP-102 in applicator.
Study 12-01-004	Phase 2	Safety and efficacy	N=94 subjects with molluscum contagiosum	Compounded topical cantharidin (0.7% w/v) applied with wooden stick 6-hour treatment every 21 days	Cantharidin was well tolerated and associated with the clearance of molluscum contagiosum.
Study 16-10-195	Phase 2	Safety and efficacy	N=30 subjects with molluscum contagiosum (all exposed to VP-102) Cohort 1: n = 14 Cohort 2: n =16	Topical VP-102 solution with wooden stick Cohort 1: 6-hour treatment every 21 days Cohort 2: 24-hour treatment every 21 days	VP-102 was well tolerated with similar efficacy compared to cantharidin 6-hour and 24-hour application demonstrated similar tolerability and efficacy

AE = adverse event; CDLQI = Children's Dermatology Life Quality Index; LSR = local skin reactions; N= number; QOL = quality of life; TEAE = treatment-emergent adverse event

4.3.1 Study VP-102-105: A Phase 2, Open Label Study to Evaluate the Efficacy, Safety and Tolerability of VP-102 in Subjects with Common Warts (Verruca Vulgaris)

This was a Phase 2, open label multi-center study [Study number VP-102-105; referred to as COVE-1 (Cantharidin and Occlusion in Verruca Epithelium)] conducted in the United States to determine the safety, efficacy and tolerability of VP-102 treatment in subjects with common warts. The primary objective of the study was to evaluate the efficacy of dermal application of VP-102 to common warts by assessing proportion of subjects achieving complete clearance of all treatable warts at Day 84. Cohort 1 utilized a treatment interval ≥ 14 days between treatments and no paring of lesions allowed. Cohort 2 utilized a treatment interval of 21 days between treatments with paring of lesions allowed. All subjects received VP-102 (0.7% cantharidin topical film forming solution) up to four times. Subjects were instructed to wash VP-102 off at 24 hours, or earlier if significant pain or blistering. Wart counts and adverse events (AEs), including local skin reactions (LSRs), were documented at each visit. Efficacy assessments included wart count (Cohort 1), measurement of diameter, and an evaluation of response to treatment (ERT).

The mean age was 38 years for the 56 subjects enrolled. The majority of subjects were female (58.9%), white (97%), and not Hispanic/Latino (97%), with a mean time since diagnosis of 16 days and no previous treatment for common warts (31%).

Treatment with VP-102 was well-tolerated. Most subjects in Cohort 1 and Cohort 2 had mild TEAEs related to study drug and LSRs; no serious adverse events (SAEs) or study drug discontinuations due to TEAE.

Clinically meaningful efficacy was obtained for the primary endpoint of complete clearance.

<u>Cohort 1</u>

- 19% subjects had complete clearance at Week 12
- Wart count decreased 44% at Week 12

<u>Cohort 2</u>

- 51% subjects had complete clearance at Week 12
- Wart count decreased 51% at Week 12

4.3.2 Study VP-102-103: Phase 2 Study Evaluating Safety, Efficacy and Systemic Exposure after VP-102 Treatment in Subjects with Childhood Molluscum

VP-102 in the proprietary applicator was determined to be safe in a 12-week, open-label, Phase 2 study (VP-102-103) implemented under Investigation New Drug (IND) application 131163/NCT03186378. The primary objective of the study was to evaluate the potential systemic exposure to cantharidin under maximum use conditions (> 21 lesions treated). Subjects ≥ 2 years of age with molluscum contagiosum were enrolled and treated with VP-102 (a single-use proprietary applicator containing a novel 0.7% w/v cantharidin solution) every 21 days for up to four treatments or until complete lesion clearance. Subjects were instructed to wash VP-102 off at 24 hours, or earlier if significant pain or blistering. Lesion counts and AEs, including LSRs, were documented at each visit. Quality of life (QOL) was measured using the Children's Dermatology Life Quality Index (CDLQI). A subset of 17 subjects with ≥ 21 Molluscum contagiosum (MC) lesions at Baseline were evaluated for systemic exposure with four blood samples (pre-dose and at 2, 6, and 24 hours post-dose). Key efficacy endpoints were percentage of subjects exhibiting complete clearance of all treated MC lesions (baseline and new) on or before Week 12 and percentage of reduction of treated MC lesions from baseline at Week 12.

The mean age was 6.7 (range 2-15) years for the 33 subjects enrolled. The majority of subjects were male (54.5%), white (90.9%), and not Hispanic/Latino (93.9%), with a mean time since diagnosis of 36 days and no previous treatment for molluscum (60.6%).

Treatment with VP-102 was well-tolerated. A total of 29 subjects (88%) reported at least one treatment-emergent adverse event (TEAE), including expected LSRs such as blistering or erythema. Most subjects had mild TEAEs; three subjects had moderate TEAEs. Overall, 21 (63.6%) subjects had TEAEs related to study drug, most of which were LSRs. There were no SAEs or TEAEs leading to premature study withdrawal.

Treatment with VP-102 was associated with significantly reduced lesion count, improved QOL, and complete clearance of MC lesions. Sixteen (16) subjects (48.5%) achieved complete clearance of all MC lesions on or before Week 12. The median lesion count was reduced 98% from baseline to Week 12. Decreases in mean CDLQI composite scores were observed, from 2.58 (standard deviation = 3.446) at Baseline to 0.38 (standard deviation =0.871) at Week 12. No subjects reported spread of molluscum lesions to any siblings during the study.

Plasma drug levels were below the limit of quantitation in 65 of 66 samples. In one subject, the level was slightly above the lower limit of quantitation 2 hours after VP-102 application but was not detectable at 6 and 24 hours. Importantly, no systemic cantharidin was detected in the patient with the highest number of lesions (113 lesions treated) nor in the two subjects with genital involvement.

In a separate double-blind, Phase 2 study (12-01-004), topical cantharidin (0.7% w/v) was well tolerated and associated with the clearance of MC in 94 subjects with childhood molluscum.[24]

4.3.3 Study 16-10-195: VP-102 Bridging Study of Subjects with Childhood Molluscum

A bridging study (16-10-195), conducted under IND 114032, was implemented to confirm VP-102's similarity in safety and efficacy to a 0.7% compounded cantharidin formulation used previously under the same IND. For this study, VP-102 was packaged in single-use, screw-top vials and applied with the wooden part of a cotton-tipped swab to two cohorts of subjects. The first cohort investigated a 6-hour treatment duration. A second cohort investigated a 24-hour treatment duration.

In total, 30 subjects were enrolled with childhood molluscum, 14 subjects in the 6-hour cohort and 16 subjects in the 24-hour cohort.

VP-102 was safe and well tolerated in the treatment of pediatric molluscum with both a 6-hour and 24-hour duration of exposure on the skin, consistent with historically used cantharidin formulations. There were no unexpected treatment-related AEs reported during application to molluscum lesions in 14 subjects in the 6-hour exposure cohort. Moreover, there were no treatment-related AEs reported with application to 712 lesions in 16 subjects in the 24-hour exposure cohort.

Overall, 11 out of 25 (44%) subjects showed complete clearance in the Per-Protocol (PP) Population. The 6-hour and 24-hour application demonstrated similar tolerability and efficacy in this study. VP-102 was similarly effective compared to compounded cantharidin, as evaluated in Study 12-01-004.

4.4 Summary of Known Benefits and Potential Risks

4.4.1 Potential Benefits

In a Phase 2 study of VP-102 conducted in subjects with common warts, clinically meaningful efficacy was obtained for the primary endpoint of complete clearance. It is

anticipated that subjects participating in this study who are randomized to the VP-102 group may experience some therapeutic benefit. Efficacy data for VP-102 and cantharidin are provided in Section 4.3.

Approximately 50% of the subjects enrolled in this study will be randomized to receive VP-102. A subject enrolled in the study, treated with either VP-102 or Placebo, may not benefit from their participation.

4.4.2 Known Risks

Clinical safety, efficacy, and PK data for VP-102 are provided in Section 4.3 and described in the IB. Nonclinical data for VP-102 are presented in Section 4.2 and described in the IB.

Although the study drug will be labeled exclusively for topical application and will be applied only by study personnel, the formulation also contains an oral deterrent (denatonium benzoate) to further help mitigate the risk of accidental ingestion, which could be toxic.

Cantharidin, when applied topically to the skin, results in the pharmacodynamic response of blistering and has the potential to cause severe chemical burns at high concentrations. Cantharidin taken internally can be poisonous to humans. Cantharidin is classified as an extremely hazardous substance in the United States and is subject to strict reporting requirements by facilities that produce, store, or use it in significant quantities.[25] However, publications have shown that cantharidin can be safely used to treat some benign skin lesions when formulated properly and applied in the clinic topically by a healthcare provider familiar with its effects and uses.[26]

The most frequently reported AEs in clinical trials with VP-102 conducted in subjects with MC were application site vesicles, application site scab, application site pain, application site erythema, and application site pruritus. These are well-known, reversible reactions of the skin that are related to the pharmacodynamic action of cantharidin, a vesicant. A less common reaction that has been reported with VP-102 and with compounded cantharidin is ring warts, an annular eruption of papilloma infection that increases the size of the treated wart. This reaction has been described with other wart treatments including cryosurgery.

4.4.3 Potential Risks

Cantharidin is a member of the Terpenoid Class. The Terpenoid Class is a large and diverse class of naturally occurring organic chemicals derived from terpenes.

Because there may be unknown and potential risks with administration of VP-102, all subjects will be closely monitored for safety and tolerability by repeated assessment of clinical, vital signs, and reporting of AEs.

4.4.4 Risk-Benefit Summary

Overall, based on risk/benefit analysis, the current study appears to be fully justified in the planned population of subjects with common warts.

4.5 Justification for Dosing Regimen

A 0.7% w/v cantharidin solution is the recognized therapeutic dose of cantharidin for both molluscum and wart treatment in dermatological clinical practice.[18, 27-30] VP-102, with a 0.7% w/v dose applied every 21 days, was determined to be safe for the treatment of molluscum in two randomized, double-blind vehicle-controlled Phase 3 studies (VP-102-101 and VP-102-102; see Table 2) enrolling over 500 subjects, the majority of which were pediatric. Additionally, multiple publications have demonstrated safety and efficacy with a 0.7% cantharidin solution in common warts both with and without the use of a surgical tape. Study VP-102-105 (see Section 4.3.1) demonstrated the safe and effective use of VP-102 in 35 subjects (Cohort 2) with common warts using a 21-day dosing regimen. Cohort 2 allowed paring of warts and demonstrated numerically higher proportion of subjects with complete clearance compared to Cohort 1 (n=21 subjects), which did not allow paring and utilized a treatment interval ≥ 14 days between treatments.

There have been no randomized controlled trials to test the frequency of cantharidin application of the specific treatment protocol in common warts. However, multiple publications and current clinical practice suggest that paring, occlusion, and a 1- to 3-week treatment interval are often utilized. A 3-week (21-day) interval, using both occlusion and paring will be used in this study. Additionally, as observed in Cohort 1 of Study VP-102-105, it can sometimes be challenging to determine if a wart is completely cleared in 14 days post treatment due to ongoing LSRs. Hence, the treatment interval is 21 days to allow adequate time for LSRs to resolve to enable evaluation of the treatment site.

In this study, lesions will be covered with surgical tape, a technique often used in the treatment of warts with cantharidin. The use of surgical tape in this manner will protect the treated lesions from being spread to other body surfaces and may facilitate drug penetration into the hyperkeratotic tissue. Paring of lesions will be conducted before measurement and treatment to remove any excess hyperkeratotic tissue and improve drug penetration into the wart. Once pared, lesions should be measured to confirm they meet the entry criteria of longest axis ≥ 3 and ≤ 8 mm; subjects with warts that exceed this size are not eligible for study participation.

Investigators are to treat a 1 to 2 mm margin of healthy skin surrounding each wart. This treatment ensures optimal debridement of infected keratinocytes. Human papilloma virus (HPV) has been detected in the normal appearing skin adjacent to a warts and therefore the

clinically identified borders of a wart are unlikely to represent the entirety of the skin infected with HPV.[31] This phenomenon likely contributes to the clinical observations of wart recurrence after treatment independent of treatment modality, as well as the typical pattern of wart clustering in discrete locations on the skin. The small margin of treatment 1-2 mm beyond the clinically observed border ensures that blister formation will include the entire wart to an adequate depth and also addresses the potential for HPV infection in the skin immediately adjacent to the wart being treated in an attempt to reduce the occurrence of ring warts which have been observed with VP-102 and compounded cantharidin treatment of common warts. The cause of ring warts is not known, but has been hypothesized that they may occur when subclinical infected tissue surrounding the visible wart is disturbed but not removed or destroyed.

No more than two applicators may be used per treatment visit on each subject.

4.6 Population to be Studied

In this study, subjects ≥ 2 years of age with common warts are to be included. The primary objective of the study will be assessed in subjects with ≤6 warts at Baseline, although enrollment into the study will take place with no upper limit placed on wart number in the eligibility criteria. This methodology allows the study to enroll an 'all comer' population that reflects the general population of patients at-large with common warts, while enabling a primary objective to address the population of patients with up to 6 warts at Baseline which has been identified by health care providers as the upper limit for warts typically treated during a therapeutic intervention.

Subjects are required to have:

- Treatable common warts (verruca vulgaris);
    - Common warts are considered treatable if they are located anywhere on the body except for the following prohibited areas: the eye area (including eyelids), lips, oral cavity, nasal cavity, inside of the ears, subungual (under the fingernails), soles of the feet, or the anogenital area *(Warts within 10 mm of a mucosal surface should not be treated).*
    - Common warts located in prohibited areas and warts that are verruca plana, filiform, subungual, genital, or anal are excluded from treatment and evaluation in this study. A subject will not be excluded from the study if they have these types of warts, but the subject must also have warts that meet the inclusion criteria. If treatment of these excluded wart types is required during the study, it should be limited to cryosurgery, laser, and curettage.
    - Subjects cannot have any warts present at Baseline in an allowed anatomic location that the subject, parent/guardian, or the investigator is unwilling to treat.

- Warts that measure at longest axis ≥ 3 and ≤ 8 mm in diameter;
  - Subjects with warts that exceed this size are not eligible for study participation.
  - Subjects with warts that are adjacent, touching or clustered may be included so long as the combined diameter at the longest axis does not exceed 8 mm and meets the minimal size of 3 mm.
  - Individual lesions that are touching or clustered should be counted as one lesion for the purposes of tracking, inclusion, and clearance.
- Warts present for ≥ 4 weeks at the time of the Baseline Visit

4.7 Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCP), the ethical principles of the Declaration of Helsinki, and applicable regulatory and Institutional Review Board (IRB) or Independent Ethics Committee requirements.

4.8 Study Rationale

For many dermatologists, 0.7% w/v cantharidin has been the treatment of choice for warts for decades.[27] However, cantharidin remains an unapproved drug, and there is no reliable or controlled source on the market. This study will evaluate VP-102, a highly pure, standardized form of topical cantharidin manufactured under Good Manufacturing Practices to demonstrate the safety and efficacy of VP-102 in subjects with common warts.

5.0 STUDY PURPOSE AND OBJECTIVES

Primary Objective

- To evaluate the efficacy of dermal application of VP-102 relative to Placebo, when applied once every 21 days for up to four applications to common warts by assessing the proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84).

Key Secondary Objective

- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects achieving complete clearance of all treatable warts (Baseline and new) at the end of treatment (EOT) visit (Day 84).

Secondary Objectives

- To assess the safety and tolerability of VP-102 relative to Placebo, by assessing physical examinations, concomitant medication use, and AEs including expected LSRs.
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4.
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4.
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the change from Baseline in the number of treatable warts (Baseline and new) at the EOT visit (Day 84).
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at the EOT visit (Day 84).
- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts present at Baseline at the EOT visit (Day 84).

Exploratory Objectives

- To evaluate the efficacy of VP-102 relative to Placebo by assessing the proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4.

- To evaluate the efficacy of VP-102 relative to Placebo with respect to the time to achieve onset of complete clearance of all treatable warts present at Baseline.
- To evaluate the efficacy of VP-102 by assessing the proportion of subjects who continue to exhibit complete clearance of all treatable warts (Baseline and new) at Follow-up Visits on Day 105 and Day 147.
- To evaluate the impact on quality of life (QOL) by assessing the change from Baseline of the composite score from the Children's Dermatology Life Quality Index (CDLQI) assessment (subjects 4 to 16 years of age) and Dermatology Life Quality Index (DLQI) (subjects 17 years of age and older) at the EOT Visit (Day 84).
- To assess endpoints other than complete clearance that may be indicative of treatment efficacy.

6.0 STUDY DESIGN

6.1 Description of the Study

This is a Phase 3, double-blind, randomized, placebo-controlled study (Study number VP-102-106; referred to as COVE-2 [Cantharidin and Occlusion in Verruca Epithelium]) to evaluate the efficacy, safety and tolerability of VP-102 treatment in subjects with common warts.

The study utilizes a treatment interval of 21 days between treatments. Approximately 606 subjects (2 years and older) will be enrolled, with at least 550 subjects with 6 or fewer warts. Approximately 23 sites will participate in the study.

6.1.1 Subject Participation

Pre-study screening for eligibility (informed consent and assent [when applicable]), demographics, physical exam, prior and current concomitant medications and medical history can occur up to 30 days before, or on the same day as the first study drug application. To assess eligibility, a dermatologic exam and measurement of diameter and height (paring can be performed, if necessary, before assessing height) of each wart will be conducted by a qualified member of the research team before the first treatment. The dermatologic exam, measurements, location of all warts and ERT must be repeated if not conducted on the same day as treatment. Warts must have a longest axis that measures ≥ 3 and ≤ 8 mm. Full inclusion/exclusion criteria are provided in Section 7.0.

Subjects who do not continue to meet criteria at Treatment Visit 1 will be considered Screen Failures, discontinued and treated at physician determination per standard of care.

Subjects who meet the enrollment criteria at Treatment Visit 1 will be randomized and treated with application of VP 102 or Placebo. Treatment will continue every 21 (±4 days) until complete clearance or a maximum of four treatment sessions during the 75-day treatment period. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. Subjects will be required to return for every treatment and follow-up visit whether or not their warts have cleared. Phone follow-ups will be conducted per protocol for those instances where the subject was treated.

Subjects will be given take home instructions describing what they might expect throughout the course of the study, as well as recommendations for wound care, when it is important to call their doctor, and instructions for who to contact in an emergency. In addition, an LSR guide will be provided and reviewed in detail at the clinic with the subject/guardian and used for reference by the subject/guardian during assessments conducted via phone call.

6.1.2 Treatment

Subjects will either receive study drug containing 0.7% cantharidin topical solution or Placebo (vehicle). Instructions for application of the study drug are outlined in the Instructions for Use included in the site regulatory packet and drug shipment.

Treatment will be applied up to four times during a 75-day treatment period. The treatment interval is 21 days. It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing LSRs. At any visit where the investigator is unable to evaluate or treat some warts due to ongoing LSRs, an "Unscheduled" visit should be documented. The timing of the next visit will be determined by the resolution of the local skin reaction. The research team should be in contact with the patient until LSRs are resolved and Treatment Visit can be scheduled within 21 days (±4) when possible. A Treatment Visit should be documented at every visit in which study drug is applied. Treatment should only take place at a visit when all warts are evaluable (i.e., not obscured by an ongoing LSR) and all warts that are not completely clear, should undergo treatment with study drug. No partial treatment of warts is permitted unless a subject would be required to exceed the maximum number of two applicators per treatment session in order to complete treatment.

Study drug is to be applied to the wart site on any Treatment Visit in which a new clinical assessment of complete clearance is made for that wart (e.g., if a patient returns for Treatment Visit 2 and is clinically assessed to have no visible evidence of remaining wart, then study drug is to be applied to this wart site at Treatment Visit 2. However, if the patient remains completely clear at that wart site when returning for Treatment Visit 3, then no study drug would be applied at Treatment Visit 3).

In instances in which the clinician can adequately assess the treatment sites, but is uncertain if residual wart is remaining, treatment should be applied, and the subject should return for evaluation per protocol. Treatment visits are to take place in order (e.g., Treatment 1, Treatment 2, Treatment 3 and Treatment 4). Subjects who receive less than four treatments within the 75-day treatment period, due to the duration of post-treatment LSRs, will not be considered a protocol deviation. No treatment should be administered after the 75-day treatment period without sponsor's approval.

Subjects will be required to attend all treatment visits regardless of whether they have achieved complete clearance of all warts at a previous visit. Once the investigator has determined a wart is clear, an additional treatment to the area should be applied. If the wart remains clear, additional treatments will not be required however the subject is to return for all subsequent visits as outlined in the protocol. Subjects who have completed their Day 84 EOT Visit (- 0/+ 8 days) will be assessed at two additional Follow-up Visits on Day 105 and Day 147.

All subjects will receive application of the study drug (VP-102 or Placebo) to common warts including a 1 to 2 mm margin of healthy, surrounding skin with an interval of every 21 days, until complete clearance of all treatable warts, or a maximum of four applications. Warts are to be treated and then covered with transparent surgical tape (e.g.; 3M™ Blenderm™ brand) that will remain on overnight and removed just before the 24-hour ERT phone call.

Subjects will undergo wart paring with a sharp surgical instrument (e.g., scalpel or flexible medical blade) to remove any adherent thick scale from a wart before application of study drug. Wart paring is required to be performed at any Treatment Visit when adherent thick scale is present, and the investigator considers that it can be safely applied. Paring should be conducted by a trained practitioner (e.g., a dermatologist or qualified designee identified at the site) and in compliance with any local regulations and should be discontinued when it results in punctate bleeding or significant pain. Not all warts may require paring and if adherent scale is not present, then study drug can be applied without paring.

Subjects should be retreated only after 17 days (i.e., 21 ±4 days) have elapsed, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. Subjects are to attend all visits regardless of whether they have achieved complete clearance before the EOT Day 84 (- 0/+ 8 days) assessment.

In the event a subject develops ring wart during the course of treatment, it is recommended that this be reported as an AE and treatment be continued with VP-102 per protocol. However, it is up to the investigator's determination to either continue treatment of that wart with VP-102, continue treatment of any other warts with VP-102 and discontinue treatment of the ring wart, or remove the subject from the study.

6.1.3 Removal of Study Drug

At 24 hours (±8 hours) after drug application, subjects are instructed to wet the treated area with water and then carefully and slowly remove the surgical tape from each wart, pulling the tape back over itself in a low and slow manner, trying not to unroof any intact blisters. Treated warts should be gently washed with soap and water after the tape is removed.

Note: The surgical tape and study drug may be gently removed from individual warts before 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. Subjects who remove study drug before 24 hours will be considered a protocol deviation if it does not meet the requirements for early removal as outlined in Section 8.2.2 of the protocol. Early removal is defined as removal before ≥ 16 hours have passed from study drug application.

The surgical tape and study drug should not be removed from any remaining unproblematic warts until the 24-hour (±8 hours) time point is reached. Washing of intact blisters should be gentle and without use of a washcloth. Washing and removal of surgical tape in a bath or shower is encouraged.

6.1.4 Assessments and Procedures

Assessments and procedures (Table 1) will include measurement of diameter and an ERT, before treatment application when applicable. All required study activities, including ERT evaluations, will be conducted per protocol. If new warts are identified during the course of the treatment period, they should be documented, evaluated, and treated per protocol.

A Blinded Assessor is required to perform wart counts before the ERT assessment at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, End of Treatment Visit (EOT), and Follow-up Visits on Day 105 and 147. The Blinded Assessor is not required to be the same person for each assessment.

An in-person ERT will also be conducted at every visit before study drug application. The ERT includes questions related to removal of the surgical tape and study drug, if applicable, and records the intensity of any LSRs, including AEs, and concomitant medications. The subject and/or guardian will have time to ask questions and review any concerns. In the event that any post-treatment LSR presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain), an “Unscheduled” clinic visit must be scheduled, and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an “unscheduled” visit.

For those visits where subjects have received treatment, additional ERT assessments will be conducted over the phone at 24 hours and 7 days after each Treatment Visit (not “Unscheduled” visits) to assess if there have been any AEs or if new warts have occurred. Phone calls conducted outside of the required 24-hour and 7-day study ERT assessments should be documented in the subject’s source note but are not required to be entered into the electronic data capture (EDC).

All ERT safety assessments must be conducted by a qualified member of the research team. Any qualified team member may conduct the screening and Treatment Visit Day 1 study activities. Any subsequent ERT and phone calls must be conducted by a study team member who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject’s participation.

Subjects will participate in an in-person EOT evaluation at Day 84 (- 0/+ 8 days). A provider End of Study Treatment Questionnaire will be completed at the EOT Visit.

Subjects will continue in the study for two additional follow-up assessments at Day 105 and Day 147 (±4 days).

At designated sites, subjects will be asked if they are interested in participating in a sub-study where photos of their treated warts will be obtained. See Section 9.7.5 Photographs of Lesions for full details.

6.2 Number of Subjects

Approximately 606 subjects will be enrolled and randomized (1:1) to VP-102 or Placebo, with at least 550 subjects with 6 or fewer warts. Enrollment will be allowed to exceed 606 subjects if required in order to meet this minimum of 550 subjects with 6 or fewer warts.

6.3 Measures Taken to Minimize Bias

Bias is minimized by subject randomization and blinding (Section 6.5).

6.4 Expected Duration of Subject Participation

Study duration from Treatment Visit 1 through the final follow-up visit is approximately 147 days (21 weeks). The length of study participation is approximately 84 (–0/+8) days for the EOT assessment (primary endpoint) and Study Day 147 (±4 days) to complete the study, in addition to the screening visit of up to 30 days before study drug administration. The study will consist of up to four applications of study drug at intervals of 21 ±4 days. All treatments will take place within a 75-day period. No treatment should be administered after Day 75 without the sponsor's approval. Post-treatment Follow-up Visits on Study Day 84 (–0/+8 days) (EOT), Study Day 105 (±4 days), and Study Day 147 (±4 days) are included for subjects to evaluate the durability of treatment response over time.

6.5 Method of Treatment Assignment and Blinding

After informed consent has been obtained, subjects will be assigned a Subject ID number and screened for study eligibility up to 30 days before or on the same day as Treatment 1/Day 1. Subjects who meet eligibility criteria on Day 1 will be randomized (1:1) to VP-102 or Placebo by the research staff utilizing an Interactive Response Technology (IRT) system. A subject is considered randomized when the randomization transaction is recorded in IRT.

In order to reduce possible functional unblinding and bias, Blinded Assessors will conduct lesion counts while separate trained members of the research team will conduct safety assessments and evaluations of response to treatment. A Blinded Assessor is a trained research team member that is not aware of a subject's ongoing response to treatment. The Blinded Assessor's role is to count and record the number of lesions at all visits after

Treatment Visit 1. After Treatment Visit 1 individuals designated as Blinded Assessor will not conduct any safety assessments including those ERT assessments conducted over the phone. It is not required that the Blinded Assessor be the same person for each subject study visit.

The sponsor will remain blinded to study medication assignment until the study is completed and the database is locked, with the exception of cases in which unblinding is required due to a safety or tolerability issue. In the case of a medical emergency requiring the Principal Investigator to know the identity of the study drug, the Principal Investigator will follow the procedures outlined in Section 8.6.

7.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

This study will enroll and treat approximately 606 subjects, ≥ 2 years of age, presenting with treatable common warts. Approximately 23 sites will participate in the study. Eligibility to participate in the study will be determined by the investigator on the basis of the inclusion and exclusion criteria.

7.1 Subject Inclusion Criteria

To qualify for inclusion in this study, subjects must:

1. Be healthy, immunocompetent males or females ≥ 2 years of age
2. Present with treatable common warts (verruca vulgaris):
    a. Common warts are considered treatable if they are located anywhere on the body except for the following prohibited areas: the eye area (including eyelids), lips, oral cavity, nasal cavity, inside of the ears, subungual (under the fingernails), soles of the feet, or the anogenital area *(Warts within 10 mm of a mucosal surface should not be treated).*
    b. Common warts located in prohibited areas and warts that are verruca plana, filiform, subungual, genital, or anal are excluded from treatment and evaluation in this study. A subject will not be excluded from the study if they have these types of warts, but the subject must also have warts that meet the inclusion criteria. If treatment of these excluded wart types is required during the study, it should be limited to cryosurgery, laser, and curettage.
    c. Subjects cannot have any warts present at Baseline in an allowed anatomic location that the subject, parent/guardian, or the investigator is unwilling to treat.
3. Have warts that measure at longest axis ≥ 3 and ≤ 8 mm; subjects with warts that exceed this size are not eligible for study participation. *Subjects with warts that are adjacent, touching, or clustered may be included so long as the combined diameter at the longest axis does not exceed 8 mm and meets the minimal size of 3 mm. Individual lesions that are touching or clustered should be counted as one lesion for the purposes of tracking, inclusion, and clearance.*
4. Have warts that have been present for ≥ 4 weeks at the time of the Baseline Visit.
5. Be free of any systemic or dermatologic disorder, which, in the opinion of the investigator, will interfere with the study results or increase the risk of AEs.

6. Refrain from swimming, bathing or prolonged immersion in water or any liquids until the study drug is removed after each treatment.
7. Have the ability, or have a guardian with the ability, to follow study instructions and be likely to complete all study requirements.
8. Agree to use no wart-removing product (prescription or over-the-counter) other than the study drug during the course of the study, with the exception of circumstances allowed under Inclusion Criterion 2b.
9. Provide written informed consent or assent in a manner approved by the IRB and/or have a parent/guardian provide written informed consent as evidenced by the signature on an IRB approved assent/consent form.
10. Provide written authorization for use and disclosure of protected health information.
11. If participating in the optional photographic sub-study, agree to allow photographs of warts to be taken at selected visits by the research team.

7.1 Subject Exclusion Criteria

Candidates will be excluded from the study if they:

1. Are unable to cooperate with the requirements or visits of the study, as determined by the investigator.
2. Are systemically immunosuppressed or have required systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days before enrollment or are planned to be required during the course of the study. (Routine use of local [e.g., topical, inhaled, or intranasal] corticosteroids and episodic use of systemic medications to treat conditions arising during the study is allowed).
3. Have any chronic or acute medical condition that, in the opinion of the investigator, may interfere with the study results or place the subject at undue risk. (e.g., human immunodeficiency virus, systemic lupus erythematosus, viral hepatitis, uncontrolled diabetes).
4. Have previously been treated with VP-102 for common warts.
5. Have more common warts to be treated than can be adequately covered with the contents of 2 applicators, in the opinion of the investigator.
6. Have had HPV immunization within the last 6 months before enrollment. NOTE that HPV immunization may NOT be administered during the course of the trial. Other immunizations (e.g., flu shots) may be administered throughout the study, but not within 5 days before or after treatment.

7. Have had any previous treatment (including an investigational agent in a clinical trial) of common warts, including but not limited to the use of imiquimod, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, iodine-based or nitric oxide-based therapies, curettage, or freezing of warts in the 30 days before treatment; in addition, no treatments, including over-the-counter wart treatment, should be implemented during the study. The wash out period for cantharidin, candida antigen, diphenylcyclopropenone, dinitrochlorobenzene, squaric acid dibutyl ester, and any other immunomodulating treatment not otherwise specified is 45 days before Treatment Visit 1.
8. Have received another investigational product as part of a clinical trial within 30 days before the first application of the study drug.
9. Currently have or have a history of epidermodysplasia verruciformis.
10. Have an active malignancy or are undergoing treatment for any malignancy.
11. Have a history or presence of clinically significant medical, psychiatric, or emotional condition or abnormality that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.
12. Have a history or presence of hypersensitivity or an idiosyncratic reaction to the study drug or related compounds, or drug product excipients (acetone, ethyl alcohol, nitrocellulose, hydroxypropyl cellulose, castor oil, camphor, gentian violet, and denatonium benzoate).
13. Have a condition or situation that may interfere significantly with the subject's participation in the study (e.g., subjects who required hospitalization in the 2 months before screening for an acute or chronic condition including alcohol or drug abuse), at the determination of the investigator.
14. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods. (e.g., combination of condoms and foam, birth control pills, intrauterine device, patch, shot and vaginal ring, etc.). Withdrawal is not an acceptable method of birth control. Females that have reached menarche must have a negative urine pregnancy test at each visit before treatment with study drug.
15. Are pregnant or breastfeeding.

7.2 Requalification for Entry

Subjects not fulfilling the entry criteria and not randomized may be rescreened once for participation if their eligibility characteristics have changed.

7.3 Subject Withdrawal Criteria

Subjects are encouraged to complete the study, but can withdraw consent at any time during the study and for any reason without any penalty or changes to care. The investigator will provide a written explanation of the reason for discontinuation in a source document and this information will also be recorded on the appropriate electronic case report form (eCRF) page. If a subject withdraws before completion, every effort should be made to complete the end of EOT Day 84 and (EOS) (Study Day 147 ±4 days) assessments. A subject may also discontinue study medication, rather than withdraw from the study altogether, in which case they are encouraged to continue study participation according to the protocol with the exception of activities related to study drug application.

A subject may be withdrawn from the study for the reasons described in Section 7.3.

Data collected to the point that the subject withdraws or is withdrawn are still assessable by the investigator. If subjects do not want their data that has already been submitted, they will need to submit a request in writing to the investigator for removal of their information.

Subjects enrolled in this study will be eligible to enroll in a Long Term Extension (LTE) study to evaluate the safety and efficacy of VP-102 over 54 weeks. Subjects who have not achieved complete clearance of all warts at Day 84 and those that have new warts or recurrence of previously treated warts after Day 84 will be eligible to transition into the LTE study where they can receive open-label VP-102 treatment. In addition, subjects that complete EOS (Day 147) of this study will be eligible to transition to the LTE for continued follow up as well as treatment with open-label VP-102, if needed.

7.3.1 Adverse Event

If a subject experiences an AE that, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the subject, the subject may be discontinued from the study. In this instance, and in the opinion of the investigator, the subject may be discontinued only from study medication, rather than withdraw from the study altogether, in which case they are encouraged to continue study participation according to the protocol with exception of activities related to study drug application.

7.3.2 Intercurrent Illness

A subject may be discontinued from the study if, in the judgment of the investigator, the subject develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal from the study.

7.3.3 Noncompliance

After the investigator, the medical monitor and/or study monitor consult (and the sponsor if appropriate), a subject may be discontinued from the study for the following administrative reasons:

- Failure to receive study medication or treatment as mandated by the specific instructions provided in Section 8.0
- Failure to comply with protocol requirements

7.3.4 Refusal of Investigational Product Administration

Any subject refusing clinical trial material for any reason will be discontinued from the study activities related to study drug application, but is encouraged to otherwise continue study participation. If a subject is unwilling to continue in the study, the reason(s) for their discontinuation will be documented on the appropriate eCRF page. Reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments after treatment discontinuation. These efforts should be documented on the appropriate eCRF page.

7.3.5 Withdrawal of Consent

Any subject who withdraws consent for any reason at any time during the study will be discontinued from the study, and the reason(s) will be documented on the appropriate source and eCRF page. If subjects do not want their data that has already been submitted, they will need to submit a request in writing to the investigator for removal of their information.

7.4 Replacement of Subjects

Subjects prematurely withdrawn from the study as dropouts (e.g., enrolled in the study but never received study drug, did not complete the EOT and EOS assessments), for noncompliance, or who request to be withdrawn from the study may be replaced at the determination of the sponsor. All subjects randomized will be accounted for in the analysis, and no subjects' data will be replaced.

7.5 Premature Study or Site Termination

If the sponsor, investigator, medical monitor, study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the site should be terminated, this action may be taken by the sponsor after

appropriate consultation among the sponsor, investigator, medical monitor, and study monitor. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product
- Termination of study conduct at an individual site may also be warranted under the following conditions:
    - Failure of the investigator to enroll subjects into the study at an acceptable rate
    - Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities
    - Submission of knowingly false information from the site to the sponsor, study monitor, or appropriate regulatory authority
    - Insufficient adherence to protocol requirements

Study termination and follow-up will comply with the conditions set forth in International Council for Harmonisation (ICH) E6, Guideline for GCP. Data from all sites, including those that have been terminated for non-compliance or unsatisfactory enrollment will be evaluated and included in the interpretation of study findings. Subjects from sites that terminate early will be considered for analysis. If a subject does not complete the study, they will still be counted as a failure for the primary endpoint.

8.0 STUDY DRUGS

8.1 Investigational Agent and Placebo

The VP-102 applicator contains 0.45 mL of 0.7% w/v cantharidin. The Placebo applicator contains the same formulation as the VP-102 applicator, but does not contain the active pharmaceutical ingredient cantharidin.

Although the study drug will be labeled exclusively for topical application, the formulation also contains an oral deterrent (denatonium benzoate) to further help mitigate the risk of accidental ingestion. The study drug is light violet to dark purple in color and has been manufactured under Good Manufacturing Practices.

8.2 Directions for Use

8.2.1 Application of Study Drug and Surgical Tape

Study drug (VP-102 or Placebo) is contained within a single-use applicator. No more than the contents of two applicators may be used per treatment visit on each subject.

Following examination, the product is applied to the skin as a viscous solution, at which point the solvents evaporate, leaving behind a thin, flexible, and resilient film. Study drug will be applied in sufficient quantity to cover the entirety of each wart, including approximately a 1 to 2 mm margin of surrounding, healthy skin. Observe subjects for 2 to 5 minutes after study drug application or until the film is formed and totally dry.

Surgical tape should be applied to lesions that have been treated and gently rubbed in order to maximize adherence to the treated area. Tape MUST NOT be applied until the product is completely dry (approximately 2-5 min). The size of the piece (or pieces) of surgical tape used is based upon investigator determination, provided that all treated warts are covered, and the surgical tape size is deemed sufficient to maintain adherence for the assigned duration of skin exposure. An adhesive bandage may be applied over the surgical tape if needed for flexible areas. It may not be feasible to apply tape to some anatomical locations, in which case an adhesive bandage may be used, when possible, to protect other skin sites from coming into contact with the treated area.

Application of study drug may not be conducted over more than one visit. Subjects may be rescheduled for the first treatment, as long as it is within the screening time period. Otherwise, they will need to be rescreened and consent reviewed to participate.

All subjects will be provided a copy of their signed Informed Consent Form (ICF). At each treatment visit, the subjects will be provided with both verbal and written take-home

instructions covering potential side effects and complications, as well as contact information of the study investigator/coordinator for any questions or concerns that may arise. Subjects will also be provided an LSR guide to assist the site in collecting the required ERT information related to the treated areas. Subjects should refrain from touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for up to 24 hours after treatment or until the study drug is removed. Strongly urge subjects not to touch or wash the treated area for 24 hours (± 8 hours) after treatment.

Subjects will receive application of study drug to all warts with a minimum of 21 ±4 days between treatment until complete clearance or a maximum of four applications. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account.

Please see the Instructions for Use provided in each subject-specific kit for step-by-step instructions.

8.2.2 Removal of Surgical Tape and Study Drug

All subjects will have reviewed and are provided with take home instructions on removal of the surgical tape and study drug, as well as descriptions of the potential LSRs they might expect throughout the course of the study; recommendations for wound care, when it is important to call their doctor, and instructions for whom to contact in an emergency.

Surgical tape should only be removed at the designated time after study drug application, when the treatment site is washed and study drug removed.

Subjects are instructed to wet the surgical tape, a bath or shower may be helpful, with water and then slowly peel back an edge of the surgical tape, pulling the surgical tape over itself in a “low and slow” manner to prevent the unroofing of any blisters that may have developed. Gently remove any remaining study drug with soap and water. Subjects will be cautioned not to use washcloths, abrasive material, or vigorous rubbing to remove the study drug, as this may cause temporary pain and damage to the external layer of the skin and slow the healing process. Subjects are encouraged to wash their hands regularly with soap and water and discouraged from scratching lesions, which can spread disease.

Note: The surgical tape and study drug may be gently removed from individual warts before the designated time in the event of significant blistering, significant pain, or a TEAE. Study drug should not be removed from any remaining unproblematic warts until the designated removal time is reached. Subjects who remove study drug before the assigned time frame of

24 hours (± 8 hour) will be considered a protocol deviation, unless early removal is due to protocol defined criteria.

8.3 Study Drug Storage

Clinical sites will be provided with an initial supply of subject specific kits containing four single-use applicators. Each applicator contains 0.45 mL of study drug (VP-102 or Placebo) and is individually packaged in a zip-top bag. Each bag is labeled with all pertinent product information including the corresponding kit number it is assigned to. Applicators should be documented on the drug accountability form as they are used. The zip-top bag should not be opened until the site is ready to initiate treatment. Do not dispose of the zip top bag, as it will be used to store the used applicator (Section 8.9).

Study drug must be stored at controlled room temperature (68°F-77°F). Storage temperature (e.g., excursions between 59°F-86°F) that are experienced in the physician's storage area and/or during shipping are allowed. Excursions from 32°F to 59°F that do not result in precipitate formation are acceptable for use. Short term storage temperature excursions (spikes < 24 hours in duration) between 86°F to 104°F may be allowed but must be evaluated for impact by the sponsor before use. Storage temperature excursion above 104°F are not allowed and will require replacement of the study drug. The study drug must be stored in a secure, dry location with limited and controlled access, and out of direct light. Extended exposure to extreme temperature conditions or to direct light should be avoided (e.g., study drug left in an unoccupied vehicle in a hot or cold environment). Contact the study sponsor or designee (i.e., clinical research organization) in the event that you believe that any materials may have been exposed to such conditions for guidance. Study drug may be administered only by the investigator or by a trained member of the clinical site staff specifically as authorized by the investigator.

8.4 Study Drug Labeling

Study drug is packaged in tamper evident, subject-specific kits, within a cardboard carton, that contains four individually packaged applicators. Applicators are surrounded by a paper-board sleeve that is to be used to crush the glass ampule and is then discarded when ready for use. Each applicator and sleeve is individually contained in an outer protective tube within a clearly labeled zip-top pouch.

The applicator is labeled with the IND application number and study protocol number. An example of the applicator label is presented in Figure 1. The label also indicates the date of manufacture and includes the required statements "Caution: New Drug--Limited by Federal Law to Investigational Use." and "Warning: Flammable Liquid." The applicator warnings

indicate characteristics of the study drug including additional labeling “Warning: Flammable Liquid” and the yellow toxic chemical symbol with the phrase “Warning: Highly Toxic”.

The pouch label includes the IND number, study protocol number, warnings that include how to address inadvertent contact in the eye and the applicator assigned subject specific kit/randomization number. The pouch label can be seen below in Figure 2.

The subject specific kit label includes the same information as indicated on the pouch including the subject specific kit and randomization number. Please confirm the pouch matches the number on the outside of the kit box before using. The kit label can be seen in Figure 3.

In an effort to make it easier for the research personnel to ensure they have pulled the correct box at each study visit, a fourth label has been added to the side of the kit box providing a space for the research team to write in the randomization number. This label is shown in Figure 4.

Clinical Trial Labeling of Study Drug (Draft)

Figure 1. Label on Applicator Sleeve

Figure 2. Label on Pouch Containing Each Applicator

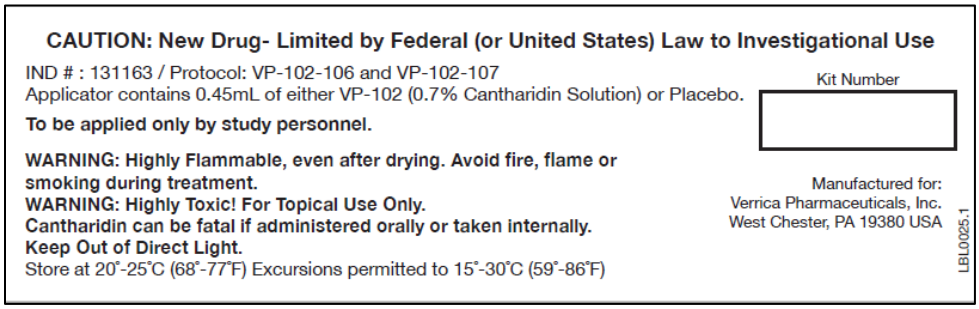


Figure 3. Kit Top Label

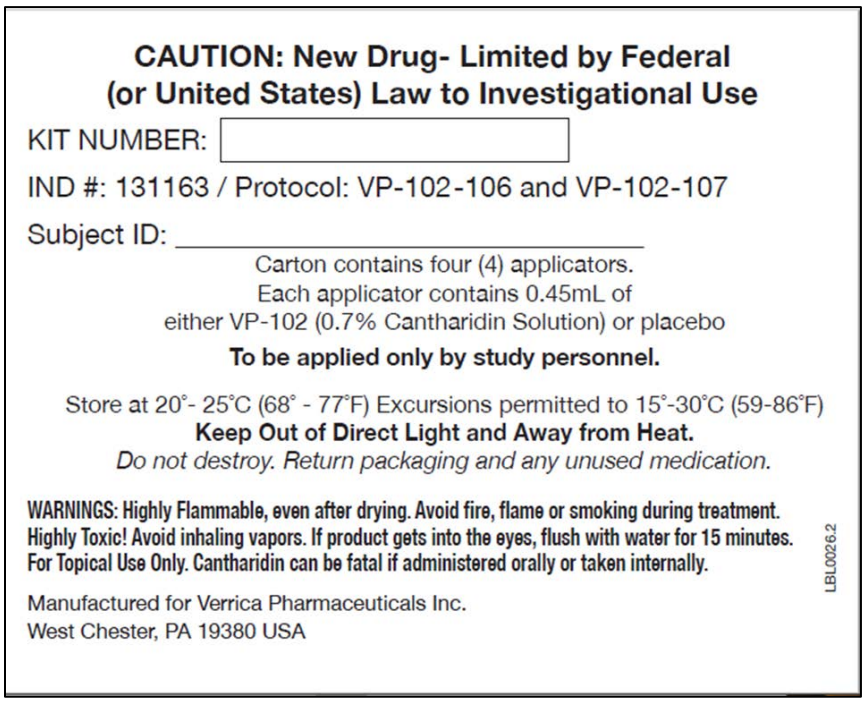
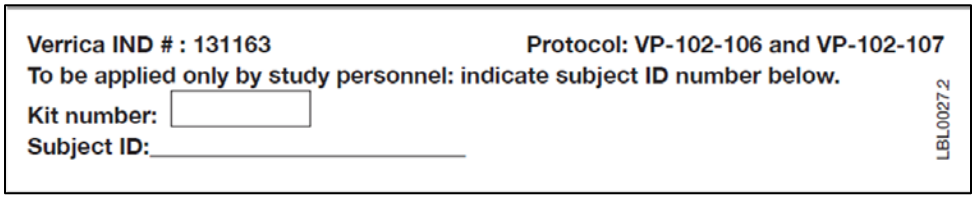


Figure 4. Kit Side Label



8.5 Compliance

Treatment compliance for study drugs will be documented in the eCRF by recording the date, subject identification, and kit number.

8.6 Breaking the Blind

This study is a double-blind design. Blinded subjects, investigators, site staff, and sponsor personnel will not make any effort to determine which study drug therapy is being applied.

In the event that unblinding of the study drug assignment is necessary for emergency treatment, it is required that the investigator contact the medical monitor immediately. Following the discussion on the urgency and requirement for knowing the exact treatment, the medical monitor will determine whether to unblind and provide the treatment assignment to the investigator. All unblinding will be reported to the sponsor.

8.7 Previous and Concomitant Medications

All medications taken within 30 days before the first dose of the study drug will be classified as prior medication; while all medications used after the first dose of study drug will be classified as concomitant medications. Prior and concomitant medications will be recorded in the eCRF, along with the reasons for administration and durations of use.

Subjects are excluded from study participation if they have had any previous treatment (including an investigational agent in a clinical trial) of common warts, including but not limited to the use of imiquimod, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, iodine-based or nitric oxide-based therapies, curettage, or freezing of warts in the 30 days before treatment. In addition, no treatments, including over-the-counter wart treatment, should be implemented during the study. The wash out period for cantharidin, candida antigen, diphenylcyclopropenone, dinitrochlorobenzene, squaric acid dibutyl ester, and any other immunomodulating treatment not otherwise specified is 45 days before Treatment Visit 1.

Subjects who have participated in another clinical trial utilizing an investigational product must observe a 30 day wash out period before the first application of the study drug.

Medications or treatments that can interfere with the evaluation of the study drug [e.g., topical steroids, PDE-4 inhibitors (such as Eucrisa®), and calcineurin inhibitors (pimecrolimus, tacrolimus)] should not be used on the day of treatment and should not be applied within 5 cm of treated skin lesions. Particular attention will be paid to treatments that can influence the intended effects or mask the side effects of the study drug (e.g., topical steroids). Lotions and creams such as sunscreens should not be used for a minimum of 4 hours before treatment and should not be applied within 5 cm or on treated skin for 24 hours following treatment. Immunizations and flu shots, with the exception of HPV immunization, may be administered throughout the study but not within 5 days before or after treatment. The HPV vaccine cannot have been administered within the last 6 months before enrollment and may not be administered during the course of the trial.

8.8 Accountability Procedures

The pharmacy or trained study personnel are responsible for ensuring that a current record of study drug inventory and accountability is maintained. The unique kit numbers on the pouch and kit labels are used for accountability purposes and are recorded on the accountability log as they are used.

The assigned research personnel and study monitor will be responsible for verifying drug accountability at the site. Inventory records must be readily available for inspection by regulatory authorities at any time. Upon receipt of study drug, the pharmacy or study personnel will visually inspect the shipment and verify the number and condition of kits received. The site will record the receipt of their inventory in the IRT system. All shipping records will be maintained in the IRT system.

8.9 Study Drug Handling and Disposal

Used applicators are not to be discarded after use, but should be returned to their zip-top bag and stored in the subject-assigned kit box. The paper board sleeve and outer tube may be discarded after use. All used applicators are to be discarded at the site in a sharps container, or per the site's Standard Operating Procedure (SOP) for disposal, after the study monitor has reviewed and confirmed accurate accountability. Those sites that are not allowed to dispose of the study drug at their site will make arrangements with the sponsor for return and destruction. All unused applicators and/or kits are to be returned to the drug distribution center after accountability is completed and the study monitor has completed the corresponding paperwork to direct the return.

9.0 EXPERIMENTAL PROCEDURES

Each subject will be evaluated and treated as follows:

9.1 Subject Restrictions

Subjects are required to:

- Use no wart-removing product (prescription or over-the-counter and including any HPV immunization) other than the study drug during the course of the study, with the exception of circumstances allowed under Inclusion Criterion 2b (Section 7.1)
- Refrain from touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for at least 24 hours after treatment or until the study drug is removed
- Refrain from swimming, bathing, or prolonged immersion in water or any other liquids until the study drug is removed

9.2 Screening Period (Up to 30 days before first treatment)

Before the initiation of screening assessments, the subject must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the subject must sign and receive a copy of an IRB-approved ICF and an authorization for use and disclosure of protected health information that was approved by the IRB (Section 13.0). Once consent is obtained, the Screening Period assessments will be performed. Subjects will be screened within 30 days before or on Treatment Visit 1 of the study. Any qualified team member may conduct the screening study activities.

- Obtain signed informed consent before initiating any study-related assessments or procedures
- Obtain relevant medical history (including relevant illnesses and previous HPV immunization) within the past 5 years
- Obtain common wart history (duration and previous treatments); if treated, confirm date of last treatment. Warts must be present for ≥ 4 weeks before screening.
- Clinical assessments
    - Conduct Directed physical examination
    - Measure subject’s height and weight

- Measure vital signs (temperature, heart rate); blood pressure is to be obtained only for subjects who are ≥ 12 years of age
- Record demographics (date of birth, sex, race, and ethnicity)

- Wart count (any qualified team member may conduct the screening study activities)
- Wart assessments (location by anatomical location, wart diameter and wart height measurements)
- Dermatologic exam (including Fitzpatrick Skin Type) by anatomical location
- Record all prior medications (including non-prescription and herbal [complementary medicine] products) within the last 14 days before Screening;
  - Record any antimicrobial, antiviral, steroidal, or topical drugs received within 30 days before Day 1
  - Record any non-pharmacologic treatments (e.g., ice packs, heat packs, warm soaks, etc.) administered in the 72 hours before application of study drug
- Confirm that the subject meets all inclusion criteria and does NOT meet any exclusion criteria

9.3 Treatment Period

Treatment visits will occur every 21 ±4 days. All treatments may be administered over the course of up to 75 days.

9.3.1 Treatment Period 1

The following evaluations will be performed and recorded in the eCRF.

9.3.1.1 Day 1 (Treatment Visit 1)

Screening and Treatment Visit 1 may occur on the same day. If the Screening Visit and Treatment Visit 1 are not on the same day, repeat the following procedures:

- Confirm that subject still meets enrollment criteria (dermatologic exam; ability to attend study visits)
- Obtain relevant medical history since Screening Visit
- Obtain common wart history (duration and previous treatments) since Screening Visit; if treated, confirm date of last treatment
- Clinical assessments
  - Measure subject's height and weight

  - Measure vital signs (temperature, heart rate) before application of study drug; blood pressure is to be obtained only for subjects who are ≥ 12 years of age

- Wart count is performed before the ERT assessment; any qualified team member may conduct the Treatment Visit Day 1 study activities
- Wart assessments (location by anatomical location, wart height, and wart diameter measurement) conducted before application of study drug
  - Confirm subject meets inclusion criteria of warts measuring with longest axis ≥ 3 and ≤ 8 mm; subjects with warts that exceed this size are not eligible for study participation
- Wart paring by dermatologist or qualified designee identified at the site; paring is required if significant hyperkeratosis is present at investigator's determination
- Dermatologic exam by anatomical location
  - Location of each wart is identified and documented on the body map and source
- Photography before application of study drug
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
- QOL questionnaire
  - Completed by each subject or parent/guardian. Subjects who are 17 years of age and older will complete the DLQI, subjects from 4 to 16 years of age will complete the CDLQI, and subjects < 4 years of age will not complete a QOL questionnaire
- Record any prior medications (including non-prescription and herbal [complementary medicine] products) since the Screening Visit
  - Record any antimicrobial, antiviral, steroidal, or topical drugs received within 30 days before Day 1
  - Record any non-pharmacologic treatments (e.g., ice packs, heat packs, warm soaks, etc.) administered in the 72 hours before application of study drug

The additional procedures listed below are also completed as part of Treatment Visit 1:

- Laboratory assessments
    - Perform urine pregnancy test on female subjects of child-bearing potential (i.e., females who are capable of menstruating) before study drug application
- ERT assessment conducted before study drug application
    - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team; any qualified team member may conduct the Treatment Visit Day 1 study activities
- Study drug application
    - Apply study drug
    - Apply surgical tape
- Assess, identify, and record any AEs
- Record any concomitant medications
- Provide subjects with take-home instructions describing how to remove the surgical tape, the possible LSR's, and what to expect over the next 24 hours to several months
- Subjects will remove surgical tape and study drug at 24 hours (±8 hours) after application
    - Removal of the surgical tape should be gentle and aided by soap and water, which will also help to prevent unroofing the blisters
    - Surgical tape should only be removed at the designated removal time, when the treatment site is washed and study drug removed
    - Surgical tape and study drug may be removed from individual warts before the designated removal time in the event of significant blistering, significant pain, or treatment-emergent AEs; surgical tape and study drug should not be removed from the remaining unproblematic warts until the designated removal time
    - Subjects who remove study drug before 24 hours will be considered a protocol deviation if it does not meet the requirements for early removal, defined as removal at < 16 hours after treatment is applied

In-person 24-hour photographic sub-study assessment:

Subjects participating in the photographic sub-study will return to the clinic at 24 (+6) hours after the 1st treatment for their ERT assessment and photos of warts where any LSR's may have occurred.

9.3.1.2 Telephone Assessments at 24 hours (±6 hours) and 7 days (±24 hours) after Study Drug Administration (Treatment Visit 1)

- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Assess, identify, and record any new AEs
- Record any new concomitant medications

9.3.2 Treatment Periods 2, 3, 4

Subjects are to be scheduled in 21-day intervals (±4 days) after each treatment. The next Treatment Visit is to be scheduled 21 (±4 days) after the last treatment, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. The research team should be in contact with the patient until LSRs are resolved and a treatment visit can be scheduled within 21 days (±4) when possible. Treatments may be administered up to Day 75.

The following evaluations will be performed and recorded in the eCRF. Subjects must attend all visits regardless of whether complete clearance of all warts has been achieved at a previous visit.

9.3.2.1 Day 1 (Treatment Visit 2, Treatment Visit 3, Treatment Visit 4)

- Clinical assessments
  - Measure vital signs (temperature, heart rate) before application of study drug; blood pressure is to be obtained only for subjects who are ≥ 12 years of age
- Wart count is performed by a Blinded Assessor before the ERT assessment; the Blinded Assessor is not required to be the same person for each assessment
- Wart assessments (location by anatomical location, wart diameter measurement) conducted before application of study drug
- Wart paring by dermatologist or qualified designee; paring is required if significant hyperkeratosis is present at investigator's determination
- Dermatologic exam by anatomical location
  - New warts should be recorded in the corresponding Source/eCRF
- Laboratory assessments

- Perform urine pregnancy test on female subjects of child-bearing potential (i.e., females who are capable of menstruating) before study drug application

- ERT assessment conducted before study drug application
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Photography conducted before study drug application
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
- Study drug application
  - Apply study drug
  - Apply surgical tape
- Assess, identify, and record any new AEs
- Record any new concomitant medications
- Provide subjects with take-home instructions describing how to remove the surgical tape, the possible LSR's, and what to expect over the next 24 hours to several months
- Subjects will remove surgical tape and study drug at 24 hours (±8 hours) after application
  - Removal of the surgical tape should be gentle and aided by soap and water, which will also help to prevent unroofing the blisters
  - Surgical tape should only be removed at the designated removal time, when the treatment site is washed and study drug removed
  - Surgical tape and study drug may be removed from individual warts before the designated removal time in the event of significant blistering, significant pain, or treatment-emergent AEs; surgical tape and study drug should not be removed from the remaining unproblematic warts until the designated removal time
  - Subjects who remove study drug before 24 hours will be considered a protocol deviation if it does not meet the requirements for early removal, defined as removal at < 16 hours after treatment is applied

9.3.2.2 Telephone Assessments at 24 hours (±6 hours) and 7 days (±24 hours) after Study Drug Administration (Treatment Visit 2, Treatment Visit 3, Treatment Visit 4)

- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation
  - Not required if there was no treatment during that treatment period
- Assess, identify, and record any new AEs
- Record any new concomitant medications

9.4 End-of-Treatment Visit: Study Day 84 (–0/+8 days)

The following evaluations will be performed and recorded in the eCRF. Treatments may be administered up to Day 75.

- Clinical assessments
  - Conduct Directed physical examination
  - Measure subject's weight
  - Measure vital signs (temperature, heart rate); blood pressure is to be obtained only for subjects who are ≥ 12 years of age
- Wart count is performed by a Blinded Assessor before the ERT assessment; the Blinded Assessor is not required to be the same person for each assessment
- Wart assessments
  - Wart anatomical location identified before dermatologic exam and ERT assessments
  - Wart measurement (diameter) conducted before dermatologic exam and ERT assessments
- Dermatologic exam by anatomical location
  - New warts should be recorded in the corresponding Source/eCRF
- Laboratory assessments

- Perform urine pregnancy test on female subjects of child-bearing potential (i.e., females who are capable of menstruating)

- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Photography
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
  - If there are no warts remaining, the same areas will be photographed regardless of whether warts are present
- QOL questionnaire
  - Completed by each subject or parent/guardian. Subjects who are 17 years of age and older will complete the DLQI, subjects from 4 to 16 years of age will complete the CDLQI, and subjects < 4 years of age will not complete a QOL questionnaire
- Assess, identify, and record any new AEs
- Record any new concomitant medications
- Complete Provider questionnaire; by a clinician who applied treatment to the subject during the course of the study

9.5 Follow-up Visits on Study Day 105 (±4 days) and Study Day 147 (±4 days) (End-of-Study)

Subjects will return to the clinical site and the following evaluations will be performed and recorded in the eCRF. Subjects are to attend all visits whether they have achieved complete clearance before and at the Day 84 (- 0/+ 8 days) EOT assessment. EOS conducted outside the Day 147 EOS visit (±4 days) window will be considered a protocol deviation.

- Clinical assessments
  - Measure subject's weight
  - Measure vital signs (temperature, heart rate); blood pressure is to be obtained only for subjects who are ≥ 12 years of age

- Wart count is performed by a Blinded Assessor before the ERT assessment; the Blinded Assessor is not required to be the same person for each assessment
- Wart assessments
  - Wart anatomical location identified before dermatologic exam and ERT assessments
  - Wart measurement (diameter) conducted before dermatologic exam and ERT assessments
- Dermatologic exam by anatomical location
  - New warts should be recorded in the corresponding Source/eCRF
- Laboratory assessments
  - Perform urine pregnancy test on female subjects of child-bearing potential (i.e., females who are capable of menstruating)
- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team before study drug application who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Photography
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
  - If there are no warts remaining, the same areas will be photographed regardless of whether warts are present
- QOL questionnaire (Day 147 only)
  - Completed by each subject or parent/guardian
  - Subjects who are 17 years of age and older will complete the DLQI
  - Subjects from 4 to 16 years of age will complete the CDLQI
  - Subjects < 4 years of age will not complete a QOL questionnaire
- Assess, identify, and record any new AEs
- Record any new concomitant medications
- Complete study completion form for all subjects (Study Day 147 [EOS] Visit only)

9.6 Unscheduled Visit

In the event that any post-treatment LSR presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain), an "Unscheduled" clinic visit must be scheduled and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an unscheduled visit. "Unscheduled" visits should also be used for visits in which treatment is unable to be applied to all warts due to ongoing LSRs.

Subjects will return to the clinical site and the following evaluations will be performed and recorded in the eCRF.

- Clinical assessments
  - Measure vital signs (temperature, heart rate); blood pressure is to be obtained only for subjects who are ≥ 12 years of age
  - Record reason why study drug was not administered at treatment visit (if applicable)
- Dermatologic exam by anatomical location
  - New warts should be recorded in the corresponding Source/eCRF
- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted (before study drug application) and recorded on ERT by a qualified member of the research team who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Assess, identify, and record any new AEs
- Record any new concomitant medications

9.7 Measurements and Evaluations

9.7.1 Skin Assessments

- Dermatologic examination, including Fitzpatrick skin type
- Wart measurement (diameter, height)
- Wart location by anatomical location

9.7.2 Identification of Skin Reactions

An LSR guide for subjects with specific photographs identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject by the research team.

9.7.3 Removal of Surgical tape

Subjects are instructed to wet the treated area with water and then carefully and slowly remove the surgical tape from each wart, pulling the surgical tape back over itself in a "low and slow" manner, trying not to unroof any intact blisters. Treated warts should be gently washed with soap and water after the surgical tape is removed. The surgical tape and study drug may be gently removed from individual warts before the assigned duration of skin exposure in the event of significant blistering, significant pain, or TEAEs. The surgical tape and study drug should not be removed from any remaining unproblematic warts until the designated time point is reached. Washing of intact blisters should be gentle and without use of a washcloth. Washing and removal of surgical tape in a bath or shower is encouraged. For subjects participating in the photo portion of the study, photographs should be taken by the subject after the surgical tape and study drug are removed.

9.7.4 Evaluation of Response to Treatment Assessments

An ERT assessment will be conducted at each treatment visit (1-4; in-person before treatment or via follow-up telephone calls) at 24 hours (±6 hours), 7 days (±24 hours) after each treatment visit (but not after "unscheduled" visits).

The ERT includes questions related to removal of surgical tape and study drug (if applicable) and collects any new AEs, LSRs, and changes in concomitant medications since the last contact. The subject will be given an opportunity to ask questions and review any concerns.

In the event that any post-treatment LSR presents a safety concern (including but not limited to patient reports of severe blistering, ulceration, edema, or pain), an "Unscheduled" clinic visit must be scheduled, and the subject assessed accordingly. In addition, if any post-

treatment AEs present a safety concern, the subject may be brought in for an "Unscheduled" visit.

The ERT assessments will be recorded by a research team member on the ERT form. All ERT safety assessments must be conducted by a qualified member of the research team. Any qualified team member may conduct the screening and Treatment Visit Day 1 study activities. Any subsequent ERT and phone calls must be conducted by a study team member who is not considered, or who has not acted as, the Blinded Assessor for the subject throughout the subject's participation.

Phone calls conducted outside of the required study visits or required ERT assessments should be documented in the subject's source note but are not required to be entered in the EDC system.

9.7.5 Photographs of Lesions

At designated sites, photography will be offered to volunteer subjects who consent to participate. Photography will take place at the clinical site at each treatment and follow-up study visit through Study Day 147 (±4 days) (EOS). In addition, subjects will be asked to return to the clinic at 24 hours after the Treatment Visit 1 for their ERT assessment and photos of any LSR's that may have occurred. These images may be used on handouts in future trials, for training purposes or future marketing materials. If there are no warts remaining, the same areas will be photographed and repeated at the Study Day 84 (–0/+8 days) EOT Visit and Study Day 147 (±4 days) EOS visit, regardless of whether warts are present. They will not be used for any portion of the efficacy or safety data. Photographs will be de-identified to those outside the research team and stored in a HIPAA-compliant manner. Efforts will be made to ensure that no photographs with identifiable features are obtained.

10.0 ASSESSMENT OF SAFETY

10.1 Safety Parameters

Safety analyses will include AEs, LSRs, medical history, physical examinations, vital signs, and concomitant medication use

- The incidence of AEs will be assessed throughout the study; AEs will include all LSRs, whether or not they are expected or related to the anticipated pharmacodynamic response of the skin to VP-102, a vesicant
- LSRs of all previously treated areas will be assessed at each treatment visit using the protocol specific ERT form
- Directed physical examinations will be completed before the first treatment, Study Day 84 (EOT) and Day 147 (EOS) Visit; additional physical examinations will be performed when clinically warranted (e.g., subject reports symptoms classified as an AE requiring further evaluation)
- Vital signs (temperature, heart rate and blood pressure) will be obtained before the treatment is applied at each treatment visit and at the start of the Study Day 84 (EOT) Visit
- Concomitant medication use will be collected at each study visit and ERT telephone contact

10.2 Definitions

10.2.1 Adverse Event

The following definition of AE will be used for this study:

> Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can be any unfavorable and unintended sign, symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product, regardless of whether it is considered to be related to the investigational product.

The following are examples of AEs:

- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency or intensity of the condition

- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Local skin reactions (erythema, scaling/flaking/dryness, edema/swelling, blisters, hyper- and hypopigmentation, scabbing/crusting, erosion/ulcerations)
- Scarring and ring warts are uncommon LSRs that can arise over the course of treatment and should be documented on the AE form as well

The following are NOT examples of AEs:

- Medical procedures (the medical condition that led to the procedure as the AE should be reported)
- Situations that are unwanted by the subject but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital
- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall
- Expected progression of the disease being studied, including signs or symptoms of the disease, unless progression is more severe than expected for the subject's condition

AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive procedures, modification of the subject's previous therapeutic regimen). AEs should be captured even if they occur during periods without drug treatment or post-treatment periods. AE collection begins after the subject has signed informed consent and will continue until the EOS visit has been completed. Only AEs occurring after the initial dose of study drug are considered to be a Treatment Emergent AE.

The investigator and study personnel will note all AEs mentioned by the subject starting from the day the informed consent is signed until the EOS visit (Study Day 147 ±4 days). All clinical complaints volunteered by or elicited from the subject during the study will be recorded on the appropriate page of the source and eCRF for the study period indicated.

All unresolved AEs will be followed until the condition resolves and/or stabilizes, the subject is lost to follow-up or 30-days after the EOS visit, whichever comes first. All AEs will be summarized in the annual report or more frequently if requested by the regulatory agency.

SAEs require special reporting in addition to documentation in the eCRF as described in Section 10.6.

10.2.2 Serious Adverse Event

In this study, an SAE is defined as an AE that meets any of the following criteria:

- Results in death
- Is life-threatening
  - The term *life-threatening* in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event
  - The term *life-threatening* does not refer to an event that hypothetically might have caused death if it were more severe
- Requires hospitalization or a prolongation of an existing hospitalization
  - In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting.
  - Complications that occur during hospitalization are AEs, but not necessarily SAEs.
  - An occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE.
  - Hospitalization for elective treatments of a preexisting condition that did not worsen from its original baseline level is not considered an SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - This definition is not intended to include AEs of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Another important medical event
  - Medical or scientific judgment should be exercised when deciding whether reporting is appropriate for other important medical events that may not result in death, be life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition.
  - These events should also be considered serious.

- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

An SAE requires additional detailed reports and follow-up. The content of these detailed reports must address the investigator's estimate of causality. The medical monitor will review the SAE to determine if it is an expected SAE (i.e., whether or not the SAE is identified in nature, severity, and frequency in the study protocol, study documents or VP-102 IB).

10.2.3 Expectedness of Serious Adverse Events

An expected AE is one that is consistent with the known risk information described in the product label (if applicable), study protocol, study documents or the current IB. The expectedness of an SAE will be assessed by the medical monitor or sponsor on receipt of the initial SAE report.

10.3 Assessment of Intensity

The investigator will assess the intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment.

The classifications in Table 3 should be used in assigning intensity of each AE recorded in the eCRF.

Table 3. Classification of Adverse Events by Intensity

Intensity	Definition
Mild AE	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
Moderate AE	An event that is sufficiently discomforting to the extent of interfering with normal everyday activities
Severe AE	An event that prevents the subject from performing normal everyday activities

AE: adverse event

Any AE that changes in intensity during its course will be recorded in the eCRF at the highest level experienced by the subject.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an AE (such as mild, moderate, or severe myocardial infarction). However, the event itself may be of relatively minor medical significance, such

as a severe headache. Both AEs and SAEs can be assessed as severe. An AE is considered serious (an SAE) when it meets one of the predefined outcomes described in Section 10.2.2.

Local Skin Reactions should be rated based on the severity ratings in the Local Skin Reaction Guide that is provided.

10.4 Assessment of Causality

The investigator must estimate the relationship between the investigational product and the occurrence of each AE or SAE by using his or her best clinical judgment. Elements to consider for this estimate include the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product. The investigator will also consult the IB or product label for marketed products in estimating the relationship.

Because of reporting timelines, the investigator might have minimal information to include in the initial SAE report. However, the investigator must always make an assessment of causality for every SAE before the transmission of the SAE report. The investigator may change his or her opinion of the causality in light of follow-up information, with subsequent amendment of the SAE report. Causality assessment is one of the criteria used to determine regulatory reporting requirements and should not be left blank in the SAE report. The same applies to AEs that are to be processed as SAEs. Some definitions to use in the assessment are provided in Table 4.

Table 4. Assessment of Causality of Adverse Events

Term	Definition
Definitely related	The AE is clearly related to the investigational agent(s) or research intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known pattern of response, and no alternative cause is present.
Possibly related	The AE may be related to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a suspected pattern of response, but an alternative cause is present.
Probably related	The AE is likely related to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known or suspected pattern of response, but an alternative cause may be present.
Unrelated (or not related)	The AE is clearly not related to the investigational agent(s) or intervention: the AE has no temporal relationship to the administration of the investigational agent(s) or research intervention, and follows no known or suspected pattern of response, and an alternative cause is present.

AE: adverse event.

10.5 Recording Adverse Events and Serious Adverse Events

When an AE or SAE occurs, the investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relative to the event(s). The investigator will record all relevant information about any AE (including SAEs) on the AE page of the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of the properly completed AE or SAE pages of the eCRF. These documents should not be sent unless they are specifically requested by the designated medical monitor. If this request occurs, all subject identifiers and protected health information should be blinded on the copies of the medical records before submission to the sponsor and to the appropriate authorities.

The investigator will also attempt to report a diagnosis, instead of signs, symptoms, or other clinical information, for the AE. The diagnosis, not the individual signs and symptoms, should be documented on the appropriate page of the eCRF as the AE or SAE. In addition, SAEs need to be reported in the SAE report. Adverse events being processed as SAEs will also require additional documentation.

10.6 Reporting of Serious Adverse Events

Any SAE occurring after the subject signs the ICF must be reported to the sponsor or designee within 24 hours of the time the investigator becomes aware of the SAE (Table 5).

Table 5. Timeline for Reporting of Serious Adverse Events

Initial SAE Report		Follow-up SAE Report	
Time Frame	**Documents**	**Time Frame**	**Documents**
24 hours	SAE report	7 days	Updated SAE report

SAE: serious adverse event.

Urgent reporting of SAEs is required for the following reasons:

- To enable the sponsor to fulfill the reporting requirements to the appropriate regulatory authority
- To facilitate discussion between the sponsor and the investigator about appropriate follow-up measures (if necessary)
- To facilitate the sponsor's rapid dissemination of information about AEs to other investigators or sites in a multicenter study
- To facilitate reporting unanticipated problems involving risk to subjects to the IRB

The SAE report must be completed as thoroughly as possible, including the following:

- Subject identification information
- Event term
- All available details about the SAE
- Causality of each SAE
- Signature of the investigator

Within 24 hours of awareness of a new SAE, the investigative site will call the Paidion Research medical monitor (Devon Kuehn, MD) by calling the SAE Hotline at 919-885-1911. The SAE Hotline may be accessed and is monitored 24 hours/day, 7 days/week. The investigative site must also initiate entry of the SAE report form into the EDC system being used for this study. The SAE report should include the essential elements.

The SAE report will be forwarded to the sponsor within the designated time frames. If additional information to complete the SAE report form is needed, the investigator will not

wait before notifying the Paidion medical monitor of the SAE via the SAE Hotline. The SAE report form will be updated by the investigator when additional information is received.

10.7 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to follow each subject until the occurrence of one of the following:

- The condition resolves and/or stabilizes
- The subject is lost to follow-up
- 30-days after the EOS visit

The appropriate SAE report form will be updated in the EDC after the SAE resolves, stabilizes, or is otherwise explained or until the subject is lost to follow-up. The investigator will also ensure that updates include any supplemental data that may explain causality of the SAE(s).

10.8 Risks for Women of Child-bearing Potential or During Pregnancy

The risks of VP-102 application during pregnancy have not been evaluated. Pregnant or lactating females who are nursing are excluded from this study.

Female and male subjects must be instructed to inform the investigator *immediately* if they become pregnant or genetically contribute to a pregnancy during the study. Should study personnel become aware of a subject's (or subject's partner's) pregnancy, the site personnel must report the pregnancy to the sponsor's medical monitor within 24 hours by using the pregnancy notification form. The female subject will discontinue study drug. The pregnancy will be followed until the outcome is known and will be reported to the sponsor.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the medical monitor.

10.9 Special Safety Considerations

- Investigators should confirm that study drug is completely dry (2-5 minutes) before applying the surgical tape or allowing the treated areas to come into contact with healthy skin, clothing, furniture, or other surface areas.

- In addition, an adhesive bandage may be applied over the surgical tape to keep it in place on areas that have a high probability of transference to healthy skin, mucous membranes, or that may experience significant flexing as in a skin fold.

- VP-102 solution is flammable, even after drying. Subjects should avoid open flame.
- VP-102 can be toxic if administered orally or taken internally. VP-102 is for topical use on lesions of the skin only. Do not apply VP-102 to eyes and mucosal surfaces. Care should be taken when applying in close proximity to eyes, mucosal tissues, and genitals. To deter potential oral ingestion, a bitter-tasting compound has been added as an oral deterrent to the study drug.
- Subjects should refrain from touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for at least 24 hours after treatment or until the study drug is removed.
- Subjects are encouraged to wash their hands regularly with soap and water (being mindful to keep treated areas on the hands dry) and discouraged from scratching or picking at warts, which can spread disease.

11.0 ASSESSMENT OF EFFICACY

11.1 Efficacy Parameters

Efficacy parameters will be summarized for all enrolled subjects in the Intent-to-Treat (ITT) and Per Protocol (PP) Populations by randomization group. Clinical response to treatment will be evaluated at 24 hours and at 7 days after each Treatment Visit.

Primary endpoint:

- Proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84)

Key Secondary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at the EOT Visit (Day 84)

Secondary endpoints:

- Proportion of subjects with up to 6 warts at Baseline exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4

- Proportion of subjects exhibiting complete clearance of all treatable warts (Baseline and new) at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4
- Mean change from Baseline in the number of treatable warts (Baseline and new) at the EOT Visit (Day 84)
- Proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at the EOT Visit (Day 84)

Exploratory endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4
- Time to achieve onset of complete clearance of all treatable warts present at Baseline
- Proportion of subjects who continue to exhibit complete clearance of all treatable warts (Baseline and new) at Follow-up Visits on Day 105 and Day 147

- Mean change from Baseline in the number of treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4
- Percent change from Baseline in the wart area based on treatable warts present at Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and at the EOT Visit (Day 84)
- Proportion of subjects who respond to treatment, defined as a ≥ 50% reduction in total wart area at the EOT Visit (Day 84) as compared to Baseline
- Mean change from Baseline of the composite score from the CDLQI assessment (subjects 4 to 16 years of age) and DLQI (subjects who are 17 years of age and older) at the EOT visit to measure the QOL and impact of skin disease
- Proportion of subjects exhibiting reduction of at least one treatable wart from Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and at the EOT Visit (Day 84)
- Proportion of subjects who continue to exhibit complete clearance of all treatable warts (Baseline and new) at Follow-up Visits on Day 105 and Day 147
- Mean number of treatments needed to achieve complete clearance of all treatable warts present at Baseline (for subjects who achieve complete clearance only)
- Mean number of new treatable warts that develop post-Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and at the EOT Visit (Day 84)
- Proportion of subjects who develop at least one new treatable wart post-Baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and at the EOT Visit (Day 84)

12.0 STATISTICAL METHODS

12.1.1 General Overview

This is a double-blind, randomized, and placebo-controlled study. The primary objective of this study is to determine the efficacy of VP-102-treated subjects relative to Placebo-treated subjects in the treatment of common warts. The primary endpoint of this study is the proportion of subjects with up to 6 warts at Baseline who achieve investigator-assessed complete clearance of all treatable warts (Baseline and new) at the Day 84 EOT visit.

The study is expected to enroll and randomize approximately 606 subjects with common warts, with at least 550 subjects with 6 or fewer warts, to test for treatment differences in the rates of complete clearance (primary endpoint). Subjects will be randomized and treated in a double-blind manner with either VP-102 or Placebo in a 1:1 ratio (approximately 303 subjects treated with VP-102 to 303 subjects treated with Placebo).

12.2 Analysis Populations

- The Intent to Treat (ITT) Population will include all randomized subjects
- The Safety Population will include all randomized subjects who receive ≥ 1 application of study drug (VP-102 or Placebo)
- The Per Protocol (PP) Population will include all subjects who receive all planned treatments of study drug (e.g., complete up to four treatments within the Day 75 treatment window or clear before Day 75), had no major protocol violations, and were assessed for clearance at the Study Day 84 (–0/+8 days) EOT Visit

12.3 Analysis of Study Population and Subject Characteristics

Subject disposition, demographics, baseline characteristics, and study drug exposure will be tabulated by treatment group at Study Day 147 (EOS) Visit. Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies, and percentages for discrete variables. Corresponding by-subject data listings will be tabulated.

12.3.1 Efficacy Analyses

The ITT population will be the primary efficacy analysis population. The main analysis for the primary efficacy endpoint and key secondary efficacy endpoint will be based on the ITT population. To fully evaluate the effectiveness of VP-102 compared to Placebo, efficacy will be evaluated in the ITT and PP Populations by treatment group. The primary efficacy

analysis will be based on all subjects who complete the Day 84 (EOT) assessments. Exploratory efficacy analyses will include data for all subjects through Day 147 (EOS).

All statistical tests will be two-sided with a significance level of $\alpha = 0.05$, unless specified otherwise. To protect the overall Type I error rate, the efficacy endpoints will be tested using a sequential testing procedure in a pre-specified order as defined in the SAP. The primary efficacy endpoint will be tested at $\alpha = 0.05$, and if significant, the key secondary endpoint will be tested at $\alpha = 0.05$. The remaining secondary endpoints will be tested in order if the key secondary efficacy endpoint is significant. Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for discrete variables. Corresponding by-subject data listings will be tabulated.

A logistic regression model, adjusting for the number of baseline warts and wart location, will be used to compare the VP-102 and Placebo groups for the primary endpoint. The key secondary efficacy endpoint and other binary endpoints also will be analyzed with this method.

Continuous endpoints will be analyzed with an analysis of variance (ANOVA) model with a factor for the site a subject is enrolled in or an analysis of covariance (ANCOVA) model with a factor for the site a subject is enrolled in, wart location, and a covariate for number of Baseline warts. Further details of analyses of other endpoints will be provided in the Statistical Analysis Plan.

12.3.2 Safety Analyses

Safety analyses will be conducted in the Safety Population by actual treatment received.

Adverse events, including LSRs, will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of subjects having treatment-emergent AEs will be tabulated by system organ class and MedDRA preferred term with a breakdown by treatment group.

12.3.3 Interim Analysis

No interim analysis is planned for the study.

12.4 Sample Size

Study assumptions include the following:

- a 10% drop out rate

- a 10% clearance rate for subjects treated with Placebo
- a 30% clearance rate for subjects treated with VP-102

Using these assumptions, a sample size of 550 subjects with 1:1 stratification of VP-102 to Placebo in each protocol based on a Pearson Chi-Square test with a two-sided significance level of 0.05 will provide ≥ 95% power to detect treatment differences in clearance rates for subjects with up to 6 warts at Baseline (primary endpoint). It is assumed that an additional 10% of subjects enrolled in the study will have >6 warts, resulting in a total of 606 subjects to be enrolled. Subjects will be stratified by wart location (palmar/periungual versus all other locations) and by number of warts (≤6 versus >6 warts).

12.5 Handling of Missing data

Subjects who do not have an assessment of complete clearance of all treatable warts at the EOS visit (Study Day 84) will be considered to have missing data for the primary endpoint. The primary method to handle missing data will be to assign all subjects with missing complete clearance data as not having achieved complete clearance.

To assess the potential impact missing data may have on study conclusions, sensitivity analyses will be performed on the primary endpoint. Sensitivity analyses based on alternative assumptions for missing data will include the following:

- Analysis using only non-imputed data (complete case analysis);
- Analysis in which all subject with missing data are assigned as having achieved complete clearance;
- Analysis in which subjects with missing data and treated with Placebo are considered to have complete clearance; subjects with missing data and treated with VP-102 are considered to not have complete clearance (worst case analysis);
- Two-dimensional tipping point analyses with assumptions that vary about the missing outcomes of the two treatment arms.

Additional details regarding sensitivity analyses to be performed will be provided in the Statistical Analysis Plan.

In the event that a subject requests to be removed from the study due to study-related adverse experiences or additional spreading of disease, data will be collected and analyzed as a treatment failure and the subject may be replaced. Further discussion of how treatment failure will be utilized in analysis will be provided in the Statistical Analysis Plan.

The procedures for handling missing data for other study endpoints will be described in the Statistical Analysis Plan.

12.6 Termination Criteria

Enrollment and withdrawals from the study and from study drug will be summarized by dose level.

12.7 Deviation Reporting

Protocol deviations are defined as any variation from the protocol, including enrollment of a subject who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frame.

13.0 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use E6 GCP: Consolidated Guidelines, the ethical principles of the Declaration of Helsinki, the National Health and Medical Research Council Statement on Ethical Conduct in Human Research (2007, incorporating all updates as of July 2018), FDA GCP guidelines, and any additional national or Human Research Ethics Committee required procedures.

The ICF and authorization for use and disclosure of protected health information, which is prepared by the investigator or the site, must have been reviewed and approved by the sponsor, the study monitor, and the investigator's IRB and privacy board (if separate from the IRB) before the initiation of the study. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The authorization for use and disclosure of protected health information must contain the elements required by Title 45 of the Code of Federal Regulations, Section 164.508(b), and any local regulations for valid authorizations.

Subjects will give written consent to participate in the study at the first visit, before initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. If applicable, it will be provided in certified translation for non-English-speaking subjects.

Written informed consent and authorization of use and disclosure of protected health information must be obtained from each subject before performing any study-specific screening/baseline period evaluations. One copy of the signed ICF and Authorization for Use and Disclosure of Protected Health Information form will be given to the subject, and the investigator will retain the original. Signed consent forms must remain in the subject's study file and be available for verification by sponsor at any time.

14.0 INVESTIGATOR REQUIREMENTS

14.1 Investigator Information

Investigator information is included in the Investigator's Brochure, which is updated as needed.

14.2 Investigator's Study Files

Documentation about the investigator and study staff, the IRB, and the institution is required before site initiation. Copies of these documents will be kept on-site in site-specific binders or electronic folders, along with the following supplemental information: a list of investigator's obligations, the IB, the clinical protocol and amendments, safety information, information about investigational product, the manual of operations and study logs, eCRFs, records of monitoring activities, and correspondence between sponsor or study monitor and the investigator. Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for source documentation.

14.2.1 Electronic Case Report Forms and Source Documentation

The investigator must make study data accessible to the Site Monitor, other authorized representatives of the sponsor, and the appropriate regulatory authority inspectors. The eCRF for each subject will be checked against source documents at the site by the Site Monitor, and a final copy of the eCRF will be signed by the investigator with an electronic signature and includes an attestation they have reviewed and attest to the accuracy of all data recorded in the EDC and any supporting documentation. A copy of the final eCRFs will be provided to the investigator in PDF on computer disc after study closure, to be kept in the investigator's study files.

14.2.2 Retention of Study Documents

According to ICH E6 guidance, all eCRFs, as well as supporting paper and electronic source documentation and administrative records, must be retained by the investigator until at least 2 years following notification that either the appropriate regulatory authority has approved the product for the indication under study, the sponsor has discontinued clinical development of the product, or notification that the marketing application was not approved.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator and institution as to when these documents no longer need to be retained. No study documents will be destroyed or moved to a new location

without prior written approval from the sponsor. If the investigator relocates, retires, or withdraws from the study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic document must be retained for a period at least as long as the period required for the subject's electronic records to which they pertain. The investigator must retain either the original of the audit trails or a certified copy of the audit trails.

14.3 Confidentiality

14.3.1 Data

The investigator must keep all information confidential about the nature of the proposed investigation provided by the sponsor or study monitor to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority).

14.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on eCRFs and other documents retrieved from the site or sent to the study monitor, sponsor, regulatory agencies, analysis laboratories, or blinded reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, or sponsor representatives.

14.4 Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject-selection criteria. Such changes must be prepared as a protocol amendment by the sponsor and implemented only upon joint approval of the sponsor and the investigator. A protocol amendment must receive IRB approval before implementation. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the ICF, the revised informed consent form prepared by the investigator must also be approved by the sponsor, study monitor, and the IRB before implementation.

In instances where there is an immediate risk to a subject that is deemed crucial for the safety and well-being of that subject, the investigator or the attending physician will contact the medical monitor as soon as possible to make them aware of such a departure. These departures do not require preapproval by the IRB; however, the IRB and medical monitor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document the reasons for the protocol deviation and the ensuing events in the subject's eCRF.

14.5 Study Monitor Functions and Responsibility

The study monitor, in accordance with the sponsor's requirements, will ensure that the study is conducted and documented properly by carrying out the activities outlined in ICH E6 guidance.

14.6 General Information

The investigator should refer to the IB and any other information provided about this investigational product and details of the procedures to be followed during this study.

15.0 DATA HANDLING AND RECORD KEEPING

The investigator is required to prepare and maintain adequate and accurate source documents designed to record all observations and other data pertinent to the study for each study subject. Electronic case report forms will be used to capture study assessments and data. The study coordinator or other delegated study personnel will enter data from source documents into the eCRFs. All eCRFs will be reviewed and source-verified by the study monitor during periodic site visits as well as via centralized monitoring, and the study monitor will ensure that all data in the eCRF are correct and complete. All information recorded on the eCRFs for this study must be consistent with the source documentation (i.e., medical records). Before or between visits, the medical monitor or study monitor may conduct a preliminary medical review of the eCRFs. After the eCRFs are completed and source-verified, the investigator must electronically sign all required pages in the eCRF, verifying the accuracy of all data contained in the eCRF.

Training will be provided for the EDC system. All study personnel using the EDC system must have the necessary education, training, and experience or any combination of these. The investigator will be responsible for documenting employee education, training, and previous experience that pertain to the EDC system for all site personnel using the EDC system.

The investigator must maintain adequate security of the EDC system, including documentation that all users have been trained on the appropriate SOP and a list of authorized users. To ensure all data entries can be tracked, all personnel responsible for data entry must obtain a unique user identification and password before any data can be entered in the eCRFs. Authorized study personnel will be assigned a unique user identification only after receiving SOP training.

If electronic data systems other than those provided and maintained by the sponsor are used for documentation and data capture, the investigator must ensure that the systems are validated and that data are backed up as described in Section 14.0.

16.0 QUALITY CONTROL AND QUALITY ASSURANCE

Written SOPs will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP, Section 1.8, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements
- Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the quality of the study

To fulfill the Quality Assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's quality control systems and recognized standards.

The purpose of an audit is to:

- Ensure participant safety
- Assure compliance to study protocol procedures, regulatory requirements, and SOPs
- Assure data quality

17.0 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

18.0 PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the sponsor and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.

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20.0 APPENDICES

20.1 Appendix 1: Version History and Summary of Changes

Version history:

Document	Version	Date
Protocol VP-102-106	1	10 February 2020
Protocol VP-102-106	2	06 March 2020

Sections/Pages Changed	Description of Changes
Administrative Update Throughout Protocol	Updated Version to 2.0 and updated version date to 06 March 2020.
Section 1.0 Protocol Synopsis: Inclusion Criteria (pg. 8) Section 4.6 Population to be Studied (pg. 38) Section 7.1 Subject Inclusion Criteria (pg. 47)	The inclusionary requirements for touching or combined warts were clarified so that the size requirement for the axis in the longest direction is ≥ 3 mm and ≤ 8 mm and is not dependent on the measurements of the individual lesion diameters.
Administrative Update to Table 1. Study Schedule of Assessments and Procedures (pg. 13-16)	The table was updated to re-order the procedures based on patient flow. There were no changes to the procedures and/or timing.