CONFIDENTIAL

CLINICAL PROTOCOL

TITLE OF STUDY:

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

Protocol VP-102-105

Version Number/Date of Issue	(Version 3) 01 November 2018
Previous Version Number/Date of Issue:	(Version 2) 15 May 2018
Date of Original Protocol:	28 February 2018
Sponsor	Verrica Pharmaceuticals Inc. 10 N. High Street, Suite 200 West Chester, PA 19380

Signatures of Approval of Protocol (Version 3)

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

Affiliation	Date:
Sponsor:	
Medical Monitor:	

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

Sponsor contact:

Medical

Acknowledgment of Responsibilities (Protocol Version 3)

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 SYNOPSIS

Name of sponsor company: Verrica Pharmaceuticals Inc.	
Name of finished product: VP-102	
Name(s) of active ingredient(s): Cantharidin	
Title of study: A Phase 2, Open Label Study to Evaluate the Efficacy, Safety and Tolerability of VP-102 in Subjects with Common Warts (Verruca Vulgaris).	
Number of sites: Up to 4 sites in the United States	
Study period: 84 Days (Cohort 1) or 147 days (Cohort 2)	**Phase of development**: Phase 2

Objectives:

Cohort 1: Primary objectives

- to evaluate the efficacy of dermal application of VP-102 when applied once every 14 days for up to 4 applications to common warts by assessing the proportion of subjects (2 years and older) achieving complete clearance of all treatable warts at the End of Study (EOS); Day 84).
- to assess the safety and tolerability of VP-102 by assessing adverse events including expected local skin reactions (LSR), physical examinations and concomitant medications.

The secondary objectives are:

- to evaluate the efficacy of VP-102 by assessing the change from baseline in the number of treatable warts (baseline and new) at the EOS visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the change from baseline in the percent of clearance of treatable warts (baseline and new) at the EOS visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and EOS Visit.

Exploratory objective is:

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

Cohort 2: Primary objectives

- to evaluate the efficacy of dermal application of VP-102 when applied once every 21 days for up to 4 applications to common warts by assessing the proportion of subjects (12 years and older) achieving complete clearance of all treatable warts at the end of treatment (EOT) visit (Day 84).
- to assess the safety and tolerability of VP-102 by assessing adverse events including expected LSRs, physical examinations, and concomitant medications.

The secondary objectives are:

- to evaluate the efficacy of VP-102 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 by assessing the change from baseline in the percent of clearance of treatable warts (baseline and new) at the EOT Visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and EOT Visit.

Exploratory objectives are:

- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at follow-up visits on Day 105, Day 126 and Day 147.
- to assess endpoints other than complete clearance that may be indicative of treatment efficacy.

Methodology: This is a Phase 2, open label study (Study number VP-102-105; referred to as COVE-1 [Cantharidin and Occlusion in Verruca Epithelium]) to evaluate the efficacy, safety and tolerability of VP-102 treatment in subjects with common warts. This study has two Cohorts.

The first Cohort (Cohort 1) utilizes a treatment interval of at least 14 days between treatments with longer treatment intervals being allowed depending on a specific patient's clinical response. No paring of lesions is allowed. Twenty Subjects (2 years and older) are targeted completing EOS visit in Cohort 1.

The second Cohort (Cohort 2) utilizes a treatment interval of 21 days between treatments. Paring of lesions is allowed. Approximately 35 subjects (12 years and older) will be enrolled in Cohort 2. Up to 4 sites will participate in the study.

All subjects will receive Study drug containing 0.7% cantharidin topical film forming solution. To assess eligibility, a dermatologic exam, wart counts (Cohort 1 only), and measurement of diameter and height of each wart will be conducted by a qualified member of the research team prior to the first treatment. For Cohort 2, wart counts will be carried out programmatically and research team does not need to count manually. Additional Treatment visits will include measurement of diameter and an evaluation of response to treatment (ERT), prior to treatment application when applicable. For those visits where subjects have received treatment, additional ERT assessments will be conducted over the phone at 24 hours and 7 days after treatment. (*Specific instructions on how to conduct the wart count (Cohort 1) and measure wart diameter and height are provided in the study specific Manual of Operations (MOP). Instructions for application of the Study drug are outlined in the Instructions for Use (IFU) included in the drug shipment as well as in the Investigator's Brochure)*.

Treatment will be applied up to four times during a 63-day treatment period for Cohort 1 and 75-day treatment period for Cohort 2. The treatment interval in Cohort 1 is determined by the subject's clinical response and will be at least 14 days. The treatment interval in Cohort 2 is 21 days. It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing local skin reactions. At any visit where the investigator is unable to evaluate or treat some warts due

to ongoing local skin reactions, an "Unscheduled" visit should be documented for both Cohort 1 and Cohort 2. 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 14 days for Cohort 1 and 21 days (+/- 4) for Cohort 2 when possible. A Treatment Visit should be documented at every visit where 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.

For Cohort 2, Study drug is to be applied to the wart site on any Treatment Visit where 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 where 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 that receive fewer than 4 treatments within the 63-day (Cohort 1) or 75-day (Cohort 2) treatment period, due to the duration of post-treatment local skin reactions, will not be considered a protocol deviation. No treatment should be administered after the 63-day treatment period in Cohort 1 or the 75-day treatment period in Cohort 2 without Sponsor's approval. Subjects in Cohort 1 that achieve complete clearance of all treatable warts prior to Treatment Visit 4, will receive ERT phone calls at the required 2-week treatment intervals to assess the status of any AEs or skin reactions since the last visit and confirm there has been no recurrence or development of new warts. In the event warts are present, the subject will be scheduled for a Treatment Visit per protocol. (*Consider calling the subject a few days prior to the 2-week interval (e.g.,11 or 12 days) to ensure adequate time for scheduling assessment and treatment if needed)*.

Subjects participating in Cohort 2, will be required to attend all visits regardless of whether they have achieved complete clearance of all warts at a previous visit. At these visits, Study drug application is not required if the warts have been clear for at least one follow up visit and the investigator determines that additional treatment is not needed. Subjects participating in Cohort 2, that have completed their Day 84 EOT Visit (- 0/+ 8 days), will be assessed at 3 additional follow-up visits conducted at Day 105, Day 126 and Day 147.

All subjects will receive application of the Study drug (VP-102) to common warts including a 1-2 mm margin of healthy, surrounding skin with an interval of at least 14 days in Cohort 1, and every 21 days in Cohort 2, until complete clearance of all treatable warts, or a maximum of 4 applications. Warts are to be treated and then occluded with transparent surgical tape (e.g.; 3M™ Blenderm™ brand) that will remain on overnight and removed just prior to the 24-hour ERT phone call. Subjects in Cohort 2 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 prior to application of Study drug. Wart paring is 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 re-treated only after 14-

days have elapsed in Cohort 1 and 17 days (i.e., 21 +/- 4 days) have elapsed in Cohort 2, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. . Subjects that achieve complete clearance of all treatable warts prior to the EOS visit, return to the clinic for a EOS/EOT visit at Day 84 in both Cohorts. Subjects in Cohort 2 are to attend all visits regardless of whether they have achieved complete clearance prior to the Day 84 (- 0/+ 8 days) assessment. Phone calls will be conducted at an interval of 24 hours and 7 days after each Treatment Visit (not "Unscheduled" visits) to assess if there have been any adverse events 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 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.

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, a local skin reaction 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. An in-person ERT will also be conducted at every visit prior to Study drug application. The ERT includes questions related to removal of the occlusive tape and Study drug, if applicable, and records the intensity of any local skin reactions, including adverse events, and concomitant medications (ConMeds). The subject and/or guardian will have time to ask questions and review any concerns. In the event any adverse events present a safety concern, an "Unscheduled" clinic visit will be made, and the subject assessed accordingly. All subjects in Cohort 1, will participate in an in-person EOS evaluation that will take place at Day 84. A Provider End of Study Treatment Questionnaire will be completed at the EOS. Subjects in Cohort 2 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. Cohort 2 subjects will continue in the study for 3 additional follow-up assessments at Day 105, Day 126 and Day 147. The follow-up visit window is +/- 4 days.

Subjects in Cohort 1 will be asked if they are interested in participating in a subset of the study where with consent, the research team may take in-office photos of each treated wart at each Treatment visit. Photos of up to 8 subjects will be obtained with a goal of obtaining sequential sets of images of each wart from Treatment visits 1-4 and EOS. Subjects will also be asked to take daily photos at home with their smart phones and either text, e-mail or bring them to the site for upload to a secure site server.

At designated sites, subjects in Cohort 2 will be asked if they are interested in participating in a subset where they will be consented for in-office photos at each treatment and follow-up study visit through Day 147. Subjects will also be asked to take photos of their warts at home with their smart phones and either text, e-mail or bring them to the site for upload to a secure site server. These photos will be obtained at 24 hours post treatment.

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.

Each subject will be evaluated and treated as follows:

- **Screening Period** (Up to 14 days prior to first treatment)
- Safety Evaluation Period (Treatment Visit 1)
  - Confirm that subject still meets enrollment criteria (dermatologic exam; ability to attend study visits),
  - Wart count (Cohort 1),
  - Measurement of each wart size (diameter, height) and location,
  - Photos of all warts, if applicable,
  - Paring of warts (Cohort 2), if applicable,
  - Study drug application and occlusion with occlusive tape,
  - Removal of occlusive tape and Study drug 24 hours after application
  - 24-hour and 7-day ERT phone call,
  - Photos taken by subject at home every 24-hours for 5 days if applicable (Cohort 1),
  - Photos taken by subject at home at 24 hours (Cohort 2).

- **Safety and Efficacy Evaluation Period** (visits targeted at least 14 days after prior treatment in Cohort 1 and every 21 +/- 4 days in Cohort 2)
- **Treatment Visit 2**:
  - Wart count (Cohort 1),
  - Measurement and location of all warts,
  - Paring of warts (Cohort 2), if applicable,
  - Photos (if applicable),
  - Dermatologic exam, ERT,
  - Study drug application and occlusion with tape (if subject has any warts remaining). Removal of occlusive tape and Study drug 24 hours after application.
  - ERT phone call at 24h and day 7,
  - Any new warts should be counted (Cohort 1), measured, documented and treated per protocol,
  - Photos taken by subject (per protocol Cohort 1 & 2).
- **Treatment Visit 3:**
  - Wart count (Cohort 1),
  - Measurement and location of all warts,
  - Paring of warts (Cohort 2), if applicable,
  - Photos (if applicable),
  - Dermatologic exam, ERT,
  - Study drug application and occlusion with tape (if subject has warts remaining),
  - Removal of occlusive tape and Study drug 24 hours after application,
  - ERT phone call at 24h and day 7,

- Any new warts should be counted (Cohort 1), measured, documented and treated per protocol,
- ERT and wart count (Cohort 1) conducted over the phone if cleared at Treatment Visit 2,

- Photos taken by subject (per protocol Cohort 1 & 2) Treatment Visit 4:
  - Wart count (Cohort 1),
  - Measurement and location of all warts,
  - Photos (if applicable),
  - Dermatologic exam, ERT,
  - Paring of warts (Cohort 2), if applicable,
  - Study drug application and occlusion with tape (if subject has warts remaining),
  - Removal of occlusive tape and Study drug 24 hours after application,
  - ERT phone call at 24h and day 7,
  - Any new warts should be counted (Cohort 1), measured, documented and treated per protocol,
  - ERT and wart count (Cohort 1) conducted over the phone if cleared at Treatment Visit 3,
  - Photos taken by subject (per protocol Cohort 1 & 2).

- **"Unscheduled" Visit:** May take place at any time, as needed, to evaluate the subjects for safety reasons or for those subjects unable to be treated due to an ongoing LSR. For those subjects evaluated at their scheduled Treatment Visit as exhibiting untreatable warts, no treatment will be administered, and an "Unscheduled" treatment form will be completed. The following information should be obtained:
  - Reason treatment was not administered,
  - Dermatologic exam,
  - ERT, including LSR, wart count (Cohort 1) and location of all warts,
  - Photos (if applicable).

  - **Cohort 1: End of Study Visit (**EOS Day 84); Cohort 2: End of Treatment Visit (EOT; Day 84)In person: Vital signs, weight, wart count (Cohort 1),
  - Measurement and location of all warts,
  - Photos (if applicable),
  - Dermatologic exam and ERT,
  - Any new warts should be counted (Cohort 1), measured and documented per protocol,
  - Provider EOS/EOT Treatment Questionnaire.

- **Follow-up Visits** Cohort 2: (Day 105, Day 126 and Day 147)
  - In person: Vital signs,
  - Measurement and location of all warts,
  - Photos (if applicable),

- Dermatological exam and ERT,
- Any new warts should be measured and documented per protocol.

Study Duration:

Cohort 1: Study duration from Treatment Visit 1 through the EOS is approximately 84 days (12 weeks, may extend up to 98 days). No treatment should be administered after Day 63 without Sponsor's approval.

Cohort 2: Study duration from Treatment Visit 1 through the final follow-up is approximately 147 days (21 weeks). No treatment should be administered after Day 75 without Sponsor's approval. Post-treatment follow-up visits are included for subjects in Cohort 2 to evaluate the durability of treatment response over time.

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 14 days before, or on the same day as the first Study drug application. The dermatologic exam, wart count (Cohort 1), measurements, location of all warts, ERT and photos must be repeated if not conducted on the same day as treatment. Warts must measure at ≤10 mm in diameter and ≤3 mm in height for both Cohorts (paring can be performed, if necessary, in Cohort 2 prior to assessing height for inclusion).

Subjects that do not continue to meet criteria at Treatment Visit 1 will be discontinued and treated at physician discretion per standard of care. Those subjects that meet the enrollment criteria will be treated with application of VP-102 at Treatment Visit 1. Treatment will continue with a minimum of 14 days, in Cohort 1, and every 21 (+/- 4 days), in Cohort 2, until complete clearance or a maximum of 4 treatment sessions. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. In Cohort 1, subjects that achieve complete clearance of all treatable warts prior to Treatment Visit 4, will receive ERT phone calls at the required 2-week treatment intervals to assess the status of any Aes or skin reactions since the last visit and confirm there has been no recurrence in treated warts or new warts have developed. Subjects that report recurrence of, or presence of new warts, will be scheduled for a Treatment Visit per protocol. *(Consider calling the subject a few days prior to the 2-week interval (e.g., 11 or 12 days) to ensure adequate time for scheduling assessment and treatment if needed.)*

For those enrolled in Cohort 2, 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.

Inclusion criteria:

To qualify for inclusion in this study, subjects must:

1. Be healthy, immunocompetent males or females at least 2 years of age and older for Cohort 1 and 12 years of age and older for Cohort 2.
2. Present with 1-6 common warts (*verruca vulgaris*) 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, palms of the hands, volar surface of the fingers or toes, under the finger nails (near and

on the sides of the nails is allowed for Cohort 1, but warts near and on the sides of the nail (e.g., periungual) are not allowed in Cohort 2), soles of the feet, or the anogenital area. *(Warts within 10 mm of a mucosal surface should not be treated).*

3. Have warts that are ≤10 mm in diameter and ≤3 mm in height. *(Subjects with warts that are adjacent, touching or clustered may be included so long as the combined diameter in the longest direction does not exceed 10 mm. Individual lesions that are adjacent, touching or clustered should be counted as distinct lesions for the purposes of tracking, inclusion and clearance)(subjects in Cohort 2 can be pared, when necessary and appropriate, prior to evaluating height eligibility)* .
4. Have warts that have been present for at least 4 weeks at the time of the baseline visit.
5. Consent to having all warts treated (the physician must also be willing to treat all warts initially present).
6. Be otherwise medically healthy with no clinically significant medical history, physical examination or vital signs as determined by the investigator.
7. 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.
8. Refrain from swimming, bathing or prolonged immersion in water or any liquids until the Study drug is removed.
9. Have the ability, or have a guardian with the ability, to follow study instructions and be likely to complete all study requirements.
10. Agree to use no wart-removing product (prescription or over-the-counter [OTC]) other than the Study drug during the course of the study.
11. 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.
12. Provide written authorization for use and disclosure of protected health information.
13. If participating in the optional photographic portion of the study, agree to allow photographs of warts to be taken at each Treatment Visit by the research team and agree to share photos taken at home with the research team via text, email or in-person upload.

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, or will require, systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days prior to enrollment or during the course of the study. (*Routine use of inhaled or intranasal corticosteroids 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).* NOTE: Immunizations and flu shots may be administered throughout the study, but not within 5 days before or after treatment.
4. Have more than 6 common warts at baseline.

5. Present with any verruca plana, mosaiform, filoform, subungual (under the nail), genital or anal warts. In Cohort 2, subjects with periungual warts are also excluded.
6. Have any warts present at baseline in an anatomic location that the subject, parent/guardian or the physician is unwilling to treat or are located in an area that cannot be easily occluded with tape.
7. Have had any previous treatment of common warts including, but not limited to, the use of cantharidin, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, candida antigen, diphencyprone, dinitrochlorobenzene, sandalwood oil, thuja oil, squaric acid dibutyl ester, povidone iodine, nitric oxide, curettage or freezing of warts in the past 14 days. In addition, these treatments or any other over-the-counter wart treatment should not be implemented during the course of the study.
8. Have been treated within 14 days with a product that contains cantharidin (topical or homeopathic preparations) for any reason prior to screening.
9. Have received another investigational product as part of a clinical trial within 30 days prior to the first application of the Study drug.
10. Currently have or have a history of epidermodysplasia verrucifomis.
11. Have a history of illness or any dermatologic disorder, which, in the opinion of the investigator, will interfere with accurate assessment of the warts or increase the risk of adverse events.
12. Have an active malignancy or are undergoing treatment for any malignancy.
13. 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.
14. 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).
15. 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 prior to screening for an acute or chronic condition including alcohol or drug abuse),* at the discretion of the investigator.
16. 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 prior to treatment with Study drug.
17. Are pregnant or breastfeeding.

Test product, dose, and mode of administration: Study drug (VP-102) is contained within a single-use applicator. Topical administration results in approximately 10-20 µL of Study drug per common wart (≤10 mm in diameter and ≤3 mm in height). The VP-102 single-use applicator contains 0.45mL of 0.7% w/v cantharidin (3.15 mg). Study drug will be applied to the entirety of each wart including a 1-2mm margin of surrounding, healthy skin.

Duration of treatment: The length of study participation is approximately 84 days (may extend up to 98 days) for Cohort 1 and 147 days for Cohort 2. The study will consist of up to 4 applications of Study drug at intervals of at least 14-days, in Cohort 1, and 21 (+/- 4) days for Cohort 2. For Cohort 1, a 63-day treatment period is followed by an EOS assessment on Day 84. Cohort 2 will have a 75-day treatment period followed by an EOT assessment on Day 84 with additional follow-up visits on Day 105, Day 126 and Day 147.

After each treatment: Process for removal: At 24 hours (+/-8 hr) after drug application, subjects are instructed to wet the treated area with warm water and then carefully and slowly remove the occlusive 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 warm water after the tape is removed.

Note: The occlusive tape and Study drug may be gently removed from individual warts prior to 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. Subjects that remove Study drug prior to 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 at least 16 hours have passed from study drug application.

The occlusive tape and Study drug should not be removed from any remaining unproblematic warts until the 24-hour (+/- 8hrs) time point is reached. Washing of intact blisters should be gentle and without use of a washcloth. Washing and removal of occlusive tape in a bath or shower is encouraged. Photos should be taken by the subject or guardian after the tape and Study drug are removed when photos are applicable.

Criteria for evaluation

Efficacy: All enrolled subjects (Intent-To-Treat) who receive at least one treatment application will be evaluated for efficacy. Clinical response to treatment of warts will be evaluated at each scheduled in-person visit until EOS by counting all remaining warts. The Day 84 EOS Visit will require a final assessment of ERT (for Cohort 1) and confirmation of the presence or absence of treated and untreated warts as well as the final size and diameter for any that are remaining. Subjects in Cohort 2 will participate in an in-person EOT evaluation at Day 84 (- 0/+ 8 days). A provider EOT Questionnaire will be completed at the EOT Visit. Cohort 2 subjects will continue in the study for 3 additional follow-up assessments on Day 105, Day 126 and Day 147.

For Cohort 1 – (14-day treatment interval)

Primary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at the EOS Visit (Day 84).

Secondary endpoints:

- Change from baseline in the number of treatable warts (baseline and new) at the EOS Visit (Day 84).
- Change from baseline in the percent of treatable warts (baseline and new) at the EOS Visit (Day 84).
- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4 and over the duration of the study.

Exploratory endpoints:

- Percent reduction of all treatable warts (baseline and new) from baseline at Visit 2, Visit 3, Visit 4 and over the duration of the study.
- Change from baseline in the number of treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4 and the EOS Visit.
- Proportion of subjects exhibiting ≥ 50% clearance of all treatable warts (baseline and new) at the EOS Visit as compared to baseline.

- Proportion of subjects who respond to treatment, defined as a ≥ 50% reduction in total wart area at EOS compared to baseline.
- Proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline at Visit 2, Visit 3, Visit 4 and at the EOS Visit.

For Cohort 2 – (21 +/- 4 -day targeted treatment interval)

Primary endpoint:

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

Secondary endpoints:

- Change from baseline in the number of treatable warts (baseline and new) at the EOT Visit Day 84)
- Change from baseline in the percent of treatable warts (baseline and new) at the EOT Visit (Day 84)
- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4 and over duration of the study.

Exploratory endpoints:

- Percent reduction of all treatable warts (baseline and new) from baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and -over duration of the study.
- Change from baseline in the number of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and the EOT Visit (Day 84).
- Proportion of subjects exhibiting ≥ 50 % clearance of all treatable warts (baseline and new) at the EOT Visit (Day 84) as compared to baseline.
- 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.
- Proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline at Visit 2, Visit 3, Visit 4 and at the EOT Visit (Day 84)
- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at follow-up visits on Day 105, Day 126 and Day 147.
- Percent reduction of all treatable warts (baseline and new) from baseline at follow-up visits on Day 105, Day 126 and Day 147.
- Change from baseline in the number of treatable warts (baseline and new) at follow-up visits on Day 105, Day 126 and Day 147.

Safety: All subjects who meet the screening eligibility criteria for the study and receive at least one application of Study drug will be evaluated for safety. The following safety parameters will be assessed:

- Incidence of adverse events (AEs) throughout the study:

- A subject-by-subject AEs data listing, including verbatim term, preferred term, treatment, severity, location and causal relationship to the Study drug, will be provided.
- The number of subjects experiencing treatment emergent Adverse Events (TEAEs) and number of TEAEs will be summarized by treatment using frequency counts.
- AEs will include all local skin reactions whether or not they are expected or related to Study drug mechanism of action.

- Local Skin Reactions (LSRs) of all previously treated areas will be assessed at each Treatment visit using the protocol specific ERT form.
  - Subjects will have reviewed and be given take home instructions on removal of the occlusive tape and also descriptions of the potential local skin reactions 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 are also included.
  - ERT assessments will be conducted at each Treatment Visit 1-4, in-person, prior to re-treatment. ERT phone calls will also be conducted at 24 hours and 7 days after Treatment Visits 1-4 to confirm removal of the occlusive tape, assess treatment response, document any local skin reactions and any medical interventions taken. ERT assessments will be conducted whether or not treatment is applied. In Cohort 1, subjects that exhibit complete clearance prior to EOS will not be required to return to the clinic until EOS Day 84. ERT phone calls will be scheduled and conducted at each two-week treatment interval until the in-person EOS visit or the subject reports recurrence or new warts that require an in-person assessment and treatment. Cohort 2 subjects will be required to return for each Treatment Visit until EOT as well as Follow-up Visits on Day 105, 126 and 147.
  - A Local Skin Reaction Guide for subjects with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. This guide will be utilized for discussion during the ERT phone assessments with the research team member. Should a subject report experiencing excessive blistering, ulceration, edema, pain or another adverse event needing physician assessment, they will be scheduled for an "Unscheduled" study visit and safety evaluation as soon as possible.

- Medical history, vital signs, and physical examinations:
  - Medical history, wart history, Fitzpatrick Skin Type and limited physical exams will be collected for each subject. A limited physical examination will be completed before the first treatment and at the EOS visit. Vital signs (temperature and heart rate) will be obtained before the treatment is applied at each visit and at the start of the Day 84 (EOS) visit. Additional physical examinations will be performed when clinically warranted (e.g., subject reports symptoms classified as an AE requiring further evaluation).

Safety considerations: Investigators should confirm the Study drug is completely dry (2-5 minutes) prior to applying the occlusive tape or the subject coming into contact with furniture, clothing or other surface areas. When warts on the fingers are treated, the occlusive tape may be wrapped loosely around the finger. In addition, an adhesive bandage may be applied over the occlusive tape to keep it in place on areas that experience significant flexing such as finger joints or fingertips. VP-102 is considered highly flammable, even after drying. Subjects should avoid fire, flame or smoking during treatment.

Cantharidin has been shown to be safe for topical use, but it is highly toxic if ingested. To deter potential oral ingestion, a bitter compound has been added 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 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.

Statistical methods: The main objectives of this study are to determine the efficacy, safety and tolerability of VP-102 treatment in subjects with common warts. The primary efficacy endpoint of this study is the proportion of subjects who achieve complete clearance of all treatable warts on the Day 84 EOS/EOT visit. Safety endpoints include incidence of adverse events, local skin reactions, physical examinations and concomitant medications.

This is an open-label study where all subjects are to receive the Study drug. The study will enroll to treat a minimum of 20 subjects, 2 years of age and older, presenting with 1-6 common warts with the goal of approximately 20 subjects completing all study activities in Cohort 1 per protocol. Cohort 2 will utilize up to 4 sites to enroll approximately 35 subjects (12 years and older). Although no formal power calculations have been performed, it is expected that a sample size of 20 subjects (Cohort 1) and 35 subjects (Cohort 2) evaluable at the EOS/EOT visit (Day 84 for both Cohorts) will be informative regarding wart clearance rates that can support assumptions in subsequent placebo-controlled trials. A sample size of 20 completed subjects for Cohort 1 and approximately 35 subjects for Cohort 2, will provide information to build an adequate safety profile of VP-102 in common warts. The primary analysis will be conducted at Day 84 for both Cohorts. The final analysis will be conducted for Cohort 2 when the last patient has completed the visit on Day 147.

Subjects who receive all planned treatments of VP-102 (e.g., up to four treatments within the 63 day treatment window, or cleared of all treatable warts prior to Day 63 in Cohort 1; and in Cohort 2 complete up to four treatments within the Day 75 treatment window or clear prior to Day 75) and have no major protocol violations are assessed for clearance at the EOS visit and included in the Per Protocol population.

Subject demographics, efficacy tables and subject dropout rates will be tabulated at the end of the study. 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.

Adverse events, including local skin reactions, will be coded with the MedDRA® dictionary. 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 – Cohort 1

	Screening [a] Up to 14 days before Day 1	**Treatment 1: Day 1[b]**	**24 hr Phone Call[m]** +/-4 hrs	**Rx 1/Day 7 Phone Call[m]** +/- 1 Day	**Treatment 2[b]**	**24 hr Phone Call[m]** +/- 4 hrs	**Rx 2/Day 7 Phone Call[m]** +/- 1 Day	**Treatment 3[b]**	**24 hr Phone Call[m]**	**Rx 3/Day 7 Phone Call[m]** +/- 1 Day	**Treatment 4[b]**	**24 hr Phone Call[m]** +/- 4 hrs	**Rx 4/Day 7 Phone Call[m]** +/- 1 Day	**End of Study: Day 84[c] (+/- 7 days)**	**Unscheduled Visit[h]**
Informed Consent and Authorization	X														
Inclusion/ Exclusion Criteria		X													
Demographics[d]	X														
Height/Weight[e]	X													X	
Prior Relevant Medical History	X	X													
Wart History	X	X													
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (T/P)[e]		X			X			X			X			X	X
Physical Exam[f]	X													X	
Wart Count[g]		X			X			X			X			X	X
Wart Location & Measurement[g]		X			X			X			X			X	
Dermatologic Exam; (includes Fitzpatrick at Screen only)[g]		X			X			X			X			X	X
Urine Pregnancy Test[i]		X			X			X			X			X	
Photos (Site/Subject)[j]		X	X		X	X	X	X	X	X	X	X	X	X	
Study Drug Application		X			X			X			X				
Apply Occlusive Tape[k]		X			X			X			X				
ERT Assessments[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Take Home Instructions, LSR guide/subject education[m]		X			X			X			X				
Provider Questionnaire[n]														X	

EOS = end of study; LSR = local skin reactions; ERT= evaluation of response to treatment; MOP=Manual of Operations; T/P= temperature, pulse;

a. Screening can occur up to 14 days prior to 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, wart count wart count, measurement, location of all warts and dermatologic exam must be repeated prior to Study drug application. An IRB-approved ICF/Assent must be signed before any study specific procedures are performed.

b. Subjects are to be scheduled in 14-day intervals after each treatment. The next Treatment Visit is to be scheduled 14 days after the last treatment or study visit, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. Treatment should be administered within 4 days of becoming eligible due to resolution of LSRs. The EOS (Day 84) visit is targeted 6 weeks after Treatment Day 4 is completed but may occur as soon as 3 weeks after the final treatment. The 24-hour phone contact may be conducted at +/- 4 hours. The 7-day phone contact may be conducted +/- 1 day. Subjects that exhibit complete clearance prior to EOS will not be required to return to the clinic until EOS Day 84. ERT phone calls will be scheduled and conducted at each two-week treatment interval until the in-person EOS visit or the subject reports recurrence or new warts that require assessment and treatment per protocol.

c. A final in person safety assessment, ERT, wart count, photos and study completion form will be completed at the Day 84 (EOS) visit for all subjects. EOS conducted outside the Day 84 EOS visit window will be considered a protocol deviation. Treatments may be administered up to Day 63. Subjects that clear or complete treatment prior to EOS will be followed per protocol until the scheduled EOS visit but do not need to complete any remaining Treatment Visits and can receive follow up via telephone until the required in-person EOS visit.

d. Demographics: date of birth, sex, race/ethnicity will be collected.

e. Vital signs (e.g., temperature & heart rate) will be obtained at each treatment prior to application of Study drug. Height and weight will be collected at Screening/Day 1 and EOS.

f. Limited physical examination. Symptom or AE-directed physical examination may be performed if warranted. (See Source/eCRF for a more detailed description)

g. Dermatologic exam including Fitzpatrick Skin Type, wart count, wart counts (head/neck, chest/abdomen, back/buttocks, groin, upper/lower extremities, including fingers, hands and arms) should be performed identifying the location of each wart and documented on the body map and source as outlined in the MOP. Measurements of warts should be recorded on Day 1 prior to treatment to confirm they meet inclusion criteria of ≤10 mm in diameter and ≤3 mm in height. Wart counts and Wart counts, and assessments are to be completed prior to each treatment application and/or each in-person visit. New warts should be recorded in the corresponding Source/eCRF. Instructions for measuring wart counts and documenting the wart count and measurements are provided in the Manual of Operations (MOP).

h. "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.

i. To be performed prior to Study drug application and at EOS in any females of childbearing potential (females that are capable of menstruating).

j. Subjects that agree to participate in the photographic portion of the study will have photos of warts taken prior to each treatment by the study team. If there are no warts remaining, the same areas will be photographed and repeated at the EOS regardless of whether warts are present. Subjects will also be asked to take photos after each treatment at home every 24 hours for 5 days with their phone and either send photos via text or email to the research team or bring them for upload and storage at the next in-person study visit. 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).

k. Occlusive tape and Study drug may be gently removed from individual warts prior to 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. The occlusive tape and Study drug should not be removed from the remaining unproblematic warts until the 24-hour time point is reached. Removal of the occlusive tape should be aided by soap and warm water. This will also help to prevent unroofing the blisters. Subjects that remove Study drug prior to 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 by removal at < 16 hours after treatment is applied.

l. Phone assessments for ERT will be conducted at 24 hours and at 7 days after each Treatment Visits 1-4 where Study drug is applied. Assessments will be recorded by the research team member on the Evaluation of Response to Treatment (ERT) form. All ERT safety assessments must be conducted by a qualified member of the research team. There will be an additional in-person assessment conducted at Day 84 (EOS) to confirm the presence or absence of warts and record any new or status update of any ongoing treatment related AE's that may have occurred. For subjects that exhibit complete clearance prior to the end of treatment, ERT phone calls will be scheduled and conducted at each two-week treatment interval until the in-person EOS visit or the subject reports recurrence or new warts that require assessment and treatment per protocol.

m. Subjects will be given take-home instructions describing how to remove the occlusive tape, the possible local skin reactions 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. A Local Skin Reaction 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.

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

Table 2 Study Schedule of Assessments and Procedures - Cohort 2

s	Screening[a] Up to 14 days before Day 1	Treatment 1: Day 1[b]	24 hr Phone Call[m] +/-6 hrs	Rx 1/Day 7 Phone Call[m]	Treatment 2 21 days +/- 4 days[b]	24 hr Phone Call[m] +/- 6 hrs	Rx 2/Day 7 Phone Call[m]	Treatment 3/ 21 days +/- 4 days[b]	24 hr Phone Call+/- 6 hrs[m]	Rx 3/Day 7 Phone Call[m]	Treatment 4/ 21 days +/- 4 days[b]	24 hr Phone Call[m] +/- 6 hrs	Rx 4/Day 7 Phone Call[m]	End of Treatment Visit (Day 84)[c] -0/+8 Days	Follow-up visits at 21-day intervals[p] (Day 105, Day 126 and Day 147)	Unscheduled Visit[i]
sInformed Consent and Authorization	X															
Inclusion/ Exclusion Criteria		X														
Demographics[d]	X															
Height/Weight[e]	X													X		
Prior Relevant Medical History	X	X														
Wart History	X	X														
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (T/P)[e]		X			X			X			X			X		X
Physical Exam[f]	X													X		
Wart Location & Measurement[g]		X			X			X			X			X	X	
Dermatologic Exam; (includes Fitzpatrick at Screen only)[g]		X			X			X			X			X	X	X
Paring[h]		X			X			X			X			X		
Urine Pregnancy Test[j]		X			X			X			X			X		
Photos (Site/Subject)[k]		X	X		X	X		X	X	X	X	X	X	X	X	
Study Drug Application[l]		X			X			X			X					
Apply Occlusive Tape[l]		X			X			X			X					
ERT Assessments[m]		X	X	X	X	X	X	X	X	X	X	X	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[n]		X			X			X			X					
Provider Questionnaire[o]														X		

EOS = end of study; EOT=end of treatment; LSR = local skin reactions; ERT= evaluation of response to treatment; MOP=Manual of Operations; T/P= temperature, pulse;

a. Screening can occur up to 14 days prior to 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 & diameter), location of all warts and dermatologic exam must be repeated prior to Study drug application. An IRB-approved ICF/Assent must be signed before any study specific procedures are performed.

b. Subjects are to be scheduled in 21-day intervals (+/- 4 days) after each treatment for subjects in Cohort 2. 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 hrs.

c. A final in person safety assessment, ERT, photos and study completion form will be completed at the Day 147 (EOS) Visit 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 in Cohort 2. Subjects in Cohort 2 are to attend all visits whether they have achieved complete clearance prior to and at the Day 84 (- 0/+ 8 days) EOT assessment.

d. Demographics: date of birth, sex, race/ethnicity will be collected.

e. Vital signs (e.g., temperature & heart rate) will be obtained at each treatment prior to application of Study drug. Height and weight will be collected at Screening/Day 1, EOT Day 84 (- 0/+ 8 days) and subsequent follow up visits Day 105, 126 and 147 (EOS).

f. Limited physical examination. Symptom or AE-directed physical examination may be performed if warranted. (See Source/eCRF for a more detailed description)

g. Dermatologic exam including Fitzpatrick Skin Type, location of each wart is identified and documented on the body map and source as outlined in the MOP. Measurements of warts should be recorded on Day 1 prior to treatment to confirm they meet inclusion criteria of ≤ 10 mm in diameter and ≤3 mm in height. Wart location, measurements and assessments are to be completed prior to each treatment application and/or each in-person visit. New warts should be recorded in the corresponding Source/eCRF. Instructions for measuring and documenting the and measurements are provided in the Manual of Operations.

h. Paring at first visit by Dermatologist or qualified designee. Paring at additional treatment visits if significant hyperkeratosis or at Investigator's discretion.

i. "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.

j. To be performed prior to Study drug application and at Day 147; (EOS) in any females of childbearing potential (females that are capable of menstruating).

k. Subjects that agree to participate in the photographic portion of the study will have photos of warts taken prior to each treatment by the study team. If there are no warts remaining, the same areas will be photographed and repeated at the EOT and EOS regardless of whether warts are present. Subjects will also be asked to take photos at 24 hours after each treatment at home with their phone and either send photos via text or email to the research team or bring them for upload and storage at the next in-person study visit. 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).

l. Occlusive tape and Study drug may be gently removed from individual warts prior to 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. The occlusive tape and Study drug should not be removed from the remaining unproblematic warts until the 24-hour time point is reached. Removal of the occlusive tape should be aided by soap and warm water. This will also help to prevent unroofing the blisters. Subjects that remove Study drug prior to 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 by removal at < 16 hours after treatment is applied.

m. Phone assessments for ERT will be conducted at 24 hours and at 7 days after each Treatment Visits 1-4 where Study Drug is applied. 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. Subjects in Cohort 2 must attend all visits regardless of whether complete clearance of all warts has been achieved at a previous visit.

n. Subjects will be given take-home instructions describing how to remove the occlusive tape, the possible local skin reactions 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.

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

p. Subjects in Cohort 2 will return for follow-up visits on Day 105,126 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.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AMES	Genetic toxicity study: in vitro bacterial reverse mutation
CDLQI	Children's dermatology life quality index
cm	Centimeter
Con Meds	Concomitant medications
COVE	Cantharidin and Occlusion in Verruca Epithelium
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
GLP	Good laboratory practice
GMP	Good manufacturing practices
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human papilloma virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IFU	Instructions for use
IND	Investigational new drug application
I.P	Intraperitoneal
IRB	Institutional review board
ITT	Intent to treat
I.V	Intravenous
LSR	Local Skin Reaction
MC	Molluscum contagiosum
MOP	Manual of Operations
mg	Milligrams
mm	millimeter
Molluscum	Molluscum contagiosum
PPP	Per protocol population
QoL	Quality of life
SAE	Serious adverse event
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TSGH 8301	Human urinary bladder carcinoma cell line

uL	Microliters
VP-102	Verrica Pharmaceuticals-102 (0.7% w/v cantharidin)
Veruca	Verruca vulgaris (common warts)
W/V	weight/volume

2 INTRODUCTION

2.1 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 alone, with a growing number discovered each year. The majority of cutaneous warts are caused by HPV serotypes 1, 2, 3, 4, 7 and 10 (2). 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 hyperkeratotic 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 8,000 base pairs. This genetic material is surrounded by a 60-nanometer capsid composed of two interlocking proteins (L1 & L2), but no envelope (3). 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 (4). 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 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 years.

The rate of resolution depends on a number of factors including host immunity, HPV type, and site of infection. Although usually benign, warts are an infectious disease of the skin that should be treated to prevent transmission of the virus from person to person or autoinoculation to multiple sites on the same individual. In addition, verrucae can cause pain or discomfort, interfering with work or daily activities (5). Warts are frequently considered cosmetically unsightly, and unacceptable to the subject, 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 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 (6-8).

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 trichloroacetic 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., diphenylcyclopropanone, 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 recently been shown to be lacking (9). 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 (2, 10), and most authors agree that adequate clinical studies are lacking for many of the treatments, including those considered first line (9, 11) and newer modalities that are being used in an "off-labeled" 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 to have a cure rate of 57% vs 37% with placebo ($p<0.001$). For cryotherapy, a meta-analysis of 3 randomized clinical trials involving a total of 227 patients showed a cure rate of 38% vs 22% with placebo (p=NS) (9). 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) and can represent a significant cost to the patient and insurer (1).

2.2 Cantharidin

Cantharidin (1,2-dimethyl-3,6-epoxyperhydrophthalic anhydride) is a lipophilic natural compound that can be isolated 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*). *Lytta vesicatoria*, a metallic green beetle, was primarily used as a source of cantharidin in the early 1900s, as it is endemic to the United States. Regardless of species of blister beetle, 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.

Cantharidin functions as a vesicant, weakening desmosomes in the epidermis when applied topically via a liquid film-forming formulation. Application to the skin causes the release of neutral serine proteases resulting in the destruction of intercellular desmosomes responsible for holding the layers of the skin together (15). Intracellular tonofilaments are also weakened, the result being a fluid-filled, thin-walled epidermal vesicle. The superficial nature of the blisters is attributed to cantharidin's lesser effect on hemidesmosomes in the basal layer compared to the more superficial desmosomes. In almost all subjects, this process does not

cause a scar, as the underlying dermal layer of skin is undamaged. Cantharidin has no known direct antiviral effects.

Many physicians prefer cantharidin to other therapies for the treatment of molluscum such as cryotherapy, curettage or pricking individual lesions with subsequent expression of molluscum bodies because it is painless upon application, requires only limited treatment cycles for significant lesion reduction or complete resolution and is well-tolerated by subjects, most of whom are children. Furthermore, cantharidin's long history of use has provided strong evidence of its safety when applied topically.

Although cantharidin has been used extensively for decades in the treatment of several dermatologic conditions including molluscum contagiosum (molluscum) and verruca vulgaris, specifications for the quality of active pharmaceutical ingredient or a standardized formulation have never been established. Furthermore, a lack of reliable and regulated vendors of the compounded drug increases the chance of the drug product being inappropriately prepared, tested, stored or applied, which in turn increases the potential for unintended or even dangerous consequences in the future. Most currently used cantharidin preparations are prepared as 0.7% w/v (weight/volume) solutions in an acetone solvent with a flexible-collodion base in a screw-top glass bottle at volumes intended for repeated use across multiple subjects by the medical professional. This type of container closure system paired with highly volatile formulations presents multiple challenges. Current clinical practice, which 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. As a consequence, patients may receive an uncertain amount of cantharidin which may be more or less than what is anticipated by the medical professional. . While this does provide evidence of the safety profile for the drug, it also introduces unnecessary risk to the patient. Further, the nature of the liquid product coupled with the traditional application strategy of using the wooden end of a cotton-tipped swab makes it difficult to apply the minimum amount of drug necessary to achieve the desired effect. Complete treatment of all warts or lesions is further confounded by the fact that there is no visual indicator present in the formulation to clearly identify for physicians, patients and caregivers where the drug has already been applied during the treatment session.

To address these current shortfalls, Verrica Pharmaceuticals Inc. has developed VP-102, a 0.7% w/v cantharidin formulation, consistent with the predominant concentration of cantharidin used by physicians. Study drug (VP-102) will be administered with a single-use applicator to minimize cross-contamination and concentration changes during use. Each VP-102 applicator contains 0.45mL of drug product, with each VP-102 unit containing 3.15 mg of cantharidin. Gentian violet, a dye common in surgical markers, has also been included to facilitate physician recognition of treated vs. untreated lesions. Finally, to afford additional safety and deter potential oral ingestion of the drug by young subjects, the oral deterrent denatonium benzoate has been included.

2.2.1 Nonclinical Studies with Cantharidin

The majority of the nonclinical information on cantharidin comes from published literature along with two GLP genotoxicity studies conducted by Verrica Pharmaceuticals, Inc. Because of established use of cantharidin for topical application in the treatment of viral skin conditions like molluscum and warts, much of the nonclinical effort has been to explore the biological nature of the clinical efficacy with topical application and clinical toxicity associated with non-topical systemic exposure to cantharidin.

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 demonstrated clinically (Section 6.1-Investigator's Brochure (IB)). Cantharidin permeates into the lipid layers of epidermal cell membranes. Topical application of cantharidin weakens desmosomes in the epidermis through the release of neutral serine proteases (15). This process leads to acantholysis and intra-epidermal blistering that results in exfoliation of the wart. Epidermal irritation producing a localized inflammatory response and stimulation of the immune system is also believed to play a role in clearing common warts.

Cantharidin is a potent inhibitor of protein phosphatases types I and II that are found in all tissues (16). 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 (17). Cantharidin is a vasoconstrictor and may also be responsible for decreases in urine volume with single oral dose administration (17, 18). 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 (17), 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 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) (19). The apparent plasma elimination half-life of cantharidin was about 20 minutes in dogs(20). 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 (i.p.), and intravenous (i.v.) 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.

2.2.2 Clinical Studies with Cantharidin

Cantharidin has been used by healthcare providers for decades to treat Verruca vulgaris. The following summarizes completed and/or ongoing safety and efficacy studies conducted with VP-102.

VP-102 prospective studies

A 12-week, open-label Phase 2 study was implemented under IND 131163/NCT03186378. Subjects ≥ 2 yrs old with Molluscum contagiosum (MC) 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 4 treatments or until complete lesion clearance. Subjects were instructed to wash VP-102 off at 24 hrs, or earlier if significant pain or blistering. Lesion counts and adverse events (AEs), including local skin reactions, 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 MC lesions at Baseline were evaluated for systemic exposure with 4 blood samples (pre-VP-102 and 2, 6, & 24-hrs post). Key efficacy endpoints were % subjects exhibiting complete clearance of all treated MC lesions (baseline and new) on or before Week 12 and % reduction of treated MC lesions from Baseline at Week 12.

The mean age was 7.3 (range=3-15) yrs for the 33 subjects enrolled, with 32 completing the study. A total of 29 subjects (88%) reported at least one AE including expected local skin reactions such as blistering or erythema with no serious adverse events (SAEs). Sixteen subjects (50%) achieved complete clearance of all MC lesions on or before Week 12. The median lesion count was reduced from 23 (range 3-113) at Baseline to 1 (0-95) at Week 12 ($p<0.0001$). 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 hrs after VP-102 application, but not detectable at 6 & 24 hrs. The mean±SD CDLQI score was notably improved from 2.6±3.4 at Baseline to 0.4±0.9 at Week 12.

Treatment with VP-102 was well-tolerated and associated with significantly reduced lesion count, improved QoL and complete clearance of MC lesions in 50% of subjects.

A bridging study, 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. In the 6-hour cohort, 14 subjects were enrolled, and 13 subjects completed all study visits. A second cohort investigated a 24-hour treatment duration. In this cohort, 16 subjects were enrolled, and 12 subjects completed all study visits.. Overall, eleven subjects showed complete clearance out of 25 subjects in the per protocol population (PPP) (44 % clearance).

In this bridging study, there were no unexpected treatment related adverse events reported during application to 1,0 molluscum lesions in 14 subjects in the 6-hour cohort. Moreover, there were no treatment related adverse events reported with application to 712 lesions in 16

subjects in the 24-hour exposure to VP-102. Thus, this bridging study demonstrated that VP-102 appears to be safe and well tolerated in the treatment of pediatric molluscum, consistent with historically used cantharidin formulations.

The following summarizes significant prospective studies using compounded cantharidin as a treatment modality and documenting safety in molluscum contagiosum and both efficacy and safety in common warts.

Additional clinical information on the safety of cantharidin comes from over 50 years of experience with cantharidin (0.7% w/v) as a treatment for molluscum and warts. In all of these studies, the most commonly reported adverse events were blistering and pain at the site of application consistent with the pharmacologic activity of cantharidin. More infrequently rash, pruritus, pigment changes, ring warts and secondary infections were reported.

(Studies utilizing cantharidin for treatment of warts have been limited however all have shown either reduction or clearance over the course of one or several treatments. Treatment with 0.7% cantharidin has been safe and well tolerated in the treatment of common warts when used under the guidance of a trained medical professional. Below are several studies outlining the efficacy and safety profile using compounded cantharidin and in some instances, occlusive tape.

Panzer, et al. (21) applied 0.7% cantharidin combined with a 40% salicylic acid plaster under occlusive tape to 51 subjects treating a total of 122 warts. Paring was not performed. Subjects were treated and returned in 2 days for removal of the bandage and, if needed, debridement of the resulting blisters and application of antibiotic ointment. Of the treated warts, 64 were digital warts, 31 were plantar warts, 21 were periungual and 6 were located on the arms and legs. Only 6 out 122 warts required a second application 1-2 weeks later. A total of 46 subjects comprising 114 warts were completely cured. In 5 of the subjects, a total of 8 warts, exhibited poor response. Subjects experienced blistering and pain associated with the treatment until the blister was removed. There were seven instances where a ring wart developed with five spontaneously resolving and 2 requiring removal with curettage. Subjects were educated that the therapy may be painful starting 6-8 hours after application for a few days. No other untoward reactions related to cantharidin occurred.

Rosenberg, et al. (22) conducted a study utilizing 0.7% cantharidin without occlusion in 100 subjects with a total of 336 common warts on the hands. Thirty of the 100 subjects were under the age of 12. Treatment was applied at home by the subject daily with instructions to cover with an adhesive bandage, until cleared. Treatment resulted in the clearance of 112 of 178 subungual or paronychial warts and 103 of 158 common warts. None of the patients experienced pain, untoward blistering, or any other side effect. One subject with a wart on the palm developed ring wart that was later removed with liquid nitrogen.

Epstein and Epstein (23) conducted a study utilizing 0.7% cantharidin with occlusion under adhesive tape in 40 subjects with digital and periungual warts. No pretreatment was conducted. Single treatment cleared 36 out of 73 warts. In some subjects, multiple treatments were administered. By 3-4 weeks, 69 of 76 warts were clinically cleared. Thirty two of 45 digital warts and 9 of 12 subungual warts were deemed a long-term cure, defined

as lasting 4-6 months. Of those subjects followed for long-term cure, only 1 of 38 cured warts had recurred 21-18 months later. About half of the subjects experienced some pain from treatment which was relieved by opening the blister. Ring warts occurred in 2 instances.

Previous studies provide evidence of the safety, efficacy, and widespread use of 0.7% w/v cantharidin topical solution in the treatment of both molluscum and common warts in children of all ages, with no serious adverse events reported. However, there is a wide variation in the quality of the research conducted, timing between applications, duration of exposure of lesions to cantharidin and the exact formulations of cantharidin used.

2.3 Study Rationale

For many dermatologists, 0.7% w/v cantharidin has been the treatment of choice for warts for decades (24). However, cantharidin remains an unapproved drug, and there is no reliable or controlled source on the market. This study will evaluate VP-102, a controlled, highly-pure, standardized form of topical cantharidin manufactured under good manufacturing practices to address the problems associated with currently available compounded cantharidin products and the needs of subjects and medical professionals.

The primary objectives of Cohort 1 are (1) to evaluate the efficacy of dermal application of VP-102 when applied once every 14 days for up to 4 applications to common warts on subjects 2 years and older by assessing the proportion of subjects achieving complete clearance of all treatable warts at EOS visit (Day 4) and (2) to assess the safety and tolerability of VP-102 applied to common warts by assessing adverse events including expected local skin reactions, physical examinations, and concomitant medications.

The primary objectives for Cohort 2 are (1) to evaluate the efficacy of dermal application of VP-102 when applied once every 21days for up to 4 applications to common warts on subjects 12 years and older by assessing the proportion of subjects achieving complete clearance of all treatable warts at the EOT Visit (Day 84), and (2) to assess the safety and tolerability of VP-102 applied to common warts by assessing adverse events including expected local skin reactions, physical examinations, and concomitant medications at EOS.

2.4 Dose and Schedule Rationale

A 0.7% w/v cantharidin solution is the recognized therapeutic dose of cantharidin for both molluscum and wart treatment in dermatological clinical practice (24-28). The 0.7% w/v dose was determined to be safe in a recent double-blind Phase 2 study of 94 subjects for the treatment of childhood molluscum (29), and in a recently completed study of VP-102 (NCT# 03017846) with 30 subjects treated. Additionally, multiple publications have demonstrated safety and efficacy with a 0.7% cantharidin solution in common warts both with and without the use of an occlusive tape.

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 1-3-week treatment interval are often utilized. In Cohort 1, a 2-week (14 Day) interval with occlusion

was implemented. In an effort to refine the approach for using VP-102 in common warts and to maximize safety and efficacy, a 3-week (21 Day) interval, using both occlusion and paring will be used in Cohort 2. Additionally, it can sometimes be challenging to determine if a wart is completely cleared in 14 days post treatment due to ongoing LSRs. Hence treatment interval in Cohort 2 is increased to 21 days to allow adequate time for LSRs to resolve to enable evaluation of the treatment site. This study will enable us to determine if 21-day treatment interval is optimal for Study drug administration.

In this study, lesions will be covered with occlusive tape, a technique often used in the treatment of warts with cantharidin. It is believed that this technique helps the drug penetrate into the hyperkeratotic tissue and may result in improved efficacy. In Cohort 2, paring of lesions will be conducted prior to 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 ≤10 mm in diameter and ≤3 mm in height.

We are also instructing investigators to treat a 1-2mm margin of healthy skin surrounding each wart in an attempt to reduce the occurrence of "ring warts" which have been reported with compounded cantharidin treatment of common warts. Ring warts may occur when subclinical infected tissue surrounding the visible wart is disturbed but not removed or destroyed. In the event a subject develops ring wart during the course of treatment, it is up to the investigators discretion 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.

The anticipated VP-102 prescribing label will focus on treatment of subjects with one or more treatable common warts. Each wart is typically about 3 mm to 7 mm (7-38 mm^2) in diameter, and Verrica estimates that approximately 10-20 µL of VP-102 is sufficient to cover each wart and a surrounding 1-2 mm margin of healthy skin. A single use applicator should be sufficient to treat all warts as outlined in the protocol. No more than 1 applicator may be used per treatment visit on each subject.

3 OBJECTIVES

3.1 Cohort 1: Primary Objectives

The primary objectives are

- to evaluate the efficacy of dermal application of VP-102 when applied once every 14 days for up to 4 applications to common warts on subjects 2 years and older by assessing the proportion of subjects (2 years and older) achieving complete clearance of all treatable warts (baseline and new) at the End of Study (EOS).
- to assess the safety and tolerability of VP-102 by assessing adverse events including expected LSR, physical examinations, and concomitant medications.

3.2 Cohort 1: Secondary Objectives

The secondary objectives are:

- to evaluate the efficacy of VP-102 by assessing the change from baseline in the number of treatable warts (baseline and new) at the EOS Visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the change from baseline in the percent of clearance of treatable warts (baseline and new) at the EOS Visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts at (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and at EOS Visit (Day 84) .

3.3 Cohort 1: Exploratory Objectives

The exploratory objective is:

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

3.4 Cohort 2: Primary Objectives

- to evaluate the efficacy of dermal application of VP-102 when applied once every 21 days for up to 4 applications to common warts by assessing the proportion of subjects (12 years and older) achieving complete clearance of all treatable warts at the EOT Visit (Day 84).
- to assess the safety and tolerability of VP-102 by assessing adverse events including expected LSRs, physical examinations, and concomitant medications.

3.5 Cohort 2: Secondary Objectives

- to evaluate the efficacy of VP-102 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 by assessing the change from baseline in the percent of clearance of treatable warts (baseline and new) at the EOT Visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts at (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and EOT Visit.

3.6 Cohort 2: Explorative Objective

- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at follow-up visits on Days 105, 126 and 147.

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

4 STUDY DESIGN

4.1 Basic Design Characteristics

This is a Phase 2, open label multi-center study [Study number VP-102-105; referred to as COVE-1 (Cantharidin and Occlusion in Verruca Epithelium)] that will be conducted in the United States to determine the safety, efficacy and tolerability of VP-102 treatment in subjects with common warts.

This study has two Cohorts. The first Cohort (Cohort 1) utilizes a treatment interval of at least 14 days between treatments with longer treatment intervals being allowed depending on a specific patient's clinical response. No paring of lesions is allowed. Twenty subjects (2 years and older) are targeted for completing EOS Visit in Cohort. 1. The second Cohort (Cohort 2) utilizes a treatment interval of 21 days between treatments. Paring of lesions is allowed in Cohort 2 only. Approximately 35 subjects (12 years and older) will be enrolled in Cohort 2. Up to 4 sites will participate in the study.

All subjects will receive the Study drug VP-102 (0.7% cantharidin topical film forming solution). Duration of warts prior to Treatment Visit 1 must be at least 4 weeks.

Study drug (VP-102) will be supplied in single-use applicators, with one applicator sufficient to treat 1-6 common warts. No more than 1 applicator will be permitted per subject per treatment. The film-forming Study drug solution will be applied and left on the warts, under occlusive tape, for 24 hours before the subject/guardian removes the occlusive tape and washes the warts with soap and warm water. Occlusive tape and Study drug may be removed prior to the 24-hour time point in the event significant blistering, significant pain or treatment-emergent AEs are experienced.

To assess eligibility, a dermatologic exam, wart counts (Cohort 1), and measurement of diameter and height of each wart will be conducted by a qualified member of the research team prior to the first treatment. Additional Treatment Visits will include wart count (Cohort 1), measurement of diameter and an evaluation of response to treatment, prior to treatment application when applicable. For those visits where subjects have received treatment, additional ERT assessments will be conducted over the phone at 24-hours and 7 days after treatment. (*Specific instructions on how to conduct the wart count (Cohort 1)and measure wart diameter and height are provided in the study specific Manual of Operations (MOP). Instructions for application of the Study drug are outlined in the Instructions for Use (IFU) included in the drug shipment as well as in the Investigator's Brochure)*. Subjects presenting with 1-6 warts may be enrolled. Clusters of warts may be enrolled as long as the cluster is no larger than 10mm in diameter. Measurements of individual warts should be obtained, even when presented in a cluster, if at all possible. For warts that are touching or adjacent, it is up to the Investigator to determine whether a wart should be measured as combined or as a separate wart. The height and longest diameter of each wart should be accurately documented on the source form and in the eCRF.

Warts will be treated in all anatomic areas excluding the eye area (including eyelids), lips, oral cavity, nasal cavity, inside of the ears, palms of hands, volar surface of the fingers or

toes, under the fingernails (near the nails is allowed), soles of the feet, or the anogenital area. For study enrollment, the physician must be willing to treat all lesions initially present.

Treatment will be applied up to four times during a 63-day treatment period for Cohort 1 and 75-day treatment period for Cohort 2. The treatment interval in Cohort 1 is determined by the subject's clinical response and will be at least 14 days. The treatment interval in Cohort 2 is 21 days.

It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing local skin reactions. At any visit where the investigator is unable to evaluate or treat some warts due to ongoing local skin reactions, an "Unscheduled" Visit should be documented. The timing of the next visit will be determined by the resolution of the local skin reaction. A Treatment Visit should be documented at every visit where 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.

For Cohort 2, Study drug is to be applied to the wart site on any Treatment Visit where 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.)* Should it become clear that the subject will be unable to complete the EOS visit within the allowed window of Day 84 (- 0/+ 8) days, the subject should be brought in for their EOS visit as soon as they are able. This will be documented as a protocol deviation.

In instances where 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 and assessments are to take place in order (e.g., Treatment 1, Treatment 2, Treatment 3 and Treatment 4). Subjects that receive fewer than 4 treatments within the 63-day (Cohort 1) or 75-day (Cohort 2) treatment period, due to the duration of post-treatment local skin reactions, will not be considered a protocol deviation. No treatment should be administered after the 63-day treatment period in Cohort 1 or the 75-day treatment period in Cohort 2 without Sponsor's approval.

Subjects in Cohort 1 that achieve complete clearance of all treatable warts prior to Treatment Visit 4, will receive ERT phone calls at the required 2-week treatment intervals to assess the status of any AEs or skin reactions since the last visit and confirm there has been no recurrence or development of new warts. In the event warts are present, the subject will be scheduled for a Treatment Visit per protocol. (*Consider calling the subject a few days prior to the 2-week interval (e.g.,11 or 12 days) to ensure adequate time for scheduling assessment and treatment if needed)*.

Subjects participating in Cohort 2, will be required to attend all visits regardless of whether they have achieved complete clearance of all warts at a previous visit. At these visits, Study drug application is not required if the warts have been clear for at least one follow up visit

and the investigator determines that additional treatment is not needed. Subjects participating in Cohort 2, that have completed their Day 84 EOT visit (- 0/+ 8 days), will be assessed at 3 additional follow-up visits conducted at Day 105, Day 126 and Day 147.

Subjects in Cohort 1who are not assessed as 100% cleared of all treatable lesions at the Day 84, (EOS) visit will have completed the study and will be further treated per standard of care at their physician's discretion but may not be re-enrolled in this study. Subjects in Cohort 2 who are not assessed as 100% cleared of all treatable lesions at the Day 147; (EOS) visit will have completed the study and will be further treated per standard of care at their physician's discretion but may not be re-enrolled in this study

All subjects will receive application of the Study drug (VP-102) to common warts including a 1-2 mm margin of healthy, surrounding skin with an interval of at least 14 days in Cohort 1, and every 21 days in Cohort 2, until complete clearance of all treatable warts, or a maximum of 4 applications. Warts are to be treated and then occluded with transparent surgical tape (e.g.; 3M™ Blenderm™ brand) that will remain on overnight and removed just prior to the 24-hour ERT phone call.

Subjects in Cohort 2 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 prior to application of Study drug. Wart paring is 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 re-treated only after 14-days have elapsed in Cohort 1 and 17 days (i.e., 21 +/- 4 days) have elapsed in Cohort 2, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. Treatment should be administered within 4 days of becoming eligible due to resolution of LSRs.

For Cohort 1,subjects that achieve complete clearance of all treatable warts prior to the EOS visit, will return to the clinic for a final EOS visit at Day 84.

For Cohort 2 subjects are to attend all visits regardless of whether they have achieved complete clearance prior to and at the Day 84, (- 0/+ 8 days) EOT assessment.

Phone calls will be conducted at an interval of 24 hours and 7 days after each Treatment Visit (not "Unscheduled" Visits) to assess if there have been any adverse events 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 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 manual of operations.

ERT will be performed in person, prior to each treatment. ERT phone calls will be conducted at 24-hours and 7 days after each Treatment 1-4 to assess treatment response, document any

local skin reactions and any medical interventions taken if treatment was administered. The following clinical responses will be recorded as part of the ERT with type and intensity recorded on the AE log: blistering, pain, pruritus, erythema, edema, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting, and pigmentation changes (hyperpigmentation or hypopigmentation). Scarring and ring wart will be assessed at each Treatment Visit and the EOS/EOT Visit by a qualified medical professional. Scarring and ring wart information will not be collected as part of the phone assessment. Additional information related to AEs and ConMeds will also be collected during each assessment. The subject and/or guardian will have time to ask questions and review any concerns. In the event any adverse events present a safety concern, an "Unscheduled" clinic visit will be made, and the subject assessed accordingly.

All subjects in Cohort 1, will participate in an in-person EOS evaluation that will take place at Day 84. A Provider EOT Questionnaire will be completed at the EOS. Subjects in Cohort 2 will participate in an in-person EOT evaluation at Day 84 (- 0/+ 8). A provider EOT Questionnaire will be completed at the EOT Visit. Cohort 2 subjects will continue in the study for 3 additional follow-up assessments at Day 105, Day 126 and Day 147. The follow-up visit window is +/- 4 days.

To assist the research team in the ERT phone calls, education materials in the form of a local skin reaction guide with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. Should a subject report experiencing excessive blistering, ulceration, edema.pain or another adverse event needing physician assessment during the ERT call, they will be scheduled for an "Unscheduled" study visit and safety evaluation as soon as possible.

Subjects in Cohort 1 will be asked if they are interested in participating in a subset of the study where with consent, the research team may take in-office photos of each treated wart at each Treatment Visit. Photos of up to 8 subjects will be obtained with a goal of obtaining sequential sets of images of each wart from Treatment Visits 1-4 and EOS. Subjects will also be asked to take daily photos at home with their smart phones and either text, e-mail or bring them to the site for upload to a secure site server.

At designated sites, subjects in Cohort 2 will be asked if they are interested in participating in a subset where they will be consented for in-office photos at each treatment and follow-up study visit through Day 147. Subjects will also be asked to take photos of their warts at home with their smart phones and either text, e-mail or bring them to the site for upload to a secure site server. These photos will be obtained at 24 hours post treatment.

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 HIPAA compliant manner. Effort will be made to ensure that no photos with identifiable features are obtained.

Subjects will be given take-home instructions describing the potential local skin reactions and what they might expect throughout the course of the study. The instructions include

recommendations for wound care, when it is important to call their doctor, who to contact in the event of emergency and a 24-hour emergency number. The additional scheduled visits and calls up through the next Treatment Visit, or EOS, will also be indicated on this form. Take-home instructions will be reviewed and provided at each Treatment Visit.

Subjects 18 and older must provide consent as required by the IRB before any study procedures are conducted. Parents or guardians must provide informed consent, and pediatric subjects older than 10 years must provide assent as required by the IRB before any study procedures are conducted. Subjects must meet all study eligibility criteria through a complete review of pertinent medical history, a dermatologic exam/lesion count and limited physical examination. Full inclusion/exclusion criteria are provided in Section 4.2.

4.2 Study Population

Cohort 1 will enroll and treat a minimum of 20 subjects, 2 years of age and older, presenting with 1-6 common warts with the goal of approximately 20 subjects completing all study activities per protocol. Cohort 2 will utilize up to 4 sites to enroll approximately 35 subjects (12 years and older). Eligibility to participate in the study will be determined by the investigator on the basis of the inclusion and exclusion criteria.

4.2.1 Inclusion Criteria

To qualify for inclusion in this study, subjects must:

1. Be healthy, immunocompetent males or females at least 2 years of age or older for Cohort 1 and 12 years and older for Cohort 2.
2. Present with 1-6 common warts (*verruca vulgaris*) 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, palms of the hands, volar surface of the fingers or toes, under the finger nails (near and on the sides of the nails is allowed for Cohort 1, but warts near and on the sides of the nail (e.g., periungual) are not allowed in Cohort 2), soles of the feet, or the anogenital area. *(Warts within 10 mm of a mucosal surface should not be treated).*
3. Have warts that are ≤10 mm in diameter and ≤3 mm in height. *(Subjects with warts that are adjacent, touching or clustered may be included so long as the combined diameter in the longest direction does not exceed 10 mm. Individual lesions that are adjacent, touching or clustered should be counted as distinct lesions for the purposes of tracking, inclusion and clearance)(subjects in Cohort 2 can be pared, when necessary and appropriate, prior to evaluating height eligibility, See manual of operations for details).*
4. All warts must be present for at least 4 weeks at baseline visit.
5. Consent to having all warts treated (the physician must also be willing to treat all warts initially present).
6. Be otherwise medically healthy with no clinically significant medical history, physical examination or vital signs as determined by the investigator.

7. Are 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.
8. Refrain from swimming, bathing or prolonged immersion in water or any liquids until the Study drug is removed.
9. Have the ability, or have a guardian with the ability, to follow study instructions and be likely to complete all study requirements.
10. Agree to use no wart-removing product (prescription or over-the-counter [OTC]) other than the Study drug during the course of the study.
11. 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.
12. Provide written authorization for use and disclosure of protected health information.
13. If participating in the optional photos portion of the study: Agree to allow photographs of warts to be taken at each Treatment Visit by the research team and agree to share photos taken at home with the research team via text, email or in-person upload.

4.2.2 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, or will require, systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days prior to enrollment or during the course of the study. (Routine use of inhaled or intranasal corticosteroids 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). NOTE: Immunizations and flu shots may be administered throughout the study, but not within 5 days before or after treatment.
4. Have more than 6 common warts at baseline.
5. Present with any verruca plana, mosaiform, filoform, subungual (under the nail), genital or anal warts. In Cohort 2, subjects with periungual warts are also excluded.
6. Have any warts present at baseline in an anatomic location the subject, parent/guardian or the physician is unwilling to treat or are located in an area that cannot be easily occluded tape.
7. Have had any previous treatment of common warts including but not limited to the use of cantharidin, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, candida antigen, diphencyprone, dinitrochlorobenzene, sandalwood oil, thuja oil, squaric acid dibutyl ester, povidone iodine, curettage or freezing of warts in the past 14 days. In addition, these treatments or any other over-the-counter wart treatment should not be implemented during the course of the study.

8. Have been treated within 14 days with a product that contains cantharidin (topical or homeopathic preparations) for any reason prior to screening.
9. Have received another investigational product as part of a clinical study within 30 days prior to the first application of the Study drug.
10. Currently have, or have a history of, epidermodysplasia verrucifomis.
11. Have a history of illness or any dermatologic disorder which, in the opinion of the investigator, will interfere with accurate assessment of the warts or increase the risk of adverse events.
12. Have an active malignancy or are undergoing treatment for any malignancy.
13. 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.
14. 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).
15. 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 prior to screening for an acute or chronic condition including alcohol or drug abuse), at the discretion of the investigator.
16. 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 prior to treatment with Study drug.
17. Are pregnant or breastfeeding

4.3 End Points

For Cohort 1 - (14-day treatment interval)

Primary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at the EOS Visit (Day 84).

Secondary endpoints:

- Change from baseline in the number of treatable warts (baseline and new) at the EOS Visit (Day 84).
- Change from baseline in the percent of treatable warts (baseline and new) at the EOS Visit.

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4, and over the duration of the study.

Exploratory endpoints:

- Percent reduction of all treatable warts (baseline and new) from baseline at Visit 2, Visit 3, Visit 4 and over the duration of the study.
- Change from baseline in the number of treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4 and at the EOS Visit.
- Proportion of subjects exhibiting ≥ 50% clearance of all treatable warts (baseline and new) at the EOS Visit as compared to baseline.
- Proportion of subjects who respond to treatment defined by a ≥ 50% reduction in total wart area at EOS Visit compared to baseline.
- Proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline at Visit 2, Visit 3, Visit 4 and at the EOS Visit.

For Cohort 2 – (21 +/- 4 -day targeted treatment interval)Primary endpoint:

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

Secondary endpoints:

- Change from baseline in the number of treatable warts (baseline and new) at the EOT Visit Day 84).
- Change from baseline in the percent of treatable warts (baseline and new) at the EOT Visit (Day 84).
- Proportion of subjects exhibiting complete clearance of all treatable warts, (baseline and new), at Visit 2, Visit 3, Visit 4 and over the duration of the study.

Exploratory endpoints:

- Percent reduction of all treatable warts (baseline and new) from baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and over the duration of the study.
- Change from baseline in the number of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and the EOT Visit (Day 84)
- Proportion of subjects exhibiting ≥ 50 % clearance of all treatable warts (baseline and new) at the EOT Visit (Day 84) as compared to baseline.
- 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.
- Proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline at Visit 2, Visit 3, Visit 4 and at the EOT Visit (Day 84).

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at follow-up visits on Day 105, Day 126 and Day 147.
- Percent reduction of all treatable warts (baseline and new) from baseline at follow-up visits on Day 105, Day 126 and Day 147.
- Change from baseline in the number of treatable warts (baseline and new) at follow-up visits on Day 105, Day 126 and Day 147

4.3.1 Safety

All subjects who meet the screening eligibility criteria for the study and receive at least one application of Study drug will be evaluated for safety. The following safety parameters will be assessed:

- Incidence of adverse events (AEs) throughout the study:
  - A subject-by-subject AEs data listing, including verbatim term, preferred term, treatment, severity, location and causal relationship to the Study drug, will be provided.
  - The number of subjects experiencing treatment emergent Adverse Events (TEAEs) and number of TEAEs will be summarized by treatment using frequency counts.
  - AEs will include all local skin reactions whether or not they are expected or related to Study drug mechanism of action.

- LSRs of all previously treated areas will be assessed at each Treatment Visit using the protocol specific ERT form.
  - Subjects will have reviewed and be given take home instructions on removal of the occlusive tape and also descriptions of the potential local skin reactions 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 are also included.
  - ERT assessments will be conducted at each Treatment Visit 1-4, in-person, prior to re-treatment. ERT phone calls will also be conducted at 24 hours and 7 days after Treatment Visits 1-4 to confirm removal of the occlusive tape, assess treatment response, document any local skin reactions and any medical interventions taken. ERT assessments will be conducted whether or not treatment is applied. Cohort 1 subjects that exhibit complete clearance prior to EOS, will not be required to return to the clinic until EOS Day 84. ERT phone calls will be scheduled and conducted at each two-week treatment interval until the in-person EOS visit or the subject reports recurrence or new warts that require an in-person assessment and treatment. Cohort 2 subjects will be required to return for each Treatment Visit until EOT as well as Follow-up Visits on Day 105, 126 and 147.
  - A LSR Guide for subjects with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. This guide will be utilized for discussion during the ERT phone

assessments with the research team member. Should a subject report experiencing excessive blistering, ulceration, edema, pain or another adverse event needing physician assessment, they will be scheduled for an "Unscheduled" study visit and safety evaluation as soon as possible.

- Medical history, vital signs, and physical examinations:
  - Medical history, wart history, Fitzpatrick Skin Type and limited physical exams will be collected for each subject. A limited physical examination will be completed before the first treatment and at the EOS visit. Vital signs (temperature and heart rate) will be obtained before the treatment is applied at each visit and at the start of the Day 84 (EOS) Visit. Additional physical examinations will be performed when clinically warranted (e.g., subject reports symptoms classified as an AE requiring further evaluation).
- Limited physical examinations will be performed by a qualified medical practitioner at screening and at EOS visits. Height and weight will be recorded at the screening visit and at the EOS Visit. Unscheduled physical examinations will be performed when clinically warranted (e.g., if a subject reports signs or symptoms requiring further evaluation).
- Vital signs (e.g., heart rate and temperature) will be obtained at all Treatment Visits prior to treatment. A final assessment of vital signs will be obtained at the EOS Visit.
- If the subject discontinues the study prematurely (after the first treatment) for any reason, attempts will be made to encourage the subject/guardian to complete the EOS assessments.
- Subjects will be monitored for signs and symptoms of AEs throughout the study. All AEs (including LSRs) will be reported on the source and in the electronic case report form (eCRF), including seriousness, severity, action taken, and relationship to the Study drug. If AEs should occur, the first concern will be the safety of the subject.
- Assessment of LSRs will be recorded at each Treatment Visit using the protocol specific ERT form. Additional assessments will be conducted at 24-hours after treatment by phone contact using the ERT form. LSRs will be considered AEs even though some LSRs may be part of the normal response to treatment and correlated with efficacy. The following LSRs will be recorded: blistering, pain, pruritus, erythema, edema, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting and pigmentation changes (hyperpigmentation or hypopigmentation). These responses will be queried for duration and intensity. Scarring and ring warts will be evaluated in person by a qualified practitioner who is a trained member of the research team at in office Treatment Visits and the EOS visit.
- If the subject develops ring wart during the course of treatment, it is up to the investigators discretion 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.
- Medical interventions taken throughout the course of the study prior to initial treatment and at 24-48 hours after treatment.

4.3.2 Efficacy

Efficacy parameters will be recorded for all enrolled subjects (Intent to treat) who receive at least one treatment application will be evaluated for efficacy. Clinical response to treatment will be evaluated at each scheduled visit until EOS by counting all treatable warts. Untreatable warts, if they arise, will be tracked and recorded.

4.4 Enrollment & Dropouts

Pre-study screening for eligibility (informed consent and assent [when applicable]), demographics, physical exam, prior and current concomitant medications, dermatologic exam with Fitzpatrick skin type, wart and medical history can occur up to 14 days before, or on the same day as the first Study drug application. The wart count (Cohort 1), measurements, location of all warts, ERT and photos must be repeated if not conducted on the same day as treatment. Subjects that do not continue to meet criteria at Treatment Visit 1 will be discontinued and treated at physician discretion per standard of care. Those subjects that meet the enrollment criteria will be treated with application of VP-102 at Treatment Visit 1. Treatment will continue with a minimum of 14 days between treatment until complete clearance or a maximum of 4 treatment sessions. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. For subjects that achieve complete clearance or all treatable warts prior to Treatment Visit 4, ERT phone calls will be conducted at the required 2-week treatment intervals to assess the status of any AE's or skin reactions since the last visit and confirm there has been no recurrence in treated warts or new warts have developed. Subjects that report recurrence of, or presence of new warts, will be scheduled for a Treatment Visit per protocol. *(Sites should consider calling the subject a few days prior to the 2-week interval (e.g.,11 or 12 days) to ensure adequate time for scheduling assessment and treatment if needed.)*

The Day 84 EOS Visit will require a final assessment of ERT (for Cohort 1) and confirmation of the presence or absence of treated and untreated warts as well as the final size and diameter for any that are remaining. Subjects in Cohort 2 will participate in an in-person EOT evaluation at Day 84 (- 0/+ 8 days). A provider EOT Questionnaire will be completed at the EOT Visit. Cohort 2 subjects will continue in the study for 3 additional follow-up assessments on Day 105, Day 126 and Day 147. Each investigator conducting this final wart assessment, must be a study qualified member of the research team.

REPLACEMENT OF DROPOUTS

Subjects who do not complete the EOS/EOT assessment will be considered dropouts. Subjects who are enrolled in the study but never receive study drug will also be considered dropouts. Dropouts will not be replaced.

All treated subjects (including dropouts) will be evaluated in the intent-to-treat population. Those subjects who do not complete the full treatment due to lack of protocol adherence or who request to be discontinued from the study will be replaced. In the event a subject request 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 will be replaced. Further discussion of how treatment failure will be utilized in analysis will be provided in the statistical analysis plan.

If a subject subsequently becomes able to provide informed consent (turns of legal age while on study) or a legally authorized representative is located after enrollment, information about the trial should be provided and procedures from the IRB/ethics committee will be followed. The subject or legally authorized representative can withdraw consent at any time during the study and for any reason without any penalty or changes to care. Data collected to the point that consent is withdrawn are still assessable by the principal investigator. If subjects do not want their data that has already been submitted or collected specimens utilized, they will need to submit a request in writing to the Investigator for removal of their information.

5 DRUGS AND DOSAGES

5.1 Identification and Description of Investigational Product

5.1.1 Investigational Product

VP-102 is a 0.7% w/v solution of cantharidin in a film-forming excipient system. 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.

VP-102 is packaged in a single-use applicator delivering up to 0.45 mL of a 0.7% w/v cantharidin formulation. Each unit contains up to 3.15 mg of cantharidin. Although the VP-102 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 (GMP).

Unlike previous studies with cantharidin, VP-102 is to be delivered via a single-use applicator. Each lot of applicators will be released for clinical use after a subset has undergone applicator suitability testing and demonstrated that they can deliver at least 50 droplets of drug product in a controlled manner without leaking or spilling. A visual assessment will confirm that the delivered drug product is free from glass particles large enough to break the skin. Once the commercial product completes all required testing they will be released for use in the clinical study.

Similar packaging systems containing crushable glass ampules in plastic housings with attached filters and/or tips are used in FDA approved medical products for the application of medical adhesives like Dermabond® (PMA number P960052) and antiseptics like Chloraprep® (NDA 21-555) as well as in commonly used OTC analgesics and antiseptics like Orajel® Singles and Medicaine®. The primary manufacturer for many of these applicators as well as the VP-102 applicator described herein is an FDA registered manufacturer of both drugs and medical devices. Many of the products they manufacturer are used directly by patients and others are used in an urgent care setting and applied to high-risk patient populations, including premature infants. VP-102 is manufactured in a GMP facility.

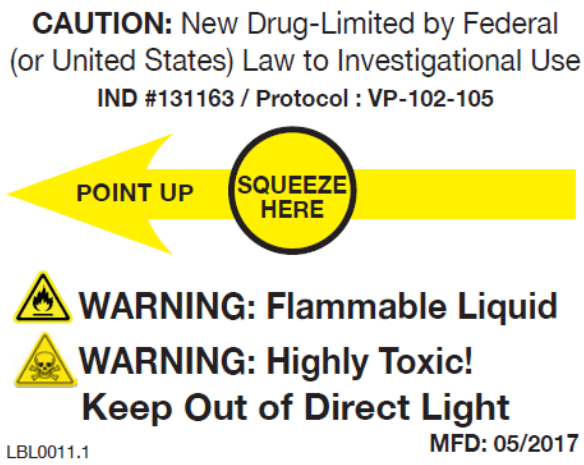
Compounded cantharidin is often used according to USP guidelines with a 180-day expiration date even though formal stability studies have not been conducted. Formal stability studies with VP-102 have shown that it is stable for at least 6 months under both controlled room temperature and under accelerated conditions. Therefore, we expect this product to be stable for at least 18-months under the recommended storage conditions. Additional formal stability is ongoing and may extend the expiration date.

5.1.2 Labeling

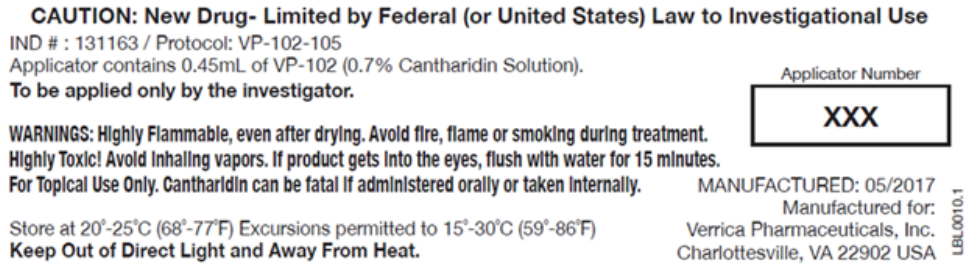
An example of the label on Study drug single-use applicator packaging is presented in Figure 1. The applicator will also display the appropriate standard flammable sign.

Figure 1 Clinical Trial Labeling of Study Drug

Label on Applicator



Label on Bag Around Each Applicator



5.2 Dosing Instructions and Schedule

Upon activation, clinical sites will be provided with an initial supply of single-use applicators that each contains 0.45mL of the Study drug (VP-102). One applicator should be used to treat up to 6 common warts.

Following examination, subjects will receive application of Study drug to all warts with a minimum of 14 days (for Cohort 1) and 21 days (for Cohort 2) between treatment until

complete clearance or a maximum of 4 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 (IFU), located in the accompanied Investigational Brochure for step-by-step instructions.

Additional points to Consider:

Given the length of time or complexity it may take to treat all warts, investigators will assess in advance if subjects will be cooperative and able to sit still during the entire application of Study drug. Application may not be conducted over more than 1 visit. Subjects may be rescheduled for the first treatment as long as it is within the 14-day screening time period. Otherwise they will need to be rescreened and consent reviewed to participate.

Make sure the entire wart is covered including a 1-2 mm margin of surrounding, healthy skin. The Study drug must be completely dry before applying the occlusive tape. Tape MUST not be applied until the product is completely dry (approx. 2-5 min). Occlusive tape should be gently rubbed in order to maximize adherence to the treated area. The size of the piece of occlusive tape used is based upon investigator discretion provided that the entire wart is covered, and the tape size is deemed sufficient to maintain adherence for 24h. An adhesive bandage may be applied over the occlusive tape if needed for flexible areas such as fingers and joints to help keep it in place.

Observe subjects for 2-5 minutes after Study drug application or until the film is formed and totally dry. 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/guardians not to touch or wash the treated area for up to 24 hours.

The occlusive tape and Study drug should be removed 24 hours (+/- 8 hours) after treatment. The occlusive tape and Study drug may be removed from individual lesions prior to 24 hours if there is significant blistering, pain or adverse reactions. To remove, wet the occlusive tape in a bath or shower with warm water and then slowly peel back an edge of the tape pulling the 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 warm water. Subjects/guardians 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.

Provide subjects/guardians with both verbal and the written take-home instructions on potential side effects and complications, contact information of the study investigator/study coordinator for questions or concerns, and a copy of their signed informed consent (Screening Day and/or Day 1 only). Subjects will be provided an LSR guide to assist the Site in collecting the required ERT information related to the treated areas.

Subjects are encouraged to wash their hands regularly with soap and water and discouraged from scratching lesions, which can spread disease.

5.3 Storage and Handling of Investigational Product

Each applicator is individually packaged in a UV protected zip-top bag. Each bag is labeled with all pertinent product information and also contains the unique numerical designator for the applicator. The zip-top bag should not be opened until you are ready to initiate treatment. Do not dispose of this zip top bag. Used applicators are not to be discarded after use but should be returned to their zip-top bag and stored in the subject-specific bag, provided in the shipping container by the Sponsor, until the study monitor completes accountability at the monitoring visit.

The applicator itself is labeled with the Investigational New Drug application number and a study identification number. The label will also display the date of production manufacture and the statement "Caution: New Drug--Limited by Federal Law to Investigational Use." and "Warning: Flammable Liquid." The applicator label will also display warnings appropriate to the characteristics of the Study drug, the specifically appropriate yellow triangular flammable symbol sticker with the phrase "Warning: Flammable Liquid" and a yellow toxic chemical symbol with the phrase "Warning: Highly Toxic" as well.

Applicators are received in bulk supply. The unique applicator designator numbers on the pouch labels are used for accountability purposes only and are recorded on the accountability log as they are used. Applicators do not need to be used in sequential order.

All used and unused study medication is to be discarded at the site in a sharps container, or per the site's 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.

Study drug must be stored at controlled room temperature (68°-77°F; excursions of 59°-86°F are acceptable for periods not exceeding eight hours) 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 in the event 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.

5.4 Concomitant Medications

All medications taken within 14 days prior to 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 who have had previous treatment of common warts, including but not limited to, cantharidin, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, candida antigen, diphencyprone, dinitrochlorobenzene, sandalwood oil, topical or homeopathic remedies containing cantharidin, thuja oil, squaric acid dibutyl ester, povidone iodine,

curettage or freezing of warts within 14 days prior to screening should not be enrolled for at least 14 days. In addition, these treatments or any other over-the-counter wart treatment should not be implemented during the course of the study.

Subjects that have participated in another clinical trial utilizing an investigational product may be enrolled within 30 days prior to 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 5cm 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 5cm or on treated skin for 24 hours following treatment. Immunizations and flu shots may be administered throughout the study but not within 5 days before or after treatment.

6 EXPERIMENTAL PROCEDURES

6.1 Overview: Schedule of Time and Events

Each subject will be evaluated and treated as follows:

- **Screening Period** (Up to 14 days prior to first treatment)
- Safety Evaluation Period (Treatment Visit 1)
  - Confirm that subject still meets enrollment criteria (dermatologic exam; ability to attend study visits),
  - Wart count (Cohort 1)
  - Measurement of each wart size (diameter, height) and location,
  - Photos of all warts if applicable,
  - Paring of warts (Cohort 2), if applicable,
  - Study drug application and occlusion with occlusive tape,
  - Removal of occlusive tape and Study drug 24 hours after application,
  - 24-hour and 7-day ERT phone call,
  - Photos taken by subject at home every 24hours for 5 days if applicable (Cohort 1),
  - Photos taken by subject at home at 24 hours (Cohort 2).

- **Safety and Efficacy Evaluation Period** (visits targeted at least 14 days after prior treatment in Cohort 1 and every 21 +/- 4 days in Cohort 2)
- **Treatment Visit 2**:
  - Wart count (Cohort 1),
  - Measurement and location of all warts,
  - Paring of warts (Cohort 2), if applicable,
  - Photos (if applicable),
  - Dermatologic exam, ERT,
  - Study drug application and occlusion with tape (if subject has any warts remaining). Removal of occlusive tape and Study drug 24 hours after application.
  - ERT phone call at 24h and day 7,
  - Any new warts should be counted (Cohort 10, measured, documented and treated per protocol,
  - Photos taken by subject (per protocol Cohort 1 & 2).
- **Treatment Visit 3:**
  - Wart count (Cohort 1),
  - Measurement and location of all warts,
  - Paring of warts (Cohort 2), if applicable,
  - Photos (if applicable),

- Dermatologic exam, ERT,
- Study drug application and occlusion with tape (if subject has warts remaining),
- Removal of occlusive tape and Study drug 24 hours after application,
- ERT phone call at 24h and day 7,
- Any new warts should be counted (Cohort 1), measured, documented and treated per protocol,
- ERT and wart count (Cohort 1) conducted over the phone if cleared at Treatment Visit 2,

• Photos taken by subject (per protocol Cohort 1 & 2). Treatment Visit 4:
- Wart count (Cohort 1),
- Measurement and location of all warts,
- Photos (if applicable),
- Dermatologic exam, ERT,
- Paring of warts (Cohort 2), if applicable,
- Study drug application and occlusion with tape (if subject has warts remaining),
- Removal of occlusive tape and Study drug 24 hours after application,
- ERT phone call at 24h and day 7,
- Any new warts should be counted (Cohort 1), measured, documented and treated per protocol,
- ERT and wart count (Cohort 1) conducted over the phone if cleared at Treatment Visit 3,
- Photos taken by subject (per protocol Cohort 1 & 2).

• **"Unscheduled" Visit:** May take place at any time, as needed, to evaluate the subjects for safety reasons or for those subjects unable to be treated due to an ongoing LSRs. For those subjects evaluated at their scheduled Treatment Visit as exhibiting untreatable warts, no treatment will be administered, and an "Unscheduled" treatment form will be completed. The following information should be obtained:
- Reason treatment was not administered,
- Dermatologic exam,
- ERT, including LSR, wart count (Cohort 1) and location of all warts,
- Photos (if applicable).

- **Cohort 1: End of Study Visit** (EOS Day 84); **Cohort 2: End of Treatment Visit** (EOT; Day 84)In person: Vital signs, weight, wart count (Cohort 1),
- Measurement and location of all warts,
- Photos (if applicable),
- Dermatologic exam and ERT,

- Any new warts should be counted (Cohort 1), measured and documented per protocol,
- Provider EOS/EOT Treatment Questionnaire.

- **Follow-up Visits** Cohort 2: (Day 105, Day 126 and Day 147)
  - In person: Vital signs,
  - Measurement and location of all warts,
  - Photos (if applicable),
  - Dermatological exam and ERT,
  - Any new warts should be measured and documented per protocol.

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 14 days before, or on the same day as the first Study drug application. The dermatologic exam, wart count (Cohort 1), measurements, location of all warts, ERT and photos must be repeated if not conducted on the same day as treatment. An IRB-approved Informed Consent and Assent (assent when applicable) will be signed before any study specific procedures are performed. The dermatologic exam, wart count (Cohort 1), measurements, location of all warts, ERT and photos must be repeated if not conducted on the same day as treatment. Warts must measure at ≤10 mm in diameter and ≤3 mm in height for both Cohorts (paring can be performed, if necessary, in Cohort 2 prior to assessing height for inclusion).

Subjects in Cohort 2 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 prior to application of Study drug. Wart paring is 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 that do not continue to meet criteria at Treatment Visit 1 will be discontinued and treated at physician discretion per standard of care. Those subjects that meet the enrollment criteria will be treated with application of VP-102 at Treatment Visit 1. Treatment will continue with an interval of at least 14 days in Cohort 1, and 21 days in Cohort 2, between treatments until complete clearance or a maximum of 4 treatment sessions. Subjects should be re-treated only after 14 days have elapsed in Cohort 1 or 21 (+/- 4 days) in Cohort 2, 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 Treatment Visit can be scheduled within 14 days for Cohort 1 and 21 days (+/- 4) for Cohort 2, when possible. Treatment should be administered within 4 days of becoming eligible due to resolution of LSRs. Treatment will be applied up to four times during a 63-day treatment period for Cohort 1 and

75-day treatment period for Cohort 2. It can sometimes be challenging to determine if a wart is completely clear 14 days post treatment due to ongoing local skin reactions. At any visit where the investigator is unable to evaluate or treat some warts due to ongoing local skin reactions, an "Unscheduled" visit should be documented. The timing of the next visit will be timed to correspond with the resolution of the local skin reaction. A Treatment Visit should be documented at every visit where any 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. In instances where 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), although it is possible that some subjects will not receive less than 4 treatments within the 63-day (Cohort 1) or 75 day (Cohort 2) treatment period, due to the duration of post-treatment local skin reactions and this will not be considered a protocol deviation. No treatments should be administered after Day 63 (Cohort 1) or Day 75 (Cohort 2) without prior approval from the Sponsor.

ERT in-person safety assessments will be conducted during the initial treatment visit and at each subsequent Treatment Visits 2-4. In addition, safety follow-ups will include ERT phone assessments at 24 hours and 7 days after each treatment. During the Safety and Efficacy Evaluation Period, subjects will be scheduled every 14 days. For instances where all warts appear to be clear, yet the clinician is not certain if residual wart is remaining, treatment may be applied and the subject return for evaluation per protocol. Subjects that miss a treatment visit and are outside the 14-day study window, may return and be treated at the next available opportunity. AEs will be assessed at every study visit.

The EOS visit will be scheduled at 42 days after Treatment Visit 4 has been completed.

For subjects that achieve complete clearance prior to Treatment Visit 4, ERT phone calls will be conducted at the required 2-week treatment intervals to assess the status of any AEs or skin reactions since the last visit and confirm there has been no recurrence in treated warts or new warts have developed. Subjects that report recurrence of, or presence of new warts, will be scheduled for a treatment visit per protocol.

6.2 Measurements and Evaluations

6.2.1 Screening Period (Up to 14 days prior to Treatment Visit 1)

Before the initiation of screening assessments, the subject/guardian must be given a complete explanation of the purpose and evaluations of the study. Subsequently and depending on the age of the subject, the subject/guardian must sign and receive a copy of an informed consent form (ICF) (Section 9.3), an IRB-required assent form (subjects 10 years or older), and an authorization for use and disclosure of protected health information (Section 9.3) that was approved by the IRB. Once consent and assent are obtained, the Screening Period assessments will be performed. Subjects will be screened within 14 days prior to or on Treatment Visit 1 of the study. Following consent and assent, review and recording of any

medical history will take place, and the following evaluations will be performed and recorded in eCRF:

1. Demographics (date of birth, sex, ethnic origin)
2. Height and weight
3. Prior relevant medical history
   - All past relevant illnesses with in the past 5 years.
   - All drugs used (including non-prescription and herbal [complementary medicine] products) within 14 days prior to screening procedures. Any anti-microbial, anti-viral, steroidal or topical drugs received within 30 days prior to Day 1.
   - Any non-pharmacologic treatments (e.g., ice packs, heat packs, warm soaks, etc.) administered in the 72 hours prior to the application of the Study drug.
4. Common wart history (duration and previous treatments). If treated with cantharidin, confirm date of last treatment. Warts must be present for at least 4 weeks prior to screening.
5. Limited physical examination.

6.2.2 Safety Evaluation Period (Treatment Visit 1)

Screening and Treatment Visit 1 may occur on the same day. The following evaluations will be performed and recorded on the source and in eCRF:

1. Confirmation that the inclusion/exclusion criteria are met.
2. Dermatologic exam: Wart count (Cohort 1) and location (head/neck, chest/abdomen, back/buttocks, groin, and upper/lower extremities) and measurement of each wart size (diameter, height) and location. Presence of any confounding dermatologic diseases such as atopic dermatitis. Fitzpatrick skin type.
3. Medical history to assess any changes since screening (as described in Section 6.2.1).
4. Review and recording of any concomitant medications and non-pharmacologic treatments or procedures in the last 30 Days prior to enrollment.
5. Vital signs (heart rate and temperature).
6. Limited physical examination.
7. Urine pregnancy test for females of child-bearing potential, defined as capable of menstruating, to determine protocol eligibility.
8. ERT assessment (LSRs, AEs, Concomitant medications [ConMeds])-prior to treatment.
9. Photographs taken before application of the Study drug if applicable.
10. Paring of warts (Cohort 2), if applicable
11. Application of Study drug and occlusive tape.
12. Subjects will be given take-home instructions describing potential local skin reactions and 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.

13. A local skin reaction guide for subjects with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. During the ERT phone call, should a subject report experiencing excessive blistering, ulceration, edema, pain or another adverse event needing physician assessment, they will be scheduled for an "unscheduled" study visit and safety evaluation as soon as possible.
14. Review and record any AEs which include local skin reactions and any concomitant medications.
15. Removal of occlusive tape and Study drug: At 24 hours (+/- 8 hours) after drug application, subjects are instructed to wet the treated area with warm water and then carefully and slowly remove the occlusive 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 warm water after the tape is removed. The occlusive tape and Study drug may be gently removed from individual warts prior to 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. The occlusive tape and Study drug should not be removed from any remaining unproblematic warts until the 24-hour time point is reached. Washing of intact blisters should be gentle and without use of a washcloth. Washing and removal of occlusive tape in a bath or shower is encouraged. Photos should be taken by the subject or guardian after the tape and Study drug are removed.
16. Post treatment ERT phone assessments: At 24-hours and 7 days after treatment, the research team will conduct an ERT assessment over the phone. The ERT includes questions related to removal of the occlusive tape and study drug, if applicable, and records the intensity of any local skin reactions, adverse events and concomitant medications (ConMeds). The subject and/or guardian will have time to ask questions and review any concerns. In the event any adverse events present a safety concern, an "Unscheduled" clinic visit will be made, and the subject assessed accordingly.
17. Occlusive tape and Study drug must be removed prior to the call.
18. Subjects participating in the photo portion of the study will take photos of all lesions every 24 hours for 5 days (Cohort 1) after each treatment up to Day 84 EOS. Cohort 2 will only obtain photos at 24 hours after each treatment and through the Day 147 Follow-up visit. Subjects will either text or e-mail the photos to the research team or bring them to the next Treatment Visit to upload and store.

6.2.3 Safety and Efficacy Evaluation Period: (Treatment Visits 2, 3 and 4)

1. Review and recording of any concomitant medications and non-pharmacologic treatments/procedures since previous visit.
2. Review and recording of any AEs (before and after Study drug application).
3. Vital signs (heart rate and temperature) before Study drug application.
4. Dermatologic exam: (as described in Section 6.2.1) Wart count (Cohort 1), measurement and location (head/neck, chest/abdomen, back/buttocks, groin, and

upper/lower extremities) of all warts. Measurement of diameter and height. Presence of any confounding dermatologic diseases such as atopic dermatitis.

5. Paring of warts (Cohort 2, if applicable)
6. ERT assessment (LSRs, AEs, ConMeds)-prior to treatment.
7. Urine pregnancy test for females of child-bearing potential to confirm continued protocol eligibility before application of study drug.
8. Photographs taken before application of the Study drug (if applicable). Upload of subject obtained photos if applicable.
9. Administration of study drug to all warts including those warts that may be newly developed. If any new warts are not treatable, this will be documented by the team member who is applying the treatment.
10. Subjects will be given take-home instructions describing the potential local skin reactions and what to expect over the next 24 hours to several months.
11. Removal of occlusive tape and Study drug. (See Section 6.2.2 for details)
12. Post treatment ERT phone calls: (See Section 6.2.2 for details) safety evaluations will be conducted by the research team via phone calls at 24 hours and 7 days after every treatment application (ERT). The phone call will review questions related to removal of occlusive tape, Study drug, and review and documentation of local skin reactions, adverse events and con-meds since the prior visit or call. If participating, a reminder to take photos of the treated areas and save or send the photos via text or e-mail to the research team will also be reviewed. The subject and/or guardian will have time to ask questions and review any concerns. In the event any adverse events present a safety concern, an "Unscheduled" clinic visit will be made, and the subject assessed accordingly.
13. In Cohort 1, subjects that achieve complete clearance prior to Treatment Visit 4, ERT phone calls will be conducted at the required 2-week treatment intervals to assess the status of any AE's or skin reactions since the last visit and confirm there has been no recurrence in treated warts or new warts have developed. Subjects that report recurrence of, or presence of new warts, will be scheduled for a Treatment Visit per protocol. *Sites should consider calling the subject a few days prior to the 2-week interval (e.g., 11 or 12 days) to ensure adequate time for scheduling assessment and treatment if needed.*
14. In Cohort 2, subjects that achieve complete clearance prior to Treatment Visit 4 will be required to return for each Treatment Visit until EOT as well as Follow-up Visits on Day 105, 126 and 147. The status of any AE's or skin reactions or any recurrence in treated warts or new warts will be assessed per protocol at each phone call and in-person visit.
15. Photos taken by subject (per protocol Cohort 1 and 2)

6.2.4 Unscheduled Visit:

May take place at any time, as needed, to evaluate the subjects for safety reasons or for those subjects unable to be treated due to an ongoing LSR. For those subjects evaluated at their

scheduled Treatment Visit as exhibiting untreatable warts, no treatment will be administered, and an "Unscheduled" treatment form will be completed. The following information should be obtained:

1. Reason treatment was not administered.
2. Dermatologic exam.
3. ERT, including LSR, wart count (Cohort 1) and location of all warts.
4. Photos (if applicable).

6.2.5 End of Study Visit (Cohort 1: Day 84) and End of Treatment Visit (Cohort 2: Day 84)

Subjects will return to the clinical site for:

1. Review and recording of any concomitant medications and non-pharmacologic treatments/procedures since previous visit.
2. Review and recording of any AEs.
3. Vital signs (heart rate and temperature) obtained at the beginning of visit.
4. Limited physical examination.
5. Any new warts counted (Cohort 1), measured and documented per protocol.
6. Dermatologic exam, ERT assessment (LSRs, AEs, ConMeds)
7. Provider EOS/EOT Treatment Questionnaire
8. Urine pregnancy test for females of childbearing potential.
9. Photographs taken by the research team/Upload of subject photos if applicable.

6.2.6 Follow-up Visits Cohort 2 (day 105, Day 126, and Day 147)

1. In person: Vital signs,
2. Measurement and location of all warts.
3. Photos (if applicable).
4. Dermatological exam and ERT.
5. Any new warts should be measured and documented per protocol.

7 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.1 Definition of an Adverse Event

The following definition of *adverse event* (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, small blisters, hyper- and hypopigmentation, scabbing/crusting, erosion/ulcerations, scarring, ring warts)
- Development of individual blisters that are greater than 25mm in diameter (the diameter of a quarter). (An aggregated blister composed of a number of smaller blisters is not considered a severe blister)
- Blistering distal to the treatment site
- Scarring-independent of any pigmentary changes; include depressed (atrophic) and elevated (hypertrophic)
- Secondary infection

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 preexisting 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 once the subject has signed informed consent and will continue until the EOS visit has been completed.

The investigator is responsible for performing periodic and special assessments for AEs. The investigator and study personnel will note all AEs mentioned by the subject starting from the day the informed consent is signed until the end of study visit (EOS; Day 84). All clinical complaints volunteered by or elicited from the subject or parent/guardian during the study will be recorded on the appropriate page of the source and eCRF for the study period indicated. The subject will receive appropriate treatment and medical supervision for any AE that occurs.

All unresolved AEs will be followed until the condition resolves and/or stabilize, the subject is lost to follow-up or 30-days after the end of study (EOS visit or up to 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 7.3.

7.2 Definition of a Serious Adverse Event

In this study, a *serious adverse event* 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 VP-102 Investigator's Brochure).

7.3 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, etc.) 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. AEs being processed as SAEs will also require additional documentation.

7.4 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 AEs 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 7.2.

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

7.5 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 Investigator's Brochure 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 AEs

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.

7.6 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) or the current Investigator's Brochure. The expectedness of an SAE will be assessed by the medical monitor or sponsor on receipt of the initial SAE report.

7.7 Reporting of Serious Adverse Events

Any SAE occurring after the subject signs the informed consent form must be reported to the Sponsor or designee by phone, or e-mail within 24 hours of the time the investigator becomes aware of the SAE (Table 5). 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.

Table 5 Timeline for Reporting of SAEs

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.

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 knowledge of a new SAE, the investigative site will enter the event as an SAE into the EDC system being used for this study and recorded into the safety module. 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 Medical Monitor via the SAE Hotline of the SAE. The SAE report form will be updated by the investigator when additional information is received.

New SAEs, or follow-up SAE information, may be reported to the Research Medical Monitor by calling the SAE Hotline at . The SAE Hotline may be accessed 24 hours/day, 7 days/week. The Hotline is monitored 24 hours/day, 7 days/week. A call to the SAE Hotline is not required and does not alleviate the Investigator of the responsibility to report a new SAE in the EDC system within 24 hours of knowledge.

7.8 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 end of study (EOS Visit).

The appropriate SAE report form will be updated in the EDC once 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).

7.9 Pregnancy

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.

8 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

8.1 Subject Discontinuation

Subjects are encouraged to complete the study; however, they may voluntarily withdraw at any time. 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 eCRF page. If a subject withdraws before completion, every effort should be made to complete the Day 84 assessments scheduled during the End of Study visit.

A subject may be removed from the study for the reasons described in Section 8.1.1 through Section 8.1.5.

8.1.1 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.

8.1.2 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.

8.1.3 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 5

Failure to comply with protocol requirements

8.1.4 Refusal of Investigational Product Administration

Any subject refusing clinical trial material for any reason will be discontinued from the study, and 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.

8.1.5 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 or specimens utilized, they will need to submit a request in writing to the Investigator for removal of their information.

8.2 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 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
- A study conducted at a single site in a multicenter study may also warrant termination 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 Good Clinical Practice. 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.

9 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

9.1 Data Collection and Processing

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 (eCRFs) 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. Once 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 electronic data capture (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 standard operating procedure (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 (user ID) and password before any data can be entered in the eCRFs. Authorized study personnel will be assigned a unique user ID 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 9.4.

9.2 Statistical Analysis

9.2.1 General Overview

Subject disposition, demographics, baseline characteristics and study drug exposure will be summarized. The data will be summarized in tables, as appropriate, showing the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. Data will also be listed as deemed appropriate.

9.2.2 Populations of Interest

The intent-to-treat (ITT) population will include all subjects enrolled in the study.

Subjects who receive all planned treatments of VP-102 (e.g., up to four treatments within the 63 day treatment window, or cleared of all treatable warts prior to Day 63 in Cohort 1; and in Cohort 2 complete up to four treatments within the Day 75 treatment window or clear prior to Day 75) are assessed for clearance at the EOS visit and have none of the following major protocol violations will be included in the Per Protocol population. The following pre-determined reasons will exclude subjects from being included in the Per Protocol population:

- Subjects who do not come in for required Treatment Visits.
- Subjects who do not return for the EOS study visit.
- Subjects who refuse to have all of their treatable warts treated or investigators who refuse to treat all treatable warts.
- Early removal of the study drug not associated with pain, blistering or other medically appropriate reason for early removal.
- Subjects who begin alternative treatments for their warts after starting the study.
- Subjects enrolled who did not meet the inclusion/exclusion criteria.

The safety population will include subjects who receive at least one treatment of VP-102.

9.2.3 Efficacy Analysis

Efficacy analysis using the ITT population will be considered the primary analysis. Analysis carried out on the per-protocol population will be considered secondary in nature.

The primary endpoint of proportion of subjects exhibiting clearance of all treatable warts (baseline and new) at the EOS/EOT Visit (Day 84 for Cohort 1 and Cohort 2) will be summarized using counts and percentages. The analysis will be separate for Cohort 1 and Cohort 2. Other binary endpoints will be analyzed with this method. Continuous endpoints will be summarized using summary statistics (n, mean, standard deviations, median, minimum, maximum). Further details of analysis of other endpoints will be described in the statistical analysis plan.

9.2.4 Safety Analysis

Safety analysis will be based on the safety population. Subjects will be assigned to the treatment received for any analysis of safety.

Adverse event data for the safety population will be listed individually, and the incidence of adverse events will be summarized by treatment, System Organ Class, and Preferred Term using frequency counts. LSRs will also be tracked by the incidence of subjects with each LSR and the maximal intensity throughout the study. These will be tabulated by total rate of occurrence and rate of severe occurrences. When calculating the incidence of adverse events, only Treatment Emergent Adverse Events (TEAEs) will be considered. In addition,

any adverse event with an onset date after the EOS visit will be considered off study and will not be included in tables summaries (though they will appear in adverse event listings). Each adverse event will be counted only once for a given subject. If the same adverse event occurs on multiple occasions for a subject, the occurrence with the highest severity and relationship to Study drug will be reported. If two or more adverse events are reported as a unit, the individual terms will be reported as separate events. Changes in vital signs, from baseline to the end of the study will be examined. Treatment-emergent changes from normal values to abnormal values will be identified as described in Section 4.3.1.

9.2.5 Interim Analysis

No interim analysis is planned for this study.

9.2.6 Sample Size

The study will enroll subjects with common warts for the main purpose of obtaining information on clearance rates of the warts in response to VP-102 therapy. Subjects in Cohort 1will continue to be enrolled in the study to a target of approximately 20 subjects completing the EOS visit. In Cohort 2, approximately 35 subjects will be enrolled.

9.2.7 Handling of Missing data

Clearance of all treatable warts is to be assessed at each Treatment Visit as well as unscheduled visits over the duration of the study. The assessment done at the EOS Visit (Day 84) will be considered to be the primary efficacy endpoint.

Subjects who do not have an assessment of complete clearance of all treatable warts at the EOS Visit (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.

The procedures for handling missing data for other study endpoints will be described in the statistical analysis plan.

9.3 Informed Consent/Assent and Authorization for Use and Disclosure of Protected Health Information

Written assent and informed consent and authorization of use and disclosure of protected health information must be obtained from each subject (or the subject's legally acceptable representative) before performing any study-specific screening/baseline period evaluations. One copy of the signed informed consent form (and IRB-required assent form) and authorization for use and disclosure of protected health information form will be given to the subject, and the investigator will retain the original. The informed consent/assent form 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 informed consent form must contain the 20 elements of informed

consent described in International Council for Harmonisation 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.

9.4 Study Documentation

9.4.1 Investigator Information

Investigator information is included in the Manual of Operations, which is updated as needed.

9.4.2 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 Investigator's Brochure, 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.

9.4.3 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.

9.4.4 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.

9.5 Confidentiality

9.5.1 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).

9.5.2 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 informed consent form) 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.

9.6 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 informed consent form and assent form, the revised informed consent and assent forms 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.

9.7 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.

9.8 General Information

The investigator should refer to the Investigator's Brochure, manual of operations, and any other information provided about this investigational product and details of the procedures to be followed during this study.

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11 APPENDICES

11.1 Appendix 1: Version History and Summary of Changes

SUMMARY OF PROTOCOL CHANGES: VP-102-105 (COVE-1)

Version history:

DOCUMENT	VERSION	DATE
Protocol VP-102-105	1	28 February 2018
Protocol VP-102-105	2	15 May 2018
Protocol VP-102-105	3	1 November 2018

Summary of changes to Protocol VP-102-105 (Revised as of 1 November 2018)

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
Template an organization of Heading numbers	This protocol is written using a new template format and the heading numbers have been revised based on the new format.
Title page	Revised by deleting reference to 2 years and older.
Synopsis: -Study period; Main protocol: Basic design characteristics (page 40)	Revised to indicate that that study period for Cohort 1 is 84 days and 147 days for Cohort 2.
Synopsis: Objectives Main protocol (Section 3, pages 35 – 37)	Revised the primary secondary and exploratory objectives for Cohort 1 and Cohort 2.
Synopsis: (Methodology) Main Protocol (Section 4: Study design, pages 38 – 42) and (Section 6.0, Experimental Procedures, pages 55 – 62)	These sections are extensively revised to describe the procedures for the treatment and evaluation of subjects in Cohort 1 and Cohort 2. Differences in the treatment intervals between Cohort 1 and Cohort 2, end of study visit (EOS) for cohort 1 and end of Treatment Visit (EOT) for Cohort 2, treatment durations and study duration differences between Cohort 1 and Cohort 2 are described. Follow-up visits for Cohort 2 on Days 105, 126 and Day 147 are described. Paring can be performed, if necessary, in Cohort 2 only prior to assessing height for inclusion. For those enrolled in Cohort 2, subjects will be required to return for every treatment and follow-up visit whether or not their warts have cleared.
Synopsis: Subject Participation (page 10) Main protocol:	Revised to indicate that warts must measure at ≤10 mm in diameter and ≤3 mm in height for both Cohorts (paring can be performed, if necessary, in Cohort 2 prior to assessing height for inclusion).

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
4.2 : Study Population (page 44)	For those enrolled in Cohort 2, 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.
Synopsis: Inclusion Criteria (page 10); Main protocol- 4.2.1 Inclusion criteria (pages 42 – 43)	Criteria # 1 was revised to specify including 2 years and older subjects for Cohort 1 and 12 years and older for Cohort 2. Criteria # 2 was revised to indicate that warts near and on the sides of the nails is allowed for Cohort 1, but warts near and on the sides of the nail (e.g., periungual) are not allowed in Cohort 2. Criteria # 3 was revised to indicate that *subjects in Cohort 2 can be pared, when necessary and appropriate, prior to evaluating height eligibility; See manual of operations for details.*
Synopsis Exclusion criteria (pages 11– 12); Main protocol- 4.2.2 Exclusion Criteria (pages 43 – 44)	Criteria # 3 was revised to indicate that NOTE: Immunizations and flu shots may be administered throughout the study, but not within 5 days before or after treatment. Criteria # 5 revised to indicate that in Cohort 2, subjects with periungual warts are also excluded.
Synopsis: Duration of treatment (page 12)	Revised as follows: The length of study participation is approximately 84 days (may extend up to 98 days) for Cohort 1 and 147 days for Cohort 2. The study will consist of up to 4 applications of Study drug at intervals of at least 14-days, in Cohort 1, and 21 (+/- 4) days for Cohort 2. For Cohort 1, a 63-day treatment period is followed by an EOS assessment on Day 84. Cohort 2 will have a 75-day treatment period followed by an EOT assessment on Day 84 (- 0/+ 8 days) with additional follow-up visits on Day 105, Day 126 and Day 147.
Synopsis: After each treatment (Page 13); Main protocol Section 9.2.2 (pages 72 – 73)	Revised as follows: Subjects that remove Study drug prior to 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.

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
	Early removal is defined as removal before at least 16 hours have passed from study drug application.
Synopsis: Criteria for evaluation (page 13); Main protocol: 4.3 Endpoints (pages 44 – 46)	Revised extensively by defining the primary, secondary and exploratory end points for Cohort 1 and Cohort 2.
Synopsis (Safety, pages 14 – 15); Main Protocol: Section 4.3.1 (pages 49 – 50)	Revised as follows: In Cohort 1, subjects that exhibit complete clearance prior to EOS will not be required to return to the clinic until EOS Day 84. Cohort 2 subjects will be required to return for each Treatment Visit until EOT as well as Follow-up Visits on Day 105, 126 and 147. Safety parameters that will be assessed during the study have been updated in the main Protocol – section 4.3.1.
Synopsis (Efficacy: page 13); Main protocol: Section 4.3.2, (page 48)	Revised as follows: The Day 84 EOS Visit will require a final assessment of ERT (for Cohort 1) and confirmation of the presence or absence of treated and untreated warts as well as the final size and diameter for any that are remaining. Subjects in Cohort 2 will participate in an in-person EOT evaluation at Day 84 (- 0/+ 8 days). A provider EOT Questionnaire will be completed at the EOT Visit. Cohort 2 subjects will continue in the study for 3 additional follow-up assessments on Day 105, Day 126 and Day 147.
Synopsis (Safety, page 15) ; Main protocol : Section 4.0 and 6.0 (pages 41, 47, and 60)	Unscheduled visits were clarified to subjects that report experiencing excessive blistering, ulceration, edema, pain or another adverse event needing physician assessment, they will be scheduled for an "Unscheduled" study visit and safety evaluation as soon as possible.
Synopsis (Statistical methods, page 16); Main protocol; Section 9.2 (pages 72 – 74)	Revised as follows: The study will enroll to treat a minimum of 20 subjects, 2 years of age and older, presenting with 1-6 common warts with the goal of approximately 20 subjects completing all study activities per protocol.

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
	Cohort 2 will utilize up to 4 sites to enroll approximately 35 subjects (12 years and older). Although no formal power calculations have been performed, it is expected that a sample size of 20 subjects (Cohort 1) and 35 subjects (Cohort 2) evaluable at the EOS/EOT visit (Day 84 for both Cohorts) will be informative regarding wart clearance rates that can support assumptions in subsequent placebo-controlled trials. A sample size of 20 completed subjects for Cohort 1 and approximately 35 subjects for Cohort 2, pooled with subjects who drop out prior to the EOS/EOT visit, will provide information to build an adequate safety profile of VP-102 in common warts. The primary analysis will be conducted at Day 84 for both Cohorts. The final analysis will be conducted for Cohort 2 when the last patient has completed the visit on Day 147. Subjects who receive all planned treatments of VP-102 (e.g., up to four treatments within the 63 day treatment window, or cleared of all treatable warts prior to Day 63 in Cohort 1 and have none of the following protocol violations; and in Cohort 2 complete up to four treatments within the Day 75 treatment window or clear prior to Day 75 and have none of the following protocol violations) are assessed for clearance at the EOS visit and have no major protocol violations will be included in the Per Protocol population.
Table 1: Study Schedule of Assessments and Procedures - Cohort 1 (pages 17 – 19)	Title of the Table was revised. In the Foot note B following sentences were added: The next Treatment Visit is to be scheduled 14 days after the last treatment or study visit, but only after any LSR has resolved sufficiently to allow evaluation of the treatment site. Treatment should be administered within 4 days of becoming eligible due to resolution of LSRs. Foot note K was revised by including the following: Subjects that remove Study drug prior to 24 hours will be considered a protocol deviation if it does not meet

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
	the requirements for early removal as outlined in Section 9.2.2 of the protocol. Early removal is defined by removal at < 16 hours after treatment is applied.
Table 2: Study Schedule of Assessments and Procedures – Cohort 2 (pages 20 – 22)	A new table was generated to list the study visits, EOT visit, follow-up visits, treatments, assessments and procedures for Cohort 2.
Table of Contents (pages 23 – 25)	Updated to include new information, Appendix 1 for protocol versions and summary of changes.
List of Abbreviations (page 26)	Updated
Main protocol: 2.2.2; Clinical Studies with Cantharidin (pages 32 – 34)	VP-102 Prospective studies was extensively revised with updated information. Descriptions of few of the previous studies and retrospective studies sections were deleted to condense this section and keep only the most relevant studies.
Main protocol: Section 2.3 Study Rationale (page 34)	Rationale for study design and for dose and schedule was updated based on the revised study design.
Section 10: References	This section was updated based on the revisions indicated above in the protocol.
Section 11.1: Appendix 1	Summary of revisions table was revised.