CLINICAL PROTOCOL

TITLE OF STUDY

CARE-1: A Phase 2, Double-Blind, Placebo-Controlled Study to Determine the Cantharidin Dose Regimen, Efficacy, Safety, and Tolerability of VP-102 in Subjects with External Genital Warts

Protocol VP-102-104

Version Number/Date of Issue:	(Version 2) 07 August 2019
Previous Version Number/Date of Issue:	(Version 1) 09 May 2019
Date of Original Protocol:	09 May 2019
Sponsor:	Verrica Pharmaceuticals Inc. 10 N. High Street, Suite 200 West Chester, PA 19380

PROTOCOL APPROVAL

Signatures of Approval of Protocol (Version 2)

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

Affiliation	Name	Signature/Date
Sponsor:		08-Aug-2019 | 6:11 PM EDT
Medical Monitor:		08-Aug-2019 | 3:41 PM PDT

Sponsor: Verrica Pharmaceuticals Inc.
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West Chester, PA 19380

Sponsor Director Clinical Operations10 N. High Street; Suite 200
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Acknowledgment of Responsibilities (Protocol Version 2)

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

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

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

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

Institution Name	Investigator Name	Signature	Date

1.0 PROTOCOL SYNOPSIS

Name of sponsor company: Verrica Pharmaceuticals Inc.	
Name of finished product: VP-102	
Name(s) of active ingredient(s): Cantharidin	
Title of study: A Phase 2, Double-blind, Placebo-controlled Study to Determine the Cantharidin Dose Regimen, Efficacy, Safety, and Tolerability of VP-102 in Subjects with External Genital Warts	
Number of sites: Up to nine sites (additional sites may be added if required to ensure successful recruitment of the study population)	
Study period: **Part A:** 147 Days; **Part B:** 147 Days	**Phase of development**: Phase 2

Objectives:

Part A (Dose Regimen Finding)

Primary objective:

- To evaluate three regimens of application of VP-102 (2-hour, 6-hour, 24-hour duration of skin exposure) in subjects with external genital warts (EGW) and identify the two best regimens by assessing safety and tolerability of VP-102 when administered topically after all subjects have completed a 48-hour assessment.

Primary efficacy objective:

- To evaluate the efficacy of VP-102 when administered topically to EGW once every 21 days for up to 4 applications by assessing the proportion of subjects achieving complete clearance of all treatable warts (baseline and new) at the Study Day 84 End-of-Treatment (EOT) Visit

Part B (Safety and Efficacy)

Primary objective:

- To evaluate two regimens of application of VP-102 in subjects with EGW and identify the regimen with the best risk:benefit profile when administered topically once every 21 days for up to 4 applications.

Part A & B (Safety and Efficacy)

Secondary objectives:

- To assess the safety and tolerability of VP-102 in subjects with EGW by evaluating adverse events (AEs) including expected local skin reactions (LSRs), vital signs, and concomitant medications
- To evaluate the efficacy of VP-102 when administered topically to EGW once every 21 days for up to 4 applications by assessing the proportion of subjects achieving complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and Follow-up Visits on Study Day 112 and Study Day 147 (End-of-Study [EOS]).
- To evaluate the efficacy of VP-102 by assessing the change from baseline in the number of treatable warts (baseline and new) at each scheduled postbaseline visit
- To evaluate the efficacy of VP-102 by assessing the percent change from baseline in the number of treatable warts (baseline and new) at each scheduled postbaseline visit
- To evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting 75% and 90% clearance of all treatable warts (baseline and new) at each scheduled postbaseline visit

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

Name(s) of active ingredient(s): Cantharidin

Exploratory objectives:

- To evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting reduction of ≥1 treatable wart from baseline at each scheduled postbaseline visit
- To evaluate the efficacy of VP-102 by assessing the proportion of subjects who are clear at the Study Day 84 (EOT) Visit and remain clear at the Follow-up Visits on Study Day 112 and Study Day 147 (EOS).
- To evaluate the efficacy of VP-102 by assessing the change from baseline in total wart area (sum of individual warts) at the scheduled post baseline visits Day 84, 112 and 147.
- To evaluate the efficacy of VP-102 by assessing the percent change from baseline in total wart area (sum of individual warts) at the scheduled post baseline visits Day 84, 112 and 147.

Methodology: This is a Phase 2, double-blind, placebo-controlled study to determine the dose regimen, safety, tolerability, and efficacy of VP-102 in subjects with EGW.

This study is divided into two parts (Part A and Part B). The Schedule of Assessments and Procedures is presented in Table 1.

Part A (dose regimen finding) study design: The aim of Part A is to determine the two best treatment regimens for evaluation of safety and efficacy in Part B.

Treatment regimens will be evaluated based on the requirement to form blisters in most patients, while maintaining a favorable safety and tolerability profile (e.g., majority of LSR AEs are mild or moderate in severity). Accordingly, increasing durations of skin exposure to study drug (VP-102 or placebo) will be evaluated in three treatment groups (n=6/group) that will enroll progressively.

Subjects will have a Screening Period of up to 14 days before the first treatment, followed by a Treatment Period starting at Treatment Visit 1 and lasting through Treatment Visit 4.

Eighteen (18) subjects at up to six sites (additional sites may be added if required to ensure successful recruitment of the study population) will be enrolled, into either the 2-hour (Group 1), 6-hour (Group 2), or 24-hour (Group 3) treatment duration of skin exposure groups (n=6 subjects/group). Each group will include a minimum of two subjects from each sex and will be randomized 5:1 (VP-102:placebo) within each group. All subjects will receive either VP-102 (containing 0.7% cantharidin [w/v] topical film-forming solution) or placebo. Warts are to be treated and then covered (unless prohibited by wart location) with transparent surgical tape (e.g., 3M™ Blenderm™ brand) that will remain on the skin until the designated time for removal. Subjects will be asked to remove the surgical tape and study drug with soap and water after the pre-determined duration of skin exposure for their group.

Study drug (VP-102 or placebo) will be administered once every 21 ±4 days for up to four applications. Enrollment will begin in Group 1, then proceed into Group 2, and lastly into Group 3. The enrollment of subjects into Groups 2 and 3 will only be allowed upon completion of a blinded review of the safety and tolerability data by a Safety Review Panel. The Safety Review Panel will be responsible for reviewing blinded safety and tolerability data and will provide determinations on trial stopping or modification rules. A blinded review of treatment-emergent adverse events (TEAEs), focusing on those of moderate or severe intensity, will be performed by the Safety Review Panel before opening enrollment

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

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for each subsequent cohort. This review will be conducted after the six subjects in a designated Group have completed the 48-hour (±8 hours) Visit. The Safety Review Panel will determine whether enrollment can be initiated into the next Group, OR if more data (e.g., waiting for additional treatments for enrolled subjects or the addition of more subjects to a group) are needed before making a determination to open enrollment into the next Group (i.e., the review conducted after six subjects have completed Group 1 could open enrollment into Group 2 and the review after Group 2 could open enrollment into Group 3). An additional blinded safety review of TEAEs, focusing on those of moderate or severe intensity, will be performed after all six subjects in Group 3 have completed the 48-hour (±8 hours) Visit, in order to support dose selection for Part B (Safety and Efficacy). Safety Review Panel members are blinded to the treatment assignment.

Part B (safety and efficacy) study design: Part B of the study will begin enrollment only after the Sponsor has selected the two dose regimens in Part A, which will be called VP-102 Regimen 1 and Regimen 2. In addition, written notification from the Sponsor must be provided to the sites prior to Part B enrollment is to begin. The study will remain blinded until completion of both parts of the study.

Approximately 90 subjects at up to 9 sites (additional sites may be added if required to ensure successful recruitment of the study population) will be enrolled and randomized to one of four treatment arms. Randomization will be stratified by sex so that neither gender exceeds ~60% of any treatment arm (e.g., placebo group for the 6-hour and 24-hour wash-off cannot have any one gender ≥ 60%). Two of the treatment arms will be VP-102 Regimen 1 and VP-102 Regimen 2. The other two treatment arms will be placebo (Placebo Regimen 1 and Placebo Regimen 2), with corresponding durations of skin exposure matching those selected for VP-102 Regimen 1 and Regimen 2. As an example, if the regimens selected from Part A are the 2-hour and 6-hour applications of VP-102, then VP-102 Regimen 1 would be VP-102 treatment for 2-hours and VP-102 Regimen 2 would be VP-102 treatment for 6-hours. Likewise, Placebo Regimen 1 would be placebo treatment for 2 hours and Placebo Regimen 2 would be placebo treatment for 6-hours. Randomization of the four treatment arms (VP-102 Regimen 1:VP-102 Regimen 2:Placebo Regimen 1:Placebo Regimen 2) will be 3:3:2:2.

In both Regimen 1 and Regimen 2, study drug will be administered to EGW once every 21 ±4 days for up to four applications. Subjects will be asked to remove the surgical tape and study drug with soap and water at the designated time selected from the dose regimen findings in Part A of the study.

Part A and Part B subject participation: Pre-study screening for eligibility (informed consent, demographics, physical exam, vital signs, prior and concomitant medications, and medical history) can occur up to 14 days before, or on the same day as Treatment Visit 1. The dermatologic exam, wart count, wart measurement (diameter), location of all warts, and photographs (if applicable) must be repeated at Treatment Visit 1 if the Screening Visit is not conducted on the same day. Warts must measure ≤ 8 mm in diameter each with a total wart area (i.e., all warts combined) ≥ 10 mm^2 at baseline. Wart count must be ≥ 2 and ≤ 30 total warts within the allowed treatment areas at the time of Treatment Visit 1.

Subjects who do not continue to meet criteria at Treatment Visit 1 will be considered a screen failure and will be treated at physician discretion per standard of care. Subjects who meet the enrollment criteria will be randomized to receive VP-102 or placebo. Treatment will continue with a minimum of every 21 ±4 days, until complete clearance or a maximum of four treatment sessions. The exact treatment

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

Name(s) of active ingredient(s): Cantharidin

interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. Subjects who achieve complete clearance of all treatable warts before Treatment Visit 4 will be required to return for every scheduled, in-person, treatment and follow-up visit, whether or not their warts have cleared. The 24-hour, 7-day, and 14-day evaluation of response to treatment (ERT) telephone follow-ups will be conducted per protocol for those instances in which the subject was treated.

Part A and Part B efficacy procedures

All required study activities, including an ERT (i.e., assessment of wart activity [count, location, diameter] and related LSRs), will be conducted per protocol. A Blinded Assessor will perform wart counts before the ERT assessment at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, End of Treatment Visit, and Follow-up Visit.

Treatment visits are to take place in order (i.e., Treatment 1, Treatment 2, Treatment 3, and Treatment 4). All subjects will receive application of study drug to EGW, including an approximate margin of healthy surrounding skin, at an interval of every 21 ±4 days until complete clearance of all treatable warts, or a maximum of four applications.

No partial treatment of warts (e.g., treating one wart and not another) is permitted. In any instance where the clinician is uncertain if a residual wart is remaining, treatment should be applied. Instructions for application of the study drug are outlined in the Instructions for Use included in the drug shipment, as well as included in the Site Regulatory Packet.

Subjects should be re-treated only after 17 to 25 days (i.e., 21 ±4 days) have elapsed since the previous treatment and only after any LSRs have resolved sufficiently to allow evaluation of the treatment site. Treatment should only take place at a visit when all warts are evaluable (i.e., not obscured by an ongoing LSR). All warts that are not completely clear should undergo treatment with study drug. Subjects exhibiting skin reactions that need additional time, at the Investigator's discretion, before they can be treated again will be evaluated and asked to return for their next treatment visit after the area is considered sufficiently resolved to allow for the next treatment (e.g., ongoing dryness or erythema is appropriate to treat). See instructions below regarding unscheduled visits.

Subjects who receive <4 treatments within the treatment period, or have visits that are outside of the visit window due to the duration of post-treatment LSRs, will not be considered a protocol deviation. In the event that a subject misses a treatment visit, and is outside the 4-day study window, they may return and be treated at the next available opportunity with the subsequent visit scheduled 21 ±4 days after the actual treatment visit. No treatment should be administered after the treatment period without the Sponsor's approval.

An ERT assessment will be conducted at each treatment visit (1-4; in-person before treatment or via follow-up telephone calls) at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after each treatment visit (but not after "unscheduled" visits). Note that the ERT telephone calls at 24 hours (±6 hours), 7 days (±24 hours) and 14 days (±24 hours) are not required if there was no treatment during that period. In Part A Treatment Period 1 only, subjects will return to the clinic for an in-person ERT assessment at 48 hours (±8 hours) after Treatment Visit 1. The ERT includes questions related to removal of surgical tape and study drug (if applicable) and collects any new AEs, LSRs, or changes in

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

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concomitant medications since the last contact. The subject will be given an opportunity to ask questions and review any concerns. In the event that any post-treatment LSR presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain), an "Unscheduled" clinic visit must be scheduled and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an unscheduled visit. The ERT assessments will be recorded by a research team member on the ERT form. The ERT visits may not be conducted by a person designated as a Blinded Assessor. Phone calls conducted outside of the required study visits or required ERT assessments should be documented in the subject's source note but are not required to be entered in the electronic data capture system.

ERT assessments, wart count, and wart location will be conducted before treatment application at all Treatment Visits 1 to 4, as well as at the EOT Visit on Study Day 84 (−0/+8 days) and at the Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days). Wart measurement will be conducted before treatment application at Treatment Visit 1, as well as at the EOT Visit on Study Day 84 (-0/+8 days) and at the Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days). Subjects who clear all warts before the Study Day 84 (EOT) Visit will still be required to return for each of the scheduled in-person treatment visits, as well as the Study Day 84 (EOT) Visit, the Study Day 112 follow-up visit, and the Study Day 147 (EOS) Visit. A Provider Treatment Questionnaire will be completed at the Study Day 84 (EOT) Visit by a clinician who applied treatment to the subject during the course of the study. All subjects will continue in the study for two additional Follow-up Visits on Study Day 112 and Study Day 147 (EOS).

All treatment visits will include a wart count, performed before treatment (if applicable) and before ERT assessment. No treatment will be required if the wart is considered clear. Genital warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) and other wart types (e.g., common warts) will not be evaluated, documented, or considered in the analysis.

Wart counts will be conducted at Screening, Treatment 1, Treatment 2, Treatment 3, Treatment 4, End of Treatment and Follow-up Visits by a trained member of the study team. Other than the screening visit and Day 1, wart counts will also be conducted by a member of the research team that has been identified and trained as a Blinded Assessor. The Blinded Assessor may be utilized for a subject's initial screening, enrollment and treatment Visit 1 activities, however, may not perform any other study related activities other than wart counts at subsequent visits (e.g., follow-up phone calls or unscheduled visits) for the same subject. The Blinded Assessor is not required to be the same person for each assessment.

It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing LSRs. At any visit in which the Investigator is unable to evaluate or treat some warts due to ongoing LSRs, an "Unscheduled" visit should be documented. The timing of the next visit will be determined by the resolution of the LSR. The research team should be in contact with the patient until LSRs are resolved sufficiently and a treatment visit can be scheduled within 21 ±4 days when possible. Specific instructions on how to conduct the initial wart count and measure wart diameter will be provided during Investigator training.

At designated sites, photography will be offered to volunteer subjects who consent to participate.

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

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Part A and Part B safety procedures

Subjects will be provided with take home instructions describing what they might expect throughout the course of the study, as well as recommendations for wound care (if needed), when it is important to call their doctor, and instructions for who to contact in an emergency. In the event that any post-treatment LSR presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain), an "Unscheduled" clinic visit must be scheduled and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an unscheduled visit.

An LSR guide for subjects, with specific photographs representing the various skin reactions and examples of intensity, will be provided and reviewed in detail at the clinic with the subject by the research team. The LSR guide will be utilized for reference by the subject during the ERT follow-up telephone assessments with the research team member. The final determination of LSR parameters, including intensity, will be made by the research team member.

Subject Participation: Pre-study screening for eligibility (informed consent, demographics, physical exam, vital signs, prior and concomitant medications, and medical history) can occur up to 14 days before, or on the same day as Treatment Visit 1. The dermatologic exam, wart count, wart measurement (diameter), location of all warts, and photographs (if applicable) must be repeated at Treatment Visit 1 if the Screening Visit is not conducted on the same day. Warts must measure ≤ 8 mm in diameter each with a total wart area (i.e., all warts combined) ≥ 10 mm^2 at baseline. Wart count must be ≥ 2 and ≤ 30 total warts within the allowed treatment areas at the time of Treatment Visit 1.

Subjects who do not continue to meet criteria at Treatment Visit 1 will be considered a screen failure and will be treated at physician discretion per standard of care. Subjects who meet the enrollment criteria will be randomized to receive VP-102 or placebo. Treatment will continue with a minimum of every 21 ±4 days, until complete clearance or a maximum of four treatment sessions. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. Subjects who achieve complete clearance of all treatable warts before Treatment Visit 4 will be required to return for every scheduled, in-person, treatment and follow-up visit, whether or not their warts have cleared. The 24-hour, 7-day, and 14-day ERT telephone follow-ups will be conducted per protocol for those instances in which the subject was treated.

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

Name(s) of active ingredient(s): Cantharidin

Inclusion Criteria:

To qualify for inclusion in this study, subjects must:

1. Be healthy, immunocompetent males or females ≥ 18 years of age
2. Present with ≥ 2 and ≤ 30 external genital and/or perianal warts in ≥ 1 of the following anatomic areas:
   - In both sexes: medial thigh (except inguinal fold); supra-pubic, perineal, and perianal areas
   - In men: over the glans penis (excluding urethral meatus), penis shaft, scrotum, and foreskin
   - In women: vulva (excluding labia minora and mucosal surfaces)
3. Have warts present for ≥ 4 weeks at the baseline visit
4. Have warts that are ≤ 8 mm in diameter each with a total wart area (i.e., all warts combined) ≥ 10 mm^2
5. Be free of any systemic or dermatologic disorder, that, in the opinion of the Investigator, will interfere with the study conduct, efficacy assessments, or increase the subject's risk of AEs
6. Refrain from swimming, bathing, or prolonged immersion in water or any other liquids until the study drug is removed
7. Have the ability to follow study instructions and be likely to complete all study requirements
8. Agree to use no wart-removing product (prescription or over-the-counter, including any human papilloma virus [HPV] immunization) other than the study drug during the course of the study
9. Provide written informed consent in a manner approved by the Institutional Review Board (IRB) and evidenced by the signature on an IRB approved consent form
10. Provide written authorization for use and disclosure of protected health information
11. If participating in the optional photographic portion of the study, agree to allow photographs of warts to be taken at each treatment and all follow-up visit by the research team

Exclusion Criteria:

Candidates will be excluded from the study if they:

1. Are unable to cooperate with the requirements or visits of the study, as determined by the Investigator
2. Have a wart within the allowed treatment area > 8 mm in diameter or with an eroded or ulcerated surface, in the Investigator's opinion
3. Have an unclear diagnosis of condyloma
4. Have warts outside of the allowed treatment area (e.g., cervical, vaginal, clitoral, rectal, within 2 mm of anus) that require treatment during the planned study period or are undergoing treatment in the last 4 weeks
5. Have any wart types other than genital warts (e.g., common or plantar warts) that require treatment during the study period
6. Have a history of genital infections or diseases within 4 weeks before enrollment
7. Have active genital herpes eruption, or had active genital herpes lesions within 4 weeks before enrollment
8. Have a history of HPV-associated malignancies within the last 5 years

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

Name(s) of active ingredient(s): Cantharidin

9. Have a dermatologic disease (e.g., psoriasis) or skin condition in the wart areas that may cause difficulty with examination
10. Are systemically immunosuppressed or have required, or will require, systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days before enrollment or during the course of the study (routine use of local [e.g., topical, inhaled, or intranasal] corticosteroids during the study is allowed)
11. 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, diabetes, clinically significant medical, psychiatric, or emotional condition or abnormality).
12. Have had HPV immunization within the last 3 months prior to enrollment. (NOTE: HPV may NOT be administered during the course of the trial. Other immunizations (e.g., flu shots) may be administered throughout the study, but not within 5 days before or after treatment.
13. Have had any previous treatment (including an investigational agent in a clinical trial) of genital warts, including but not limited to the use of imiquimod, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, iodine-based or nitric oxide-based therapies, curettage, or freezing of warts in the 14 days before screening; in addition, these treatments, or any other over-the-counter wart treatment, should not be implemented during the study. The wash-out period for cantharidin, candida antigen, diphencyprone, dinitrochlorobenzene, squaric acid dibutyl ester, and any other immunomodulating treatment not otherwise specified is 30 days before the screening visit.
14. Have history of, or current, epidermodysplasia verruciformis
15. Have an active malignancy or are undergoing treatment for any malignancy
16. Have a history or presence of hypersensitivity or an idiosyncratic reaction to VP-102 (including cantharidin or related compounds) or study drug product excipients (acetone, ethyl alcohol, nitrocellulose, hydroxypropyl cellulose, castor oil, camphor, gentian violet, and denatonium benzoate)
17. Have a condition or situation that may interfere significantly with the subject's participation in the study (e.g., subjects who required hospitalization within 2 months before screening for an acute or chronic condition including alcohol or drug abuse), at the discretion of the Investigator
18. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods (e.g., birth control pills, intrauterine device, patch, shot, vaginal ring, and combination of condoms and foam); NOTE that withdrawal and/or sterilization of self or partner are not acceptable methods of birth control. Females that have reached menarche must have a negative urine pregnancy test at each study visit before treatment with study drug
19. Are pregnant or breastfeeding

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

Name(s) of active ingredient(s): Cantharidin

Test Product, Dose, and Mode of Administration: Study drug (VP-102 or placebo) is contained within a single-use applicator. Study drug will be applied in sufficient quantity to cover the entirety of each wart including approximately a 1 mm margin of surrounding, healthy skin. The VP-102 single-use applicator contains 0.45 mL of 0.7% w/v cantharidin, (Lot # 108107172).

The placebo single-use applicator contains the same formulation as the VP-102 applicator but does not contain the active pharmaceutical ingredient cantharidin (Lot # 108207171.)

Duration of Treatment: Study duration from Treatment Visit 1 through the final follow-up visit is approximately 147 days (21 weeks). The length of study participation is approximately 84 (–0/+8) days for the EOT assessment (primary endpoint) and Study Day 147 (±7 days) to complete the study, in addition to the screening visit of up to 14 days before study drug administration. The study will consist of up to four applications of study drug at intervals of 21 ±4 days. All treatments will take place within a 75-day period. No treatment should be administered after Day 75 without the Sponsor's approval. Post-treatment Follow-up Visits on Study Day 84 (–0/+8 days) (EOT), Study Day 112 (±7 days),), and Study Day 147 (±7 days) are included for subjects to evaluate the durability of treatment response over time.

Criteria for Evaluation

Primary efficacy endpoint:

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

Secondary efficacy endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Proportion of subjects exhibiting 90% and 75% clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Change from baseline in the number of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Change from baseline in the percent of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, at Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

Name of finished product: VP-102

Name(s) of active ingredient(s): Cantharidin

Exploratory efficacy endpoints:

- Proportion of subjects exhibiting reduction of ≥ 1 treatable wart from baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Proportion of subjects who are clear at the Study Day 84 (EOT) Visit and remain clear at the Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Change from baseline in total wart area (sum of individual warts) at Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Change from baseline in the percent of total wart area (sum of individual warts) at Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

Safety endpoints:

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

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

Statistical Methods:

Although no formal power calculations have been performed, it is expected that a sample size of 18 subjects in Part A and 90 subjects in Part B, evaluable at the Study Day 84 (–0/+8 days) EOT Visit, will be informative regarding wart clearance rates that can support assumptions in subsequent placebo-controlled trials.

Analysis populations:

- The Intent-to-Treat (ITT) Population will include all randomized subjects
- The Safety Population will include all randomized subjects who receive ≥ 1 application of study drug (VP-102 or placebo)

PROTOCOL SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals Inc.

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

Summaries of data from subjects enrolled in Part A will be pooled with corresponding subjects in Part B. For instance, if one of the two regimens selected for Part B is the 6-hour application of VP-102, then results from subjects who received the 6-hour application of VP-102 from Part A will be pooled with results from subjects who received the 6-hour application of VP-102 from Part B.

An additional set of tables will be generated that summarize subjects from Part A of the study who are not used in Part B of the study. Summary statistics for continuous variables and counts and percentages for categorial variables will be shown by treatment. However, due to the limited number of subjects for this set of tables (expected n=6), analyses to be carried out will only be descriptive in nature.

Subject demographics, efficacy tables, and subject dropout rates will be tabulated at the Study Day 84 (EOT) Visit and Study Day 147 (EOS) Visit. Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies, and percentages for discrete variables. Corresponding by-subject data listings will be tabulated.

Efficacy will be evaluated in the ITT and PP Population by treatment group. At the end of the study, tables will be generated that pool subjects from Part A and Part B for VP-102 Regimen 1, VP-102 Regimen 2, Placebo Regimen 1, and Placebo Regimen 2. For the efficacy endpoints, summary statistics for continuous variables and counts and percentages for categorical variables will be presented. In addition, statistical comparisons will be carried out to compare VP-102 Regimen 1 to Placebo Regimen 1 and VP-102 Regimen 2 to Placebo Regimen 2. Comparisons made within Regimen 1 (VP-102 vs Placebo) will be independent of comparisons made within Regimen 2. Comparisons may be carried across Regimens; however, no formal statistical testing will be carried out with comparisons being considered only observational.

An additional set of tables will be generated that summarize subjects from Part A of the study who do not participate in Part B of the study. Summary statistics for continuous variables and counts and percentages for categorial variables will be shown by treatment. However, due to the limited number of subjects for this set of tables (expected n=6), analyses to be carried out will only be descriptive in nature.

Safety analyses will be conducted in the Safety Population by actual treatment received. AEs, including LSRs, will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.0. The number and percentage of subjects having TEAEs will be tabulated by system organ class and MedDRA preferred term with a breakdown by treatment group. 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 TEAEs and number of TEAEs will be summarized by treatment using frequency counts.

Table 1. Study Schedule of Assessments and Procedures (Part A and Part B)

Period	**Screen**	**Treatment Period 1**				**Treatment Period 2**			**Treatment Period 3**			**Treatment Period 4**			**Follow-up and Unscheduled Visits**		
Task	Screen[a]	Tx 1	ERT Phone Call	ERT In-person (Part A only)	ERT Phone Call	Tx 2	ERT[b] Phone Call	ERT[b] Phone Call	Tx 3	ERT[b] Phone Call	ERT[b] Phone Call	Tx 4	ERT[b] Phone Call	ERT[b] Phone Call	EOT[c]	Follow -up	Unsched-uled[d]
Study Day Post-treatment time for each period	**-14 to 1**	1	24±6 hours	48±8 hours	7 and 14 days (±24 hours)	**1**[e]	24±6 hours	7 and 14 days (±24 hours)	**1**[e]	24±6 hours	7 and 14 days (±24 hours)	**1**[e]	24±6 hours	7 and 14 days (±24 hours)	**84** (-0/+8 days)	**112, 147** (EOS)[f] (±7 days)	
Informed consent/ authorization	X																
Inclusion/ exclusion criteria	X	X															
Demographics[g]	X																
Height and weight	X														X	X	
Prior relevant medical history, including HPV immunization	X	X															
Wart History	X	X															
Vital signs (T/P)[h]	X	X		X		X			X			X			X	X	X
Physical exam[i]	X														X		
Wart count [j] (BA only)	X	X				(X)			(X)			(X)			(X)	(X)	
Wart location [j]	X	X				X			X			X			X	X	
Wart measurement [j]	X	X													X	X	
Dermatologic exam (includes Fitzpatrick at screen only) [j]	X	X				X			X			X			X	X	X

Table 1. Study Schedule of Assessments and Procedures (Part A and Part B) (continued)

Period	Screen	Treatment Period 1				Treatment Period 2			Treatment Period 3			Treatment Period 4			Follow-up and Unscheduled Visits		
Task	Screen[a]	Tx 1	ERT Phone Call	ERT In-person (Part A only)	ERT Phone Call	Tx 2	ERT[b] Phone Call	ERT[b] Phone Call	Tx 3	ERT[b] Phone Call	ERT[b] Phone Call	Tx 4	ERT[b] Phone Call	ERT[b] Phone Call	EOT[c]	Follow-up	Unsched-uled[d]
Study Day Post-treatment time for each period	**-14 to 1**	**1**	24±6 hours	48±8 hours	7 and 14 days (±24 hours)	**1**[e]	24±6 hours	7 and 14 days (±24 hours)	**1**[e]	24±6 hours	7 and 14 days (±24 hours)	**1**[e]	24±6 hours	7 and 14 days (±24 hours)	**84** (-0/+8 days)	**112, 147** (EOS)[f] (±7 days)	
Urine pregnancy test[k]		X				X			X			X			X	X	
Photographs (site/subject)[l]	X	X				X			X			X			X	X	X
Study drug application[m]		X				X			X			X					
Apply surgical tape[m]		X				X			X			X					
ERT assessments[n] (No BA)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications, including HPV immunization	X	X	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	X
Take-home instructions, LSR guide/subject education[o]		X				X			X			X					
Provider questionnaire															X		

Table 1. Study Schedule of Assessments and Procedures (Part A and Part B) (continued)

AE = adverse event; BA = Blinded Assessor; eCRF = electronic Case Report Form; EOS = end of study; EOT=end of treatment; ERT= evaluation of response to treatment; h = hour; HIPAA = Health Insurance Portability and Accountability Act; ICF = Informed Consent Form; IRB = Institutional Review Board; LSR = local skin reactions; T/P = temperature, pulse; Tx = treatment

Footnotes to Table 1

a. Screening can occur up to 14 days before study drug application on Treatment Visit 1 (Day 1) or on the same day as Treatment Visit 1. If treatment is not applied on the same day as screening, repeat the assessments and procedures of subject eligibility, medical history, genital wart history, vital signs, wart assessments (wart count, wart measurement [diameter and area], location of all warts), dermatologic exam, photography (if applicable), and prior medication use at Treatment Visit 1 before study drug application. An IRB-approved ICF must be signed before any study specific procedures are performed.

b. The ERT telephone calls should be conducted based on the time of study drug application. The ERT telephone calls at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after each treatment visit are not required if there was no treatment during that treatment period. The ERT telephone call at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after each treatment will only collect information since the last contact.

c. All treatments may be administered over the course of up to 75 days. Provider questionnaire to be completed at the Study Day 84 (EOT) Visit by a clinician who applied treatment to the subject during the course of the study.

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

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

f. Subjects will return for additional Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days) (EOS) for an assessment of warts to determine the durability of previous responses and/or LSRs. Subjects are to attend all planned in-person visits, whether they have achieved complete clearance before or at the Study Day 84 (−0/+8 days) EOT assessment.

g. Demographics: date of birth, sex, race, and ethnicity will be collected.

h. Vital signs (e.g., temperature, heart rate) will be obtained at each treatment visit before application of study drug.

i. Additional limited physical examination, symptom, or AE-directed physical examination may be performed if warranted (see Source/eCRF for a more detailed description)

j. Dermatologic exam (including Fitzpatrick Skin Type at Screening only) and location of each wart is specified by anatomical location. Wart count, location, and measurements (diameter) should be recorded at Treatment Visit 1, before treatment, to confirm that the subject meets inclusion criteria of ≥ 2 to ≤ 30 warts and that the warts are ≤ 8 mm in diameter each with a total wart area (i.e., all warts combined) ≥ 10 mm^2. Wart area should be calculated at Screening/Treatment 1, End of Treatment, and Follow-up Visits using the formula "area= πr^2", where r= radius of wart. Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis. Wart counts will be conducted at Screening, Treatment 1, Treatment 2, Treatment 3, Treatment 4, End of Treatment, and Follow-up Visits by a trained member of the study team. Other than the screening visit and Day 1, wart counts will also be conducted by a designated Blinded Assessor. Wart counts completed at Treatment Visit 2, Treatment Visit 3, and Treatment Visit 4; and Follow-up Visits on Study Day 84 (−0/+8 days) (EOT); Study Day 112 (±7 days), and Study Day 147 (±7 days) (EOS) should be performed before the dermatologic exam and ERT assessments and will be obtained by a Blinded Assessor. The Blinded Assessor does not have to be the same person at each visit. Blinded assessors must be trained to the study, complete Good Clinical Practices, and be listed on the FDA FORM 1572 and the site Delegation of Authority Log. A separate wart count including wart measurement, wart location, and dermatologic examination are conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

Table 1. Study Schedule of Assessments and Procedures (Part A and Part B) (continued)

k. Pregnancy test is to be performed before study drug application at each treatment visit (1-4) and at Follow-up Visits on Study Day 84 (−0/+8 days) (EOT), Study Day 112 (±7 days), and Study Day 147 (±7 days) (EOS) in any females of childbearing potential (i.e., females who are capable of menstruating).

l. Subjects who agree to participate in the photographic portion of the study will have photographs of warts taken before each treatment by the study team. If there are no warts remaining, the same areas will be photographed and repeated at the Follow-up Visits on Study Day 84 (−0/+8 days) (EOT) and Study Day 147 (±7 days) (EOS) regardless of whether warts are present. 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. Efforts will be made to ensure that no photographs with identifiable features are obtained.

m. Application of study drug and surgical tape must be conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation. Surgical tape should only be removed at the designated removal time, when the treatment site is washed and study drug removed. Surgical tape and study drug may be gently removed from individual warts before the designated removal time in the event of significant blistering, significant pain, or treatment-emergent AEs. The surgical tape and study drug should not be removed from the remaining unproblematic warts until the designated removal time is reached. Removal of the surgical tape should be aided by soap and water, which will also help to prevent unroofing the blisters. Subjects who remove study drug before the assigned time frame will be considered a protocol deviation unless early removal is due to protocol defined criteria. Early removal is defined as removal of study drug outside of the following windows: ±1-hour window for the 2-hour duration of skin exposure group; ±2-hour window for the 6-hour duration of skin exposure group, and ±6-hour window for the 24-hour duration of skin exposure group.

n. In both Part A and Part B, an in-person follow-up ERT assessment will be conducted at each treatment visit (1-4) before study drug application and at Follow-up Visits on Study Day 84 (−0/+8 days) (EOT), Study Day 112 (±7 days), and Study Day 147 (±7 days) (EOS). In addition, for Part A Treatment Period 1 only, an in-person follow-up ERT assessment will be conducted at 48 hours (±8 hours). Follow-up telephone assessments for ERT will be conducted at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after each treatment visit (1-4) in which 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. ERT assessments and telephone calls must be conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation.

o. Subjects will be provided with take-home instructions describing how to remove the surgical tape, the possible LSR's, and what to expect over the next 24 hours to several months. 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 by the research team, with copies provided for home use in the required post-treatment ERT follow-up telephone 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.

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2.2 List of In-Text Figures

3.0 LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
BA	Blinded Assessor
CDLQI	Children's Dermatology Life Quality Index
CREST	calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia
eCRF	electronic case report form
EGW	external genital warts
EOS	End-of-Study
EOT	End-of-Treatment
EDC	electronic data capture
ERT	evaluation of response to treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HEK	human embryonic kidney
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HPBL	human peripheral blood lymphocytes
HPV	human papilloma virus
IB	Investigator's Brochure
IC_{50}	concentration required for 50% inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat (population)
IV	intravenous
LSR	local skin reaction
MC, molluscum	molluscum contagiosum
MedDRA	Medical Dictionary for Regulatory Activities
MN	micronucleus
N, n	number
PP	Per-Protocol (population)
QoL	quality of life
SAE	serious adverse event
SOP	standard operating procedure
TCA	trichloroacetic acid
TEAE	treatment-emergent adverse event
T/P	temperature, pulse
Tx	treatment
VP-102	Verrica Pharmaceuticals-102 (0.7% w/v cantharidin)
w/v	weight/volume

4.0 BACKGROUND AND RATIONALE

4.1 Introduction

4.1.1 Genital Warts

Genital warts (also known as anogenital warts or condyloma acuminatum) is a sexually transmitted viral disease caused by multiple different types of the human papilloma virus (HPV).[1] Human papilloma virus is spread through direct skin-to-skin contact, usually during oral, genital, or anal sex with an infected partner.[2] Human papilloma virus affects the epidermis, vulva, vagina, cervix, and rectum. Diagnosis of genital warts is usually made by visual inspection and can be confirmed by biopsy.[3] The four morphologic types of genital warts are cauliflower-shaped, smooth papular, keratotic, and flat. Genital warts cause few symptoms but can occasionally be painful. Conditions known to predispose women to infection with HPV include local trauma, diabetes, and immuno-suppression.[1]

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States.[4] Approximately 1% of people in the United States have genital warts.[5] Risk factors for genital warts include multiple sex partners, early onset of sexual activity, long-term oral contraceptive use in women and previous history of other sexually transmitted diseases (e.g., chlamydia, gonorrhea, genital herpes or trichomoniasis, human immunodeficiency virus, herpes).[6]

Safe and effective HPV vaccines are available for adolescents and young adults, but do not protect against all HPV types that can cause genital warts[5] Abstinence is the only completely effective way of avoiding genital warts.

4.1.2 Approved Treatments

The goal of treatment is to eliminate lesions. Most treatments for warts focus on destruction of the lesion through electrocautery, chemical burning, cryotherapy, or immune mediators.[1] Currently available treatments for genital warts include podophyllin, imiquimod, sinecatechins, and procedural therapies such as cryotherapy, trichloroacetic acid (TCA), laser, surgical, and electrocautery). A recently published clinical study explored the efficacy of topical compounded cantharidin compared to TCA (Section 4.4.3).[1] No single treatment is ideal for all patients and all warts.

Treatment of anogenital warts is guided by wart size, number, anatomic site, patient preference; convenience; and provider experience. In addition, each of these treatments have shortcomings related to multiple applications, erosions and erythema, adverse effects, long times for resolution, and expense.[1] Because of these shortcomings, some clinicians have employed combination therapy (e.g., provider-administered cryotherapy with patient-applied topical therapy between visits to the provider).[3] However, limited data has been published on the safety and efficacy of combination therapies.[3]

4.1.3 Cantharidin

For many dermatologists, 0.7% w/v cantharidin has been the treatment of choice for common warts and molluscum contagiosum (MC) for decades.[7]. However, cantharidin remains an unapproved drug and there is no reliable or controlled source on the market.

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. The *Mylabris* species of beetle contains a much greater concentration of cantharidin than other species and is the primary type of beetle used in modern cantharidin preparations.

In contrast to currently available therapies, 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 activation of neutral serine proteases resulting in the destruction of intercellular desmosomes responsible for holding the layers of the skin together.[8] 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. This process is not associated with scarring, as the underlying dermal layer of skin is undamaged. Cantharidin has no known direct antiviral effects. Cantharidin application also can stimulate an immune response in the skin that can cause local inflammation, which may be a contributing factor in treating viral skin disease.[9]

4.1.4 VP-102

VP-102, a 0.7% w/v topical film-forming cantharidin formulation has been developed to be consistent with the predominant concentration of cantharidin used by physicians. VP-102 is administered with a single-use applicator to minimize cross-contamination and concentration changes during use. Each VP-102 applicator contains 0.45 mL of drug product. Gentian violet, a dye common in surgical markers, has also been included to facilitate physician recognition of treated versus untreated lesions. Finally, to afford additional safety and deter potential oral ingestion of the drug, the oral deterrent denatonium benzoate has been included.

4.2 Nonclinical Studies

Cantharidin is a potent inhibitor of protein phosphatases that are found in all tissues.[10] 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 Investigator's Brochure [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/m^2) of cantharidin, cardiac waveform and function were adversely affected, likely related to its inhibitory effect on protein phosphatases.[11]. Cantharidin is a vasoconstrictor and may also be responsible for decreases in urine volume with single oral dose administration.[11, 12] 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,[11] 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).[13] The apparent plasma elimination half-life of cantharidin was about 20 minutes in dogs.[14] Tissue distribution of cantharidin was ubiquitous, consistent with the widespread distribution of protein phosphatases.

Nonclinical toxicity information available on cantharidin is predominantly from single dose (acute) studies by the dermal, oral, intraperitoneal, and intravenous (IV) 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.

With an extensive history of use of cantharidin in humans, a limited nonclinical program has been developed to support the use of topical (dermal) VP-102. No nonclinical primary pharmacodynamic or pharmacokinetic studies were conducted by Verrica using either VP-102 or cantharidin. A single Good Laboratory Practices (GLP)-compliant study evaluating inhibition of the human ether-à-go-go-related gene (hERG) channel as an in vitro cardiovascular safety pharmacology endpoint was conducted.

The safety profile of topical cantharidin is already well established from its history of use in patients, as well as studies conducted in animals. With negligible systemic exposure after topical application, the strategy for the nonclinical toxicology program for VP-102 developed by Verrica focused on addressing the pending concerns associated with its use as a topical treatment; thus, Verrica completed the GLP in vitro genetic toxicity testing battery with cantharidin, including a bacterial reverse mutation assay, a mammalian cell chromosomal aberration assay, and a mammalian cell micronucleus assay.

An overview of the Verrica-sponsored toxicology studies conducted with cantharidin is provided in Table 2.

Table 2. Summary of VP-102 Nonclinical Program

Type of Study	Category	Test Article	Route	Test System	Key Finding(s)
Pharmacology	Safety pharmacology: cardiovascular (hERG assay)	Cantharidin	In vitro	hERG-transfected HEK293 cells	Mean ± SEM inhibition of hERG current was 1.9 ±0.3% (n = 3) for 30 µM, cantharidin and 3.5 ±0.4% for 300 µM cantharidin; neither statistically significant compared with vehicle control (2.1 ±0.4%). IC_{50} of cantharidin on hERG current > 300 µM
Toxicology	Genetic toxicity: bacterial reverse mutation assay	Cantharidin	In vitro	*Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* tester strain WP2 *uvr*A	Cantharidin negative at all concentrations tested (15.0-5000 µg/plate) in all strains tested in presence or absence of S9 activation. Cantharidin does not possess mutagenic properties
	Genetic toxicity: mammalian cell chromosomal aberration assay	Cantharidin	In vitro	HPBL	Study inconclusive and terminated before completion due to overly condensed metaphase chromosomes at several concentrations, which did not allow for adequate evaluation of test samples that would meet criteria for a valid assay in accordance with ICH S2(R1) guidance
	Genetic toxicity: mammalian cell micronucleus assay	Cantharidin	In vitro	TK6 human lymphoblastoid cells	Cantharidin at ≥ 1 µg/mL induced formation of MN with 27-hour exposure, but increase in MN not observed at similar concentrations with 4-hour exposure. Subsequent CREST staining revealed MN formed via aneugenic, not clastogenic, mechanism of action

CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; HEK = human embryonic kidney; hERG = human ether-à-go-go-related gene; HPBL = human peripheral blood lymphocytes; IC_{50} = concentration required for 50% inhibition; ICH = International Conference on Harmonisation; MN = micronucleus

Verrica completed one in vitro GLP safety pharmacology study that evaluated the concentration response relationship of the effect of cantharidin on the hERG potassium channel current in stably transfected mammalian cells that express the hERG gene (Study 170922.WFU). Specifically, the study examined the inhibitory effects of cantharidin on the hERG channel current at near-physiologic temperature. The study reported no change in hERG current across the cantharidin concentration range (30 and 300 μM). The IC_{50} for the inhibitory effect of cantharidin on hERG potassium current was estimated to be > 300 μM (> 60,000 ng/mL). At 300 μM, the concentration of cantharidin is > 17,000-fold higher than the highest level of cantharidin detected systemically (3.4 ng/mL) in a clinical exposure study conducted with topical administration of VP-102 in molluscum patients (Study VP-102-103).

Verrica completed a GLP-compliant in vitro genetic toxicity test battery with cantharidin. Three in vitro genotoxicity studies were conducted: a bacterial reverse mutation assay (Ames test), a mammalian cell micronucleus assay in TK6 human lymphoblastoid cells, and a mammalian cell chromosomal aberration assay in human peripheral blood lymphocytes (HPBL).

For the bacterial reverse mutation assay (Study AE58BG.502ICH.BTL), cantharidin was evaluated for its mutagenic potential by measuring its ability to induce reverse mutations at selected loci of *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537, and at the tryptophan locus of *Escherichia coli*WP2 *uvr*A in the presence and absence of an exogenous metabolic activation system. Based on the results of the preliminary toxicity assay, the maximum dose to be tested in the mutagenicity assay was 5000 μg/plate. At all concentrations tested, cantharidin was negative at select loci of several *S. typhimurum* and *E. coli* tester strains, suggesting that cantharidin does not possess mutagenic properties.

In the mammalian cell chromosomal aberration assay, cantharidin was evaluated for its potential to induce structural chromosomal aberrations using HPBL in either the presence or the absence of an exogenous metabolic activation system (Study AE58BG.341ICH.BTL). Overly condensed and distorted metaphase chromosomes were noted during the assay at several concentrations with < 50% cytotoxicity, which did not allow for an adequate evaluation of the test samples that would meet the criteria for a valid assay in accordance with ICH S2(R1) guidance, and thus the study was terminated before completion.

The mammalian cell genotoxicity study assessed the clastogenic potential of cantharidin (Study AE58BG.361CRESTICH.BTL). Specifically, cantharidin was evaluated for its potential to induce micronuclei in TK6 human lymphoblastoid cells in either the presence or absence of an exogenous metabolic activation system. A dose-dependent increase in micronuclei formation was observed in the non-activated 27-hour treatment group with cantharidin doses of 1 µg/mL (1.25%) to 1.6 µg/mL (2.25%) compared with vehicle (0.65%). An increase in micronuclei formation was not observed at similar concentrations with a 4-hour exposure. Compared with the vehicle group, an increase in micronucleus induction in either the absence or presence of an exogenous metabolic activation system was observed at higher cantharidin concentrations of 3.5 µg/mL (1.40% vs 0.55%, respectively) and 5.5 µg/mL (1.20% vs 0.60%, respectively) in the 4-hour treatment groups. Subsequent analysis with calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) staining revealed that a high frequency of micronuclei in the presence of kinetochore staining was observed in the cantharidin-treated cells, suggesting that cantharidin induces micronuclei formation through an aneugenic, and not a clastogenic, mechanism of action.

4.3 Clinical Experience

A summary of VP-102 Phase 2 and Phase 3 clinical studies in subjects with molluscum contagiosum are presented in Table 3. A phase 2 study (VP-102-105) evaluating the safety and efficacy of VP-102 in subjects with common warts is ongoing. No clinical studies have been conducted to date with VP-102 in subjects with external genital warts.

In addition to the summary information in Table 3, additional results are provided for two of the VP-102 studies:

1. Results from Phase 2 study VP-102-103 are presented in Section 4.3.1 because this study provides relevant information on the systemic exposure in subjects with molluscum after treatment with VP-102

2. Results from Phase 2 study 16-10-195 are presented in Section 4.3.2 because this study treated subjects with molluscum for 6 hours and 24 hours

Results from a study of cantharidin in subjects with genital warts are presented in Section 4.3.3.

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

Study	Study Design	Objectives	Number of Subjects	Drug/Device and Dosing Regimen	Results
VP-102 -101 (CAMP-1)	Pivotal Phase 3, randomized, double-blind, placebo-controlled	Primary: To evaluate efficacy (proportion subjects achieving complete clearance of all treatable lesions) of VP-102 relative to placebo at Day 84 Secondary: • To assess safety and tolerability (AEs, LSRs, physical examinations, and concomitant medications) of VP-102 compared to baseline at Day 84 • To assess efficacy (proportion of subjects achieving complete clearance of all treatable lesions) of VP-102 relative to placebo at Visit 2, Visit 3, and Visit 4	N=266 subjects with molluscum contagiosum lesions n=161 VP-102 n=105 placebo (3:2 VP-102: placebo randomization)	VP-102 solution and applicator Single 24-hour treatment every 21 days for up to 4 applications	Statistically significant primary efficacy endpoint met (p<.0001) Secondary efficacy endpoints met at Visits 2, 3, and 4 Confirmed safety and efficacy with VP-102 in applicator
VP-102 -102 (CAMP-2)	Pivotal Phase 3, randomized, double-blind, placebo-controlled	Primary: To evaluate efficacy (proportion subjects achieving complete clearance of all treatable lesions) of VP-102 relative to placebo at Day 84 Secondary: • To assess safety and tolerability (AEs, LSRs, physical examinations, and concomitant medications) of VP-102 compared to baseline at Day 84 • To assess efficacy (proportion of subjects achieving complete clearance of all treatable lesions) of VP-102 relative to placebo at Visit 2, Visit 3, and Visit 4	N=262 subjects with molluscum contagiosum lesions n=150 VP-102 n=112 placebo (3:2 VP-102: placebo randomization)	VP-102 solution and applicator Single 24-hour treatment every 21 days for up to 4 applications	Statistically significant primary efficacy endpoint met (p<.0001) Secondary efficacy endpoints met at Visits 3 and 4 Confirmed safety and efficacy with VP-102 in applicator
VP-102 -103	Phase 2 open-label	Primary: To determine presence or absence of systemic cantharidin exposure from single 24-hour dermal application of VP-102 applied to molluscum lesions. Secondary: • To assess safety (AEs, LSRs, physical examinations, concomitant medications) of VP-102 • To assess efficacy (clearance or reduction of treated lesions compared to baseline) of VP-102. • To assess impact of VP-102 treatment on QoL (assessed via CDLQI)	N=33 subjects (all exposed to VP-102) with molluscum contagiosum lesions	VP-102 solution and applicator Single 24-hour treatment every 21 days for up to 4 applications	Negligible systemic exposure under maximal use conditions. Confirmed safety and efficacy with VP-102 in applicator.

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

Study	Study Design	Objectives	Number of Subjects	Drug/Device and Dosing Regimen	Results
Study 12-01-004	Phase 2	Safety and efficacy	N=94 subjects with molluscum contagiosum	Compounded topical cantharidin (0.7% w/v) applied with wooden stick 6-hour treatment every 21 days	Cantharidin was well tolerated and associated with the clearance of molluscum contagiosum.
Study 16-10-195	Phase 2	Safety and efficacy	N=30 subjects with molluscum contagiosum (all exposed to VP-102) Cohort 1: n = 14 Cohort 2: n =16	Topical VP-102 solution with wooden stick Cohort 1: 6-hour treatment every 21 days Cohort 2: 24-hour treatment every 21 days	VP-102 was well tolerated with similar efficacy compared to cantharidin 6-hour and 24-hour application demonstrated similar tolerability and efficacy

AE = adverse event; CDLQI = Children's Dermatology Life Quality Index; LSR = local skin reactions; N= number; QoL = quality of life

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

VP-102 in the proprietary applicator was determined to be safe in a 12-week, open-label, Phase 2 study (VP-102-103) implemented under Investigation New Drug (IND) application 131163/NCT03186378. The primary objective of the study was to evaluate the potential systemic exposure to cantharidin under maximum use conditions (> 21 lesions treated). Subjects ≥ 2 years of age with molluscum contagiosum were enrolled and treated with VP-102 (a single-use proprietary applicator containing a novel 0.7% w/v cantharidin solution) every 21 days for up to 4 treatments or until complete lesion clearance. Subjects were instructed to wash VP-102 off at 24 hours, or earlier if significant pain or blistering. Lesion counts and adverse events (AEs), including local skin reactions (LSRs), were documented at each visit. Quality of life (QoL) was measured using the Children's Dermatology Life Quality Index (CDLQI). A subset of 17 subjects with ≥ 21 MC lesions at baseline were evaluated for systemic exposure with 4 blood samples (pre-dose and at 2, 6, and 24 hours post-dose). Key efficacy endpoints were percentage of subjects exhibiting complete clearance of all treated MC lesions (baseline and new) on or before Week 12 and percentage of reduction of treated MC lesions from baseline at Week 12.

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

Treatment with VP-102 was well-tolerated. A total of 29 subjects (88%) reported at least one treatment-emergent adverse event (TEAE), including expected LSRs such as blistering or erythema. Most subjects had mild TEAEs; 3 subjects had moderate TEAEs. Overall, 21 (63.6%) subjects had TEAEs related to study drug, most of which were LSRs. There were no serious adverse events (SAEs) or TEAEs leading to premature study withdrawal.

Treatment with VP-102 was associated with significantly reduced lesion count, improved QoL, and complete clearance of MC lesions. Sixteen (16) subjects (48.5%) achieved complete clearance of all MC lesions on or before Week 12. The median lesion count was reduced 98% from baseline to Week 12. Decreases in mean CDLQI composite scores were observed, from 2.58 (standard deviation = 3.446) at baseline to

0.38 (standard deviation =0.871) at Week 12. No subjects reported spread of molluscum lesions to any siblings during the study.

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

In a separate double-blind, Phase 2 study (12-01-004), topical cantharidin (0.7% w/v) was well tolerated and associated with the clearance of MC in 94 subjects with childhood molluscum.[15]

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

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

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

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

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

4.3.3 Cantharidin Study in Subjects with Genital Warts

One study of cantharidin for the treatment of genital warts has been published. A randomized, controlled trial of cantharidin was conducted in 12 patients with non-mucosal genital warts.[1] Patients were randomized to either compounded cantharidin (n=6 patients with 15 warts) or TCA (n=6 patients with 14 warts) treatment.Cantharidin was applied to the skin and allowed to dry, covered with a transparent adhesive waterproof film dressing, and after 4 to 6 hours, the treatment area was washed with soap and water to control skin exposure. Cantharidin was more effective and better tolerated than TCA for the treatment of lesions. Complete clearance of warts occurred in 100% of patients treated with cantharidin and 66% of patients treated with TCA (P=0.45). Patients treated with cantharidin, compared to TCA, healed with less scarring (P<0.034), had less pain during treatment (P<0.01), and required fewer treatments to eradicate warts (P<0.01).

4.4 Summary of Known Benefits and Potential Risks

4.4.1 Potential Benefits

No studies with VP-102 have been conducted in subjects with genital warts and the potential benefit is uncertain. It is anticipated that subjects participating in this study who are randomized to the VP-102 group will experience at least similar therapeutic benefits as subjects treated with VP-102 or 0.7% w/v cantharidin in previous clinical studies. Efficacy data for VP-102 and cantharidin are provided in Section 4.3 and described in the IB.

Approximately 80% of the subjects enrolled in Part A of this study will be randomized to receive VP-102. Approximately 60% of the subjects enrolled in Part B of this study will be randomized to receive VP-102.

4.4.2 Known Risks

No studies with VP-102 have been conducted in subjects with genital warts, and thus the potential risks are uncertain. Safety and PK data for VP-102 are provided in Section 4.3 and described in the IB. Nonclinical data for VP-102 are presented in Section 4.2 and described in the IB. Although the study drug will be labeled exclusively for topical application and will be applied only by study personnel, the formulation also contains an oral deterrent (denatonium benzoate) to further help mitigate the risk of accidental ingestion.

The mechanism of action of cantharidin, when applied externally, is that of a vesicant (blistering agent) and can cause severe chemical burns at high concentrations. Cantharidin taken internally can be poisonous to humans. Cantharidin is classified as an extremely hazardous substance in the United States and is subject to strict reporting requirements by facilities that produce, store, or use it in significant quantities.[16] However, cantharidin can be safely and effectively used to treat some benign skin lesions when formulated properly and applied in the clinic topically by a medical provider familiar with its effects and uses.[17]

The most frequently reported AEs in clinical trials with VP-102 conducted in subjects with MC were application site vesicles, application site scab, application site pain, application site erythema, and application site pruritus. These are well-known, reversible reactions of the skin that are related to the mechanism of action of cantharidin, a vesicant.

4.4.3 Potential Risks

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

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

4.4.4 Risk-Benefit Summary

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

4.5 Justification for Dosing Regimen

This study will evaluate VP-102, a controlled, highly-pure, standardized form of topical cantharidin manufactured under Good Manufacturing Practices (GMP) to address the problems associated with currently available compounded cantharidin products and the needs of subjects and medical professionals.

A 0.7% w/v cantharidin solution is the recognized therapeutic dose of cantharidin for wart treatment in dermatological clinical practice.[7, 18-21] VP-102, a drug-device combination containing 0.7% w/v cantharidin, was determined to be safe and effective in two recently completed double-blind, randomized, placebo-controlled, Phase 3 studies that enrolled > 500 subjects ≥ 2 years of age with molluscum contagiosum. The only published study of cantharidin for the treatment of genital warts demonstrated enhanced safety and efficacy with a 0.7% cantharidin solution applied for 4 to 6 hours with occlusion compared to TCA.[1] Additionally, multiple publications have demonstrated safety and efficacy with a 0.7% cantharidin solution in common warts, both with and without the use of surgical tape.[7, 18-24].

In this study, lesions will be covered with surgical 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. This will also eliminate unintentional transference of study drug to healthy tissue.

Study drug will be applied in sufficient quantity to cover the entirety of each wart, including approximately a 1 mm margin of surrounding, healthy skin.

The duration of skin exposure to cantharidin, the active ingredient in VP-102, will be controlled in this study. In Part A, VP-102 will remain on the skin for up to 2 hours in group 1 and the exposure will be increased to 6 and 24 hours in subsequent groups based on the assessment of safety and tolerability. The duration of skin exposure will be modulated by washing of the treatment area at either the pre-determined time per protocol or based on clinical response (e.g., significant blistering or pain), consistent with current clinical practice with the use of cantharidin (directions for use are provided in Section 8.2).[17] The 2-hour duration of skin exposure was selected as the starting point based on a published clinical study with 0.7% cantharidin, which demonstrated favorable safety and efficacy with a 4- to 6-hour treatment duration. The 6-hour and 24-hour time periods were selected to allow a safe and controlled step-wise increase in

skin exposure that would be expected to result in a meaningful increase in the pharmacodynamic response in the skin (e.g., blistering).

The dosing regimen for Part B will be selected based on the response observed in subjects during the dose regimen finding performed in Part A.

4.6 Population to be Studied

In this study, adult subjects ages 18 and older, with external genital warts (EGW), will be included. External genital warts are defined as warts located in the medial thigh (except inguinal fold); supra-pubic, perineal, and perianal areas, vulva (excluding labia minora and mucosal surfaces), over the glans penis (excluding urethral meatus), penis shaft, scrotum, and foreskin.

4.7 Statement of Compliance

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

5.0 STUDY PURPOSE AND OBJECTIVES

Part A (Dose Regimen Finding)

Primary objective:

- To evaluate three regimens of application of VP-102 (2-hour, 6-hour, 24-hour duration of skin exposure) in subjects with EGW and identify the two best regimens by assessing safety and tolerability of VP-102 when administered topically after all subjects have completed a 48-hour assessment.

Primary efficacy objective:

- To evaluate the efficacy of VP-102 when administered topically to EGW once every 21 days for up to 4 applications by assessing the proportion of subjects achieving complete clearance of all treatable warts (baseline and new) at the Study Day 84 End-of-Treatment (EOT) Visit

Part B (Safety and Efficacy)

Primary objective:

- To evaluate two regimens of application of VP-102 in subjects with EGW and identify the regimen with the best risk:benefit profile when administered topically once every 21 days for up to 4 applications.

Part A & B (Safety and Efficacy)

Secondary objectives:

- To assess the safety and tolerability of VP-102 in subjects with EGW by evaluating AEs including expected LSRs, vital signs, and concomitant medications

- To evaluate the efficacy of VP-102 when administered topically to EGW once every 21 days for up to 4 applications by assessing the proportion of subjects achieving complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and Follow-up Visits on Study Day 112 and Study Day 147 (End-of-Study [EOS])

- To evaluate the efficacy of VP-102 by assessing the change from baseline in the number of treatable warts (baseline and new) at each scheduled postbaseline visit

- To evaluate the efficacy of VP-102 by assessing the percent change from baseline in the number of treatable warts (baseline and new) at each scheduled postbaseline visit

- To evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting 75% and 90% clearance of all treatable warts (baseline and new) at each scheduled postbaseline visit

Exploratory objectives

- To evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting reduction of ≥1 treatable wart from baseline at each scheduled postbaseline visit

- To evaluate the efficacy of VP-102 by assessing the proportion of subjects who are clear at the Study Day 84 (EOT) Visit and remain clear at the Follow-up Visits on Study Day 112 and Study Day 147 (EOS).

- To evaluate the efficacy of VP-102 by assessing the change from baseline in total wart area (sum of individual warts) at the scheduled post baseline visits Day 84, 112 and 147.

- To evaluate the efficacy of VP-102 by assessing the percent change from baseline in total wart area (sum of individual warts) at the scheduled post baseline visits Day 84, 112 and 147.

6.0 STUDY DESIGN

6.1 Description of the Study

This is a Phase 2, double-blind, placebo-controlled study to determine the dose regimen, safety, tolerability, and efficacy of VP-102 in subjects with EGW. This study is divided into two parts (Part A and Part B). The Schedule of Assessments and Procedures is presented in Table 1.

6.1.1 Part A (dose regimen finding) Study Design

The aim of Part A is to determine the two best treatment regimens for evaluation of safety and efficacy in Part B.

Treatment regimens will be evaluated based on the requirement to form blisters in most patients, while maintaining a favorable safety and tolerability profile (e.g., majority of LSR AEs are mild or moderate in severity). Accordingly, increasing durations of skin exposure to study drug (VP-102 or placebo) will be evaluated in three treatment groups (n=6/group) that will enroll progressively.

Subjects will have a Screening Period of up to 14 days before the first treatment, followed by a Treatment Period starting at Treatment Visit 1 and lasting through Treatment Visit 4.

Eighteen (18) subjects at up to six sites (additional sites may be added if required to ensure successful recruitment of the study population) will be enrolled, into either the 2-hour (Group 1), 6-hour (Group 2), or 24-hour (Group 3) treatment duration of skin exposure groups (n=6 subjects/group). Each group will include a minimum of two subjects from each sex and will be randomized 5:1 (VP-102:placebo) within each group. All subjects will receive either VP-102 (containing 0.7% cantharidin [w/v] topical film-forming solution) or placebo. Warts are to be treated and then covered (unless prohibited by wart location) with transparent surgical tape (e.g., 3M™ Blenderm™ brand) that will remain on the skin until the designated time for removal. Subjects will be asked to remove the surgical tape and study drug with soap and water after the pre-determined duration of skin exposure for their group.

Study drug (VP-102 or placebo) will be administered once every 21 ±4 days for up to four applications. Enrollment will begin in Group 1, then proceed into Group 2, and lastly into Group 3. The enrollment of subjects into Groups 2 and 3 will only be allowed upon completion of a blinded review of the safety and tolerability data by a Safety Review Panel. The Safety Review Panel will be responsible for reviewing blinded safety and tolerability data and will provide determinations on trial stopping or modification rules. A blinded review of TEAEs, focusing on those of moderate or severe intensity, will be performed by the Safety Review Panel prior to opening enrollment for each subsequent cohort. This review will be conducted after the six subjects in a designated Group have completed the 48-hour (±8 hours) Visit. The Safety Review Panel will determine whether enrollment can be initiated into the next Group, OR if more data (e.g., waiting for additional treatments for enrolled subjects or the addition of more subjects to a group) are needed prior to making a determination to open enrollment into the next Group (i.e., the review conducted after six subjects have completed Group 1 could open enrollment into Group 2 and the review after Group 2 could open enrollment into Group 3). An additional blinded safety review of TEAEs, focusing on those of moderate or severe intensity, will be performed after all six subjects in Group 3 have completed the 48-hour (±8 hours) Visit, in order to support dose selection for Part B (Safety and Efficacy). Safety Review Panel members are blinded to the treatment assignment.

6.1.2 Part B (safety and efficacy) Study Design

Part B of the study will begin enrollment only after the Sponsor has selected the two dose regimens in Part A, which will be called VP-102 Regimen 1 and Regimen 2. In addition, written notification from the Sponsor must be provided to the sites prior to Part B enrollment. The study will remain blinded until completion of both parts of the study.

Approximately 90 subjects at up to 9 sites (additional sites may be added if required to ensure successful recruitment of the study population) will be enrolled and randomized to one of four treatment arms. Randomization will be stratified by sex so that neither gender exceeds ~60% of any treatment arm (e.g., placebo group for the 6-hour and 24-hour wash-off cannot have any one gender ≥ 60%). Two of the treatment arms will be VP-102 Regimen 1 and VP-102 Regimen 2. The other two treatment arms will be placebo (Placebo Regimen 1 and Placebo Regimen 2), with corresponding durations of skin exposure matching those selected for VP-102 Regimen 1 and Regimen 2. As an

example, if the regimens selected from Part A are the 2-hour and 6-hour applications of VP-102, then VP-102 Regimen 1 would be VP-102 treatment for 2-hours and VP-102 Regimen 2 would be VP-102 treatment for 6-hours. Likewise, Placebo Regimen 1 would be placebo treatment for 2 hours and Placebo Regimen 2 would be placebo treatment for 6-hours. Randomization of the four treatment arms (VP-102 Regimen 1:VP-102 Regimen 2: Placebo Regimen 1:Placebo Regimen 2) will be3:3:2:2.

In both Regimen 1 and Regimen 2, study drug will be administered to EGW once every 21 ±4 days for up to four applications. Subjects will be asked to remove the surgical tape and study drug with soap and water at the designated time selected from the dose regimen findings in Part A of the study.

6.1.3 Part A and Part B Procedures

6.1.3.1 Subject Participation

Pre-study screening for eligibility (informed consent, demographics, physical exam, vital signs, prior and concomitant medications, and medical history) can occur up to 14 days before, or on the same day as Treatment Visit 1. The dermatologic exam, wart count, wart measurement (diameter), location of all warts, and photographs (if applicable) must be repeated at Treatment Visit 1 if the Screening Visit is not conducted on the same day. Warts must measure ≤ 8 mm in diameter each with a total wart area (i.e., all warts combined) ≥ 10 mm^2 at baseline. Wart count must be ≥ 2 and ≤ 30 total warts within the allowed treatment areas at the time of Treatment Visit 1.

Subjects who do not continue to meet criteria at Treatment Visit 1 will be considered a screen failure and will be treated at physician discretion per standard of care. Subjects who meet the enrollment criteria will be randomized to receive VP-102 or placebo. Treatment will continue with a minimum of every 21 ±4 days, until complete clearance or a maximum of four treatment sessions. The exact treatment interval will be determined by evaluation of the treatment site and take any ongoing LSRs into account. Subjects who achieve complete clearance of all treatable warts before Treatment Visit 4 will be required to return for every scheduled, in-person, treatment and follow-up visit, whether or not their warts have cleared. The 24-hour, 7-day, and 14-day evaluation of response to treatment (ERT) telephone follow-ups will be conducted per protocol for those instances in which the subject was treated.

6.1.3.2 Efficacy Procedures

All required study activities, including an ERT (i.e., assessment of wart activity [count, location, diameter] and related LSRs), will be conducted per protocol. A Blinded Assessor will perform wart counts before the ERT assessment at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, End of Treatment Visit, and Follow-up Visit.

Treatment visits are to take place in order (i.e., Treatment 1, Treatment 2, Treatment 3, and Treatment 4). All subjects will receive application of study drug to EGW, including an approximate margin of healthy surrounding skin, at an interval of every 21 ±4 days until complete clearance of all treatable warts, or a maximum of four applications.

No partial treatment of warts (e.g., treating one wart and not another) is permitted. In any instance where the clinician is uncertain if a residual wart is remaining, treatment should be applied. Instructions for application of the study drug are outlined in the Instructions for Use included in the drug shipment, as well as included in the Site Regulatory Packet.

Subjects should be re-treated only after 17 to 25 days (i.e., 21 ±4 days) have elapsed since the previous treatment and only after any LSRs have resolved sufficiently to allow evaluation of the treatment site. Treatment should only take place at a visit when all warts are evaluable (i.e., not obscured by an ongoing LSR). All warts that are not completely clear should undergo treatment with study drug. Subjects exhibiting skin reactions that need additional time, at the Investigator's discretion, before they can be treated again will be evaluated and asked to return for their next treatment visit after the area is considered sufficiently resolved to allow for the next treatment (e.g., ongoing dryness or erythema is appropriate to treat). See instructions below regarding unscheduled visits.

Subjects who receive <4 treatments within the treatment period, or have visits that are outside of the visit window due to the duration of post-treatment LSRs, will not be considered a protocol deviation. In the event that a subject misses a treatment visit, and is outside the 4-day study window, they may return and be treated at the next available opportunity with the subsequent visit scheduled 21 ±4 days after the actual treatment visit. No treatment should be administered after the treatment period without the Sponsor's approval.

An ERT assessment will be conducted at each treatment visit (1-4; in-person before treatment or via follow-up telephone calls) at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after each treatment visit (not "unscheduled" visits). Note that the ERT telephone calls at 24 hours (±6 hours), 7 days (±24 hours) and 14 days (±24 hours) are not required if there was no treatment during that period. In Part A Treatment Period 1 only, subjects will return to the clinic for an in-person ERT assessment at 48 hours (±8 hours) after Treatment Visit 1. The ERT includes questions related to removal of surgical tape and study drug (if applicable) and collects any new AEs, LSRs, and changes in concomitant medications since the last contact. The subject will be given an opportunity to ask questions and review any concerns. In the event that any post-treatment LSR presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain) an "Unscheduled" clinic visit must be scheduled, and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an unscheduled visit. The ERT assessments will be recorded by a research team member on the ERT form. The ERT visits may not be conducted by a person designated as a Blinded Assessor. Phone calls conducted outside of the required study visits or required ERT assessments should be documented in the subject's source note but are not required to be entered in the electronic data capture (EDC) system.

ERT assessments, wart count, and wart location will be conducted before treatment application at all Treatment Visits 1 to 4, as well as at the EOT Visit on Study Day 84 (0/+8 days) and at the Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days). Wart measurement will be conducted before treatment application at Treatment Visit 1, as well as at the EOT Visit on Study Day 84 (–0/+8 days) and at the Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days). Subjects who clear all warts before the Study Day 84 (EOT) Visit will still be required to return for each of the scheduled in-person treatment visits, as well as the Study Day 84 (EOT) Visit, the Study Day 112 follow-up visit, and the Study Day 147 (EOS) Visit. A Provider Treatment Questionnaire will be completed at the Study Day 84 (EOT) Visit by a clinician who applied treatment to the subject during the course of the study. All subjects will continue in the study for two additional Follow-up Visits on Study Day 112 and Study Day 147 (EOS).

All treatment visits will include a wart count, performed before treatment (if applicable) and before ERT assessment. No treatment will be required if the wart is considered clear. Genital warts that develop in areas that are unable to be treated, (e.g., close to a

mucous membrane) and other wart types (e.g., common warts) will not be evaluated, documented, or considered in the analysis.

Wart counts will be conducted at the Screening Visit, Treatment Visit 1, Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, End of Treatment Visit, and Follow-up Visit by a trained member of the study team. Other than the screening visit and Day 1, wart counts will also be conducted by a member of the research team that has been identified and trained as a Blinded Assessor. The Blinded Assessor may be utilized for a subject's initial screening, enrollment and treatment Visit 1 activities, however, may not perform any other study related activities other than wart counts at subsequent visits (e.g., follow-up phone calls or unscheduled visits) for the same subject. The Blinded Assessor is not required to be the same person for each assessment.

It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing LSRs. At any visit in which the Investigator is unable to evaluate or treat some warts due to ongoing LSRs, an "Unscheduled" visit should be documented. The timing of the next visit will be determined by the resolution of the LSR. The research team should be in contact with the patient until LSRs are resolved sufficiently and a treatment visit can be scheduled within 21 ±4 days when possible. Specific instructions on how to conduct the initial wart count and measure wart diameter will be provided during Investigator training.

At designated sites, photography will be offered to volunteer subjects who consent to participate. Photography will take place at the clinical site at each treatment and follow-up study visit through Study Day 147 (±7 days; EOS). If there are no warts remaining, the same areas will be photographed and repeated at the Study Day 84 (0/+8 days) EOT Visit and Study Day 147 (±7 days) EOS visit, regardless of whether warts are present. 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. Efforts will be made to ensure that no photographs with identifiable features are obtained.

6.1.3.3 Safety Procedures

Subjects will be provided with take home instructions describing what they might expect throughout the course of the study, as well as recommendations for wound care (if needed), when it is important to call their doctor, and instructions for who to contact in an emergency. In the event that any post-treatment LSR presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain), an "Unscheduled" clinic visit must be scheduled and the subject assessed accordingly. In addition, if any post-treatment AEs present a safety concern, the subject may be brought in for an unscheduled visit.

An LSR guide for subjects, with specific photographs representing the various skin reactions and examples of intensity, will be provided and reviewed in detail at the clinic with the subject by the research team. The LSR guide will be utilized for reference by the subject during the ERT follow-up telephone assessments with the research team member. The final determination of LSR parameters, including intensity, will be made by the research team member.

6.2 Number of Subjects

In Part A, 18 subjects will be enrolled into one of three duration of skin exposure groups (n=6 subjects/group). Each group will include a minimum of two subjects from each sex and will be randomized 5:1 (VP-102:placebo) within each group.

In Part B, 90 subjects will be enrolled, randomized to one of four treatment arms. Randomization will be stratified by sex so that neither gender exceeds ~60% of any treatment arm (e.g., placebo group for the 6-hour and 24-hour wash-off cannot have any one gender ≥ 60%).

6.3 Measures Taken to Minimize Bias

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

6.4 Expected Duration of Subject Participation

Study duration from Treatment Visit 1 through the final follow-up visit is approximately 147 days (21 weeks). The length of study participation is approximately

84 (–0/+8) days for the EOT assessment (primary endpoint) and Study Day 147 (±7) days to complete the study, in addition to the screening visit of up to 14 days before study drug administration. The study will consist of up to four applications of study drug at intervals of 21 ±4 days. All treatments will take place within a 75-day period. No treatment should be administered after Day 75 without the Sponsor's approval. Post-treatment Follow-up Visits on Study Day 84 (–0/+8 days) (EOT), Study Day 112 (±7 days),), and Study Day 147 (±7 days) are included for subjects to evaluate the durability of treatment response over time.

6.5 Method of Treatment Assignment and Blinding

After informed consent has been obtained, subjects will be screened for study eligibility before randomization. Subjects will be assigned a subject number and randomized. In Part A, each group will include a minimum of two subjects from each sex randomized 5:1 (VP-102: or placebo). In Part B, randomization of the four treatment arms (VP-102 Regimen 1:VP-102 Regimen 2: Placebo Regimen 1:Placebo Regimen 2) will be 3:3:2:2. The study site's pharmacist (or pharmacist designee) will obtain the study drug assignment from the Interactive Response Technology (IRT). A subject is considered randomized when the randomization transaction is recorded in the IRT.

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

7.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

The study will enroll and treat approximately 18 adult subjects in Part A and approximately 90 subjects in Part B presenting with EGW and a wart count of 2 to 30, inclusive. Eligibility to participate in the study will be determined by the Investigator on the basis of the inclusion and exclusion criteria.

7.1 Subject Inclusion Criteria

To qualify for inclusion in this study, subjects must:

1. Be healthy, immunocompetent males or females ≥ 18 years of age
2. Present with ≥ 2 and ≤ 30 external genital and/or perianal warts in ≥ 1 of the following anatomic areas:
    a. In both sexes: medial thigh (except inguinal fold); supra-pubic, perineal, and perianal areas
    b. In men: over the glans penis (excluding urethral meatus), penis shaft, scrotum, and foreskin
    c. In women: vulva (excluding labia minora and mucosal surfaces)
3. Have warts present for ≥ 4 weeks at the baseline visit
4. Have warts that are ≤ 8 mm in diameter each with a total wart area (i.e., all warts combined) ≥ 10 mm2
5. Be free of any systemic or dermatologic disorder, that, in the opinion of the Investigator, will interfere with the study conduct, efficacy assessments, or increase the subject's risk of AEs
6. Refrain from swimming, bathing, or prolonged immersion in water or any other liquids until the study drug is removed
7. Have the ability to follow study instructions and be likely to complete all study requirements

8. Agree to use no wart-removing product (prescription or over-the-counter, including any HPV immunization) other than the study drug during the course of the study

9. Provide written informed consent in a manner approved by the IRB and evidenced by the signature on an IRB approved consent form

10. Provide written authorization for use and disclosure of protected health information

11. If participating in the optional photographic portion of the study, agree to allow photographs of warts to be taken at each treatment and all follow-up visit by the research team

7.2 Subject Exclusion Criteria

Candidates will be excluded from the study if they:

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

2. Have a wart within the allowed treatment area > 8 mm in diameter or with an eroded or ulcerated surface, in the Investigator's opinion

3. Have an unclear diagnosis of condyloma

4. Have warts outside of the allowed treatment area (e.g., cervical, vaginal, clitoral, rectal, within 2 mm of anus) that require treatment during the planned study period or are undergoing treatment in the last 4 weeks

5. Have any wart types other than genital warts (e.g., common or plantar warts) that require treatment during the study period

6. Have a history of genital infections or diseases within 4 weeks before enrollment

7. Have active genital herpes eruption, or had active genital herpes lesions within 4 weeks before enrollment

8. Have a history of HPV-associated malignancies within the last 5 years

9. Have a dermatologic disease (e.g., psoriasis) or skin condition in the wart areas that may cause difficulty with examination

10. Are systemically immunosuppressed or have required, or will require, systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days before enrollment or during the course of the study (routine use of local [e.g., topical, inhaled, or intranasal] corticosteroids during the study is allowed)

11. 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, diabetes, clinically significant medical, psychiatric, or emotional condition or abnormality).

12. Have had HPV immunization within the last 3 months prior to enrollment. (NOTE: HPV may NOT be administered during the course of the trial. Other immunizations (e.g., flu shots) may be administered throughout the study, but not within 5 days before or after treatment.

13. Have had any previous treatment (including an investigational agent in a clinical trial) of genital warts, including but not limited to the use of imiquimod, antivirals, retinoids, salicylic acid, lactic acid, hydrogen peroxide, iodine-based or nitric oxide-based therapies, curettage, or freezing of warts in the 14 days before screening; in addition, these treatments, or any other over-the-counter wart treatment, should not be implemented during the study. The wash out period for cantharidin, candida antigen, diphencyprone, dinitrochlorobenzene, squaric acid dibutyl ester and any other immunomodulating treatment not otherwise specified is 30 days before the Screening Visit.

14. Have history of, or current, epidermodysplasia verruciformis

15. Have an active malignancy or are undergoing treatment for any malignancy

16. Have a history or presence of hypersensitivity or an idiosyncratic reaction to VP-102 (including cantharidin or related compounds) or study drug product excipients (acetone, ethyl alcohol, nitrocellulose, hydroxypropyl cellulose, castor oil, camphor, gentian violet, and denatonium benzoate)

17. Have a condition or situation that may interfere significantly with the subject's participation in the study (e.g., subjects who required hospitalization within 2 months before screening for an acute or chronic condition including alcohol or drug abuse), at the discretion of the Investigator

18. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods (e.g., birth control pills, intrauterine device, patch, shot, vaginal ring, and combination of condoms and foam); NOTE that withdrawal and/or sterilization of self or partner are not acceptable methods of birth control. Females that have reached menarche must have a negative urine pregnancy test at each study visit before treatment with study drug

19. Are pregnant or breastfeeding

7.3 Requalification for Entry

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

7.4 Subject Withdrawal Criteria

Subjects are encouraged to complete the study, but can withdraw consent at any time during the study and for any reason without any penalty or changes to care. The Investigator will provide a written explanation of the reason for discontinuation in a source document and this information will also be recorded on the appropriate electronic case report form (eCRF) page. If a subject withdraws before completion, every effort should be made to complete the EOS (Study Day 147) assessments scheduled during the EOS visit.

A subject may be withdrawn from the study for the reasons described in Section 7.4.1 through Section 7.4.5.

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

7.4.1 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.

7.4.2 Intercurrent Illness

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

7.4.3 Noncompliance

After the Investigator, the Medical Monitor and/or Study Monitor consult (and the Sponsor if appropriate), a subject may be discontinued from the study for the following administrative reasons:

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

7.4.4 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.

7.4.5 Withdrawal of Consent

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

7.5 Replacement of Subjects

Subjects prematurely withdrawn from the study as dropouts (e.g., enrolled in the study but never received study drug, did not complete the EOT and EOS assessments), for noncompliance, or who request to be withdrawn from the study may be replaced at the discretion of the Sponsor.

7.6 Premature Study or Site Termination

If the Sponsor, Investigator, Medical Monitor, Study Monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the site should be terminated, this action may be taken by the Sponsor after appropriate consultation among the Sponsor, Investigator, Medical Monitor, and Study Monitor. Conditions that may warrant termination of the study include, but are not limited to, the following:

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

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

8.0 STUDY DRUGS

8.1 Investigational Agent and Placebo

The VP-102 single-use applicator contains 0.45 mL of 0.7% w/v cantharidin. The placebo single-use applicator is comprised of the same formulation as the VP-102 applicator but does not contain the active pharmaceutical ingredient cantharidin.

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

Each lot of applicators will be released for clinical use after a subset has undergone applicator suitability testing and demonstrated that they can deliver drug product in a controlled manner, without leaking or spilling. After the commercial product completes all required testing, they will be released for use in the clinical study.

8.2 Directions for Use

8.2.1 Application of Study Drug and Surgical Tape

Study drug (VP-102 or placebo) is contained within a single-use applicator. Per protocol, one applicator may be used to treat all EGW lesions at each subject treatment visit.

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

Surgical tape should be applied to lesions that have been treated and gently rubbed in order to maximize adherence to the treated area. Tape MUST NOT be applied until the product is completely dry (approximately 2-5 min). The size of the piece (or pieces) of surgical tape used is based upon Investigator discretion, provided that all treated warts are covered, and the surgical tape size is deemed sufficient to maintain adherence for

the assigned duration of skin exposure. An adhesive bandage may be applied over the surgical tape if needed for flexible areas. It may not be feasible to apply tape to some anatomical locations, in which case an adhesive bandage may be used, when possible, to protect other skin sites from coming into contact with the treated area.

Given the length of time or complexity it may take to treat all warts, Investigators will assess, in advance, if subjects will be able to complete treatment in one treatment session. Application of study drug may not be conducted over more than one visit. Subjects may be rescheduled for the first treatment, as long as it is within the 14-day screening time period. Otherwise, they will need to be rescreened and consent reviewed to participate.

All subjects will be provided a copy of their signed Informed Consent Form (ICF). At each treatment visit, the subjects will be provided with both verbal and written take-home instructions covering potential side effects and complications, as well as contact information of the study Investigator/ Coordinator for any questions or concerns that may arise. Subjects will also be provided an LSR guide to assist the site in collecting the required ERT information related to the treated areas. Subjects should refrain from touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for up to 48 hours after treatment or until the study drug is removed. Strongly urge subjects not to touch or wash the treated area for the assigned duration of skin exposure.

Subjects will receive application of study drug to all warts with a minimum of 21 ±4 days between treatment until complete clearance or a maximum of 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 provided in each subject-specific kit, as well as your regulatory file, for step-by-step instructions.

8.2.2 Removal of Surgical Tape and Study Drug

All subjects will have reviewed and are provided with take home instructions on removal of the surgical tape and study drug, as well as descriptions of the potential LSRs they might expect throughout the course of the study; recommendations for

wound care, when it is important to call their doctor, and instructions for whom to contact in an emergency.

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

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

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

Early removal is defined as removal of study drug outside of the following windows:

- ±1-hour window for 2-hour duration of skin exposure group
- ±2-hour window for 6-hour duration of skin exposure group
- ±6-hour window for 24-hour duration of skin exposure group

8.3 Study Drug Storage

Clinical sites will be provided with an initial supply of subject specific kits containing 4 single-use applicators. Each applicator contains 0.45 mL of study drug (VP-102 or placebo) and is individually packaged in a UV protected, zip-top bag. Each bag is labeled with all pertinent product information including the corresponding kit number it is assigned to. Applicators are not numbered in sequential order, but each should be

documented on the drug accountability form as they are used. The zip-top bag should not be opened until the site is ready to initiate treatment. Do not dispose of the zip top bag, as it will be used to store the used applicator (Section 8.9).

Study drug must be stored at controlled room temperature (68°F-77°F). Short term storage temperature excursions between 59°F-86°F that are experienced in the physician's storage area and/or during shipping are allowed, provided the mean kinetic temperature remains below 25ºC. Excursions from 38°F to 59°F that do not result in precipitate formation are acceptable for use. Short term storage temperature excursions (spikes less than 24 hours in duration) between 86°F to 104°F may be allowed but must be evaluated for impact by the Sponsor before use. Storage temperature excursion above 104°F are not allowed and will require replacement of the study drug. The study drug must be stored in a secure, dry location with limited and controlled access, and out of direct light. Extended exposure to extreme temperature conditions or to direct light should be avoided (e.g., study drug left in an unoccupied vehicle in a hot or cold environment). Contact the study Sponsor or designee (i.e., clinical research organization) in the event that you believe that any materials may have been exposed to such conditions for guidance. Study drug may be administered only by the Investigator or by a trained member of the clinical site staff specifically as authorized by the Investigator.

Stability studies with VP-102 ampules have shown that they are stable for 18 months under controlled room temperature conditions. Therefore, this product is considered stable for at least 30 months under the recommended storage conditions. Stability studies are ongoing and may extend the expiration date. In the event there are any changes in extension of the expiration date, sites will be notified by the Sponsor accordingly.

8.4 Study Drug Labeling

Study drug is packaged in tamper evident, subject-specific kits, within a cardboard carton, that contains 4 individually packaged applicators. Each applicator is individually contained in UV protected and labeled zip-top pouch.

The applicator is labeled with the IND application number and study protocol number. An example of the applicator label is presented in Figure 1.

The label also indicates the date of manufacture and includes the required statements "Caution: New Drug--Limited by Federal Law to Investigational Use." and "Warning: Flammable Liquid." The applicator warnings indicate characteristics of the study drug including additional labeling "Warning: Flammable Liquid" and the yellow toxic chemical symbol with the phrase "Warning: Highly Toxic".

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

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

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

Clinical Trial Labeling of Study Drug

Figure 1. Label on Applicator

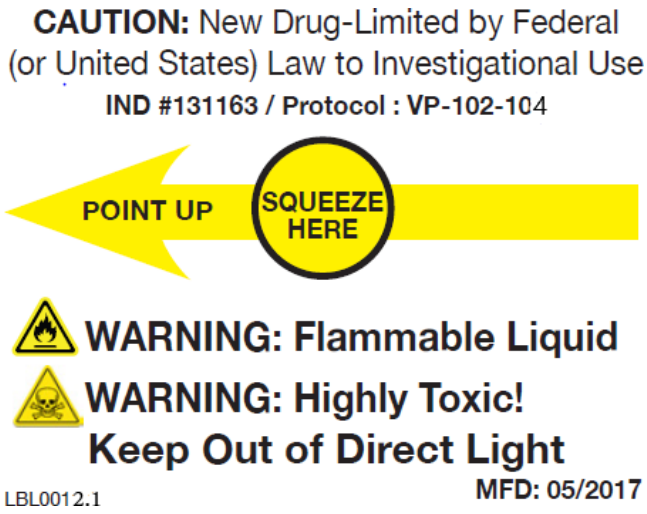


Figure 2. Label on Pouch Containing Each Applicator

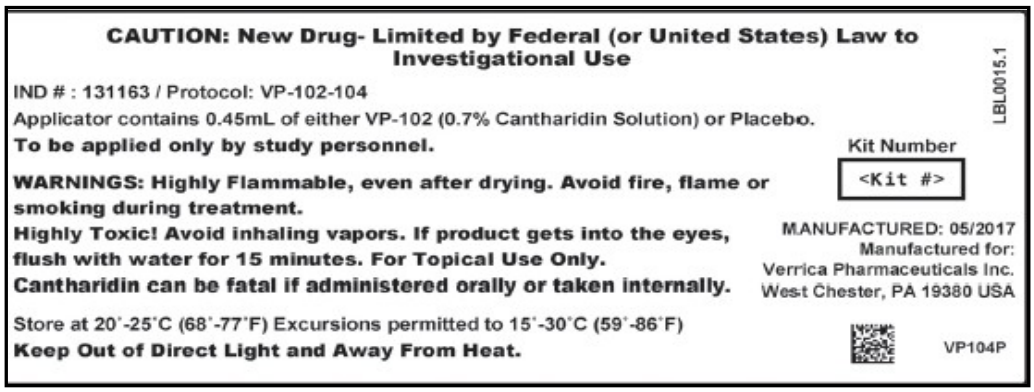


Figure 3. Kit Top Label

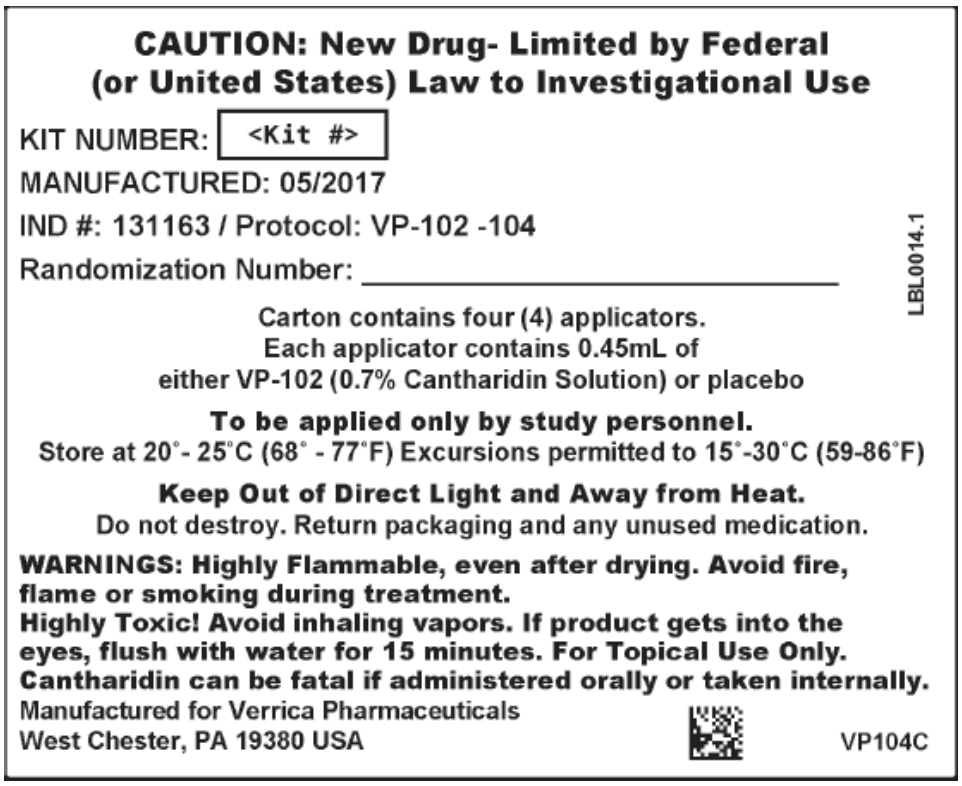
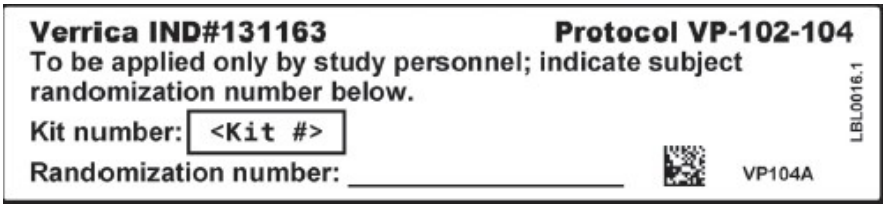


Figure 4. Kit Side Label



8.5 Compliance

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

8.6 Breaking the Blind

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

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

8.7 Previous and Concomitant Medications

All medications taken within 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.

Treatment of warts with any prescription or over-the-counter wart medication (including any HPV immunization), curettage, or freezing of warts should not be implemented during the study. Treatments for genital warts include, but are 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, any other over-the-counter wart treatment; curettage; or freezing of warts.

Potential subjects who are systemically immunosuppressed or have required, or will require, systemic immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days before enrollment or during the course

of the study will be excluded. Note that routine use of local (e.g., topical, inhaled, or intranasal) corticosteroids during the study is allowed.

Immunizations and flu shots may be administered throughout the study but not within 5 days before or after treatment.

8.8 Accountability Procedures

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

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

8.9 Study Drug Handling and Disposal

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

9.0 SUBJECT PROCEDURES

Each subject will be evaluated and treated as follows:

9.1 Subject Restrictions

Subjects are required to:

- Use no wart-removing product (prescription or over-the-counter and including any HPV immunization) other than the study drug during the course of the study
- Refrain from sexual activity involving the treated area as well as touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for at least 48 hours after treatment or until the study drug is removed
- Refrain from swimming, bathing, or prolonged immersion in water or any other liquids until the study drug is removed

9.2 Screening Period (up to 14 days before first treatment)

Before the initiation of screening assessments, the subject must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the subject must sign and receive a copy of an IRB-approved ICF and an authorization for use and disclosure of protected health information that was approved by the IRB (Section 13.0). Once consent is obtained, the Screening Period assessments will be performed. Subjects will be screened within 14 days prior to or on Treatment Visit 1 of the study.

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

- Record demographics (date of birth, sex, race, and ethnicity)
- Measure height and weight
- Measure vital signs (temperature, heart rate)

- Wart assessments
  - Wart count
  - Wart location by anatomical location
- Wart measurement (diameter and area);
- Dermatologic exam including Fitzpatrick Skin Type
- Photography
- Subjects who agree to participate in the photographic portion of the study will have photographs of warts taken before treatment by the study team. Confirm that the subject meets all inclusion criteria and does NOT meet any exclusion criteria
- Record all prior medications (including non-prescription and herbal [complementary medicine] products) within the last 14 days before Screening;
  - Record any antimicrobial, antiviral, steroidal, or topical drugs received within 30 days before Day 1.
  - Record any non-pharmacologic treatments (e.g., ice packs, heat packs, warm soaks, etc.) administered in the 72 hours before application of study drug.

9.3 Treatment Period

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

9.3.1 Treatment Period 1

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

9.3.1.1 Day 1 (Treatment Visit 1)

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

- Confirm that subject still meets enrollment criteria (dermatologic exam; ability to attend study visits)
- Obtain relevant medical history since Screening Visit
- Obtain genital wart history (duration and previous treatments) since Screening Visit; if treated, confirm date of last treatment
- Clinical assessments
  - Measure vital signs (temperature, heart rate) before application of study drug
- Wart assessments (wart count, location by anatomical location, wart diameter measurement) conducted before application of study drug
  - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Dermatologic exam
- Photography before application of study drug
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
- Record any prior medications (including non-prescription and herbal [complementary medicine] products) since the Screening Visit
  - Record any antimicrobial, antiviral, steroidal, or topical drugs received within 30 days before Day 1.
  - Record any non-pharmacologic treatments (e.g., ice packs, heat packs, warm soaks, etc.) administered in the 72 hours before application of study drug.

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

- Laboratory assessments
  - Perform urine pregnancy test on female subjects of child-bearing potential (i.e., females who are capable of menstruating) before study drug application
- ERT assessment conducted before study drug application
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team; ERT assessments must be conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
  - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis
- Study drug application
  - Apply study drug
  - Apply surgical tape
- Assess, identify, and record any AEs
- Record any concomitant medications
- Provide subjects with take-home instructions describing how to remove the surgical tape, the possible LSR's, and what to expect over the next 24 hours to several months.
- Subjects will remove surgical tape and study drug at the designated removal time (2 hours (±1 hour), 6 hours (±2 hours), or 24 hours (±6 hours) after application
  - Removal of the surgical tape should be gentle and aided by soap and water, which will also help to prevent unroofing the blisters
  - Surgical tape should only be removed at the designated removal time, when the treatment site is washed and study drug removed
  - Surgical tape and study drug may be removed from individual warts before the designated removal time in the event of significant blistering, significant pain, or treatment-emergent AEs; surgical tape and study drug should not be removed from the remaining unproblematic warts until the designated removal time.

9.3.1.2 Telephone Assessments at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after Study Drug Administration

- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team.
- Assess, identify, and record any new AEs
- Record any new concomitant medications

9.3.1.3 In-person Visit at 48 hours (±8 hours) after Study Drug Administration (Part A only)

- Clinical assessments
  - Measure vital signs (temperature, heart rate)
- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded by a qualified member of the research team.
- Assess, identify, and record any new AEs
- Record any new concomitant medications

9.3.2 Treatment Periods 2, 3, 4

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

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

- Clinical assessments
  - Measure vital signs (temperature, heart rate) before application of study drug
- Wart assessments conducted before application of study drug

- Wart count conducted before dermatologic exam and ERT assessment
  - Conducted by a designated Blinded Assessor; Blinded Assessors are trained to the study and GCP, and listed on the FDA FORM 1572 and the site Delegation of Authority Log; the Blinded Assessor does not have to be the same person at each visit
  - Also conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Wart anatomical location identified before dermatologic exam and ERT assessment
  - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
  - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis

- Dermatologic exam by anatomical location
  - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Laboratory assessments
  - Perform urine pregnancy test on female subjects of child-bearing potential (i.e., females who are capable of menstruating) before study drug application
- ERT assessment conducted before study drug application
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team; ERT assessments must be conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

  - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis

- Photography conducted before study drug application
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team,
- Study drug application
  - Apply study drug
  - Apply surgical tape
  - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- Assess, identify, and record any new AEs
- Record any new concomitant medications
- Provide subjects with take-home instructions describing how to remove the surgical tape, the possible LSR's, and what to expect over the next 24 hours to several months.
- Subjects will remove surgical tape and study drug at the designated removal time (2 hours [±1 hour], 6 hours [±2 hours], or 24 hours [±6 hours]) after application
  - Removal of the surgical tape should be gentle and aided by soap and water, which will also help to prevent unroofing the blisters
  - Surgical tape should only be removed at the designated removal time, when the treatment site is washed and study drug removed
  - Surgical tape and study drug may be removed from individual warts before the designated removal time in the event of significant blistering, significant pain, or treatment-emergent AEs; surgical tape and study drug should not be removed from the remaining unproblematic warts until the designated removal time.

9.3.2.2 Telephone Assessments at 24 hours (±6 hours), 7 days, and 14 days after Study Drug Administration

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

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

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

- Clinical assessments
  - Conduct limited physical examination
  - Measure height and weight
  - Measure vital signs (temperature, heart rate)
- Wart assessments
  - Wart count conducted before dermatologic exam and ERT assessments
    - Conducted by a designated Blinded Assessor; Blinded Assessors are trained to the study and GCP, and listed on the FDA FORM 1572 and the site Delegation of Authority Log; the Blinded Assessor does not have to be the same person at each visit

- Also conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

– Wart anatomical location identified before dermatologic exam and ERT assessments

- Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

- Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis

– Wart measurement (diameter and area) conducted before dermatologic exam and ERT assessments

- Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

- Dermatologic exam by anatomical location

  – Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

- Laboratory assessments

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

- ERT assessment

  – Only collect new information since the last contact

  – All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team; ERT assessments must be conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

  - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis

- Photography
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
  - If there are no warts remaining, the same areas will be photographed regardless of whether warts are present
- Assess, identify, and record any new AEs
- Record any new concomitant medications
- Complete Provider questionnaire; by a clinician who applied treatment to the subject during the course of the study

9.5 Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days) (End-of-Study)

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

- Clinical assessments
  - Measure height and weight
  - Measure vital signs (temperature, heart rate)
- Wart assessments
  - Wart count conducted before dermatologic exam and ERT assessments
    - Conducted by a designated Blinded Assessor; Blinded Assessors are trained to the study and GCP, and listed on the FDA FORM 1572 and the site Delegation of Authority Log; the Blinded Assessor does not have to be the same person at each visit

    - Also conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

  - Wart anatomical location identified before dermatologic exam and ERT assessments

    - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

    - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis

  - Wart measurement (diameter and area) conducted before dermatologic exam and ERT assessments

    - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

- Dermatologic exam by anatomical location

  - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

- Laboratory assessments

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

- ERT assessment

  - Only collect new information since the last contact

  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team before study drug application; ERT assessments must be conducted by a study team member who is not considered,

or has not acted as, the Blinded Assessor for the subject throughout the subject's participation

  - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis

- Photography

  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team

  - If there are no warts remaining, the same areas will be photographed regardless of whether warts are present

- Assess, identify, and record any new AEs

- Record any new concomitant medications

- Complete study completion form for all subjects (Study Day 147 (EOS) Visit only)

9.6 Unscheduled Visit

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

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

- Clinical assessments

  - Measure vital signs (temperature, heart rate)

  - Record reason why study drug was not administered at treatment visit (if applicable)

- Dermatologic exam by anatomical location
  - Conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
- ERT assessment
  - Only collect new information since the last contact
  - All ERT safety assessments must be conducted and recorded on ERT by a qualified member of the research team before study drug application; ERT assessments must be conducted by a study team member who is not considered, or has not acted as, the Blinded Assessor for the subject throughout the subject's participation
  - Warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) will not be evaluated, documented, or considered in the analysis
- Photography
  - Subjects who previously agreed to participate in the photographic portion of the study will have photographs of warts taken by the study team
- Assess, identify, and record any new AEs
- Record any new concomitant medications

9.7 Measurements and Evaluations

9.7.1 Skin Assessments

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

9.7.2 Identification of Skin Reactions

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

9.7.3 Removal of Surgical tape

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

9.7.4 Evaluation of Response to Treatment Assessments

An ERT assessment will be conducted at each treatment visit (1-4; in-person before treatment or via follow-up telephone calls) at 24 hours (±6 hours), 7 days (±24 hours), and 14 days (±24 hours) after each treatment visit (but not after “unscheduled” visits). Note that the ERT telephone calls at 24 hours (±6 hours), 7 days (±24 hours) and 14 days (±24 hours) after treatment are not required if there was no treatment during that period. In Part A Treatment Period 1 only, subjects will return to the clinic for an in-person ERT assessment at 48 hours (±8 hours) after Treatment Visit 1.

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

In the event that any AE presents a safety concern (including but not limited to severe blistering, ulceration, edema, or pain) an "Unscheduled" clinic visit may be scheduled and the subject assessed accordingly.

The ERT assessments will be recorded by a research team member on the ERT form. The ERT visits may not be conducted by a person designated as a Blinded Assessor. Phone calls conducted outside of the required study visits or required ERT assessments should be documented in the subject's source note but are not required to be entered in the EDC system.

9.7.5 Photographs of Lesions

At designated sites, photography will be offered to volunteer subjects who consent to participate. Photography will take place at the clinical site at each treatment and follow-up study visit through Study Day 147 (±7 days) (EOS). If there are no warts remaining, the same areas will be photographed and repeated at the Study Day 84 (-0/+8 days) EOT Visit and Study Day 147 (±7 days) EOS visit, regardless of whether warts are present. 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. Efforts will be made to ensure that no photographs with identifiable features are obtained.

10.0 ASSESSMENT OF SAFETY

10.1 Safety Parameters

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

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

10.2 Definitions

10.2.1 Adverse Event

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

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

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

The following are examples of AEs:

- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency or intensity of the condition
- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Local skin reactions (erythema, scaling/flaking/dryness, edema/swelling, small blisters, hyper- and hypopigmentation, scabbing/crusting, erosion/ulcerations, scarring, ring warts)
- Development of individual blisters that are > 25 mm 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 pre-existing disease or condition (present or detected before enrollment) that does not worsen overall

- Expected progression of the disease being studied, including signs or symptoms of the disease, unless progression is more severe than expected for the subject's condition.

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

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

All unresolved AEs will be followed until the condition resolves and/or stabilizes, the subject is lost to follow-up or 30-days after the EOS visit, whichever comes first. All AEs will be summarized in the annual report or more frequently if requested by the regulatory agency. SAEs require special reporting in addition to documentation in the eCRF as described in Section 10.6.

10.2.2 Serious Adverse Event

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

- Results in death
- Is life-threatening
  - The term *life-threatening* in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event
  - The term *life-threatening* does not refer to an event that hypothetically might have caused death if it were more severe

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

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

10.2.3 Expectedness of Serious Adverse Events

An expected AE is one that is consistent with the known risk information described in the product label (if applicable) or the current IB. The expectedness of an SAE will be assessed by the Medical Monitor or Sponsor on receipt of the initial SAE report.

10.3 Assessment of Intensity

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

The classifications in Table 4 should be used in assigning intensity of each AE recorded in the eCRF.

Table 4. Classification of Adverse Events by Intensity

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

AE: adverse event.

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

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an AE (such as mild, moderate, or severe myocardial infarction). However, the event itself may be of relatively minor medical significance, such as a severe headache. Both AEs and SAEs can be assessed as severe. An AE is considered serious (an SAE) when it meets one of the predefined outcomes described in Section 10.2.2.

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

10.4 Assessment of Causality

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

Because of reporting timelines, the Investigator might have minimal information to include in the initial SAE report. However, the Investigator must always make an assessment of causality for every SAE before the transmission of the SAE report. The Investigator may change his or her opinion of the causality in light of follow-up information, with subsequent amendment of the SAE report. Causality assessment is one of the criteria used to determine regulatory reporting requirements and should not be left blank in the SAE report. The same applies to AEs that are to be processed as SAEs. Some definitions to use in the assessment are provided in Table 5.

Table 5. 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.

10.5 Recording Adverse Events and Serious Adverse Events

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

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

10.6 Reporting of Serious Adverse Events

Any SAE occurring after the subject signs the ICF must be reported to the Sponsor or designee within 24 hours of the time the Investigator becomes aware of the SAE (Table 6).

Table 6. Timeline for Reporting of Serious Adverse Events

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

SAE: serious adverse event.

Urgent reporting of SAEs is required for the following reasons:

- To enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority
- To facilitate discussion between the Sponsor and the Investigator about appropriate follow-up measures (if necessary)

- To facilitate the Sponsor's rapid dissemination of information about AEs to other Investigators or sites in a multicenter study
- To facilitate reporting unanticipated problems involving risk to subjects to the IRB.

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

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

Within 24 hours of awareness of a new SAE, the investigative site will call the Paidion Research Medical Monitor (xxxxx) by calling the SAE Hotline at xxxxx. The SAE Hotline may be accessed and is monitored 24 hours/day, 7 days/week. The investigative site must also initiate entry of the SAE report form intothe EDC system being used for this study. The SAE report should include the essentialelements.

The SAE report will be forwarded to the Sponsor within the designated time frames. If additional information to complete the SAE report form is needed, the Investigator will not wait before notifying the Paidion Medical Monitor of the SAE via the SAE Hotline. The SAE report form will be updated by the Investigator when additional information is received.

10.7 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

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

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

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

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

10.9 Special Safety Considerations

- Investigators should confirm that study drug is completely dry (2-5 minutes) before applying the surgical tape or allowing the treated areas to come into contact with healthy skin, clothing, furniture, or other surface areas.
  - In addition, an adhesive bandage may be applied over the surgical tape to keep it in place on areas that have a high probability of transference to healthy skin, mucous membranes, or that may experience significant flexing as in a skin fold.
- VP-102 is considered highly flammable, even after drying. Subjects should avoid fire, flame, or smoking until study drug has been removed from the skin.

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

- Subjects should refrain from sexual activity involving the treated area as well as touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for at least 48 hours after treatment or until the study drug is removed.

- Subjects are encouraged to wash their hands regularly with soap and water (being mindful to keep treated areas on the hands dry) and discouraged from scratching or picking at warts, which can spread disease

11.0 ASSESSMENT OF EFFICACY

11.1 Efficacy Parameters

Efficacy parameters will be recorded for all enrolled subjects in the Intent-to-Treat (ITT) and PP Populations by randomization group. Clinical response to treatment will be evaluated at each scheduled visit until EOS by counting all treatable warts. Genital warts that develop in areas that are unable to be treated, (e.g., close to a mucous membrane) and other wart types (e.g., common warts) will not be evaluated, documented, or considered in the analysis.

Primary Efficacy Endpoint:

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

Secondary Efficacy Endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Proportion of subjects exhibiting 90% and 75% clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Change from baseline in the number of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)
- Change from baseline in the percent of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, at Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

Exploratory Efficacy Endpoints:

- Proportion of subjects exhibiting reduction of ≥ 1 treatable wart from baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

- Proportion of subjects who are clear at the Study Day 84 (EOT) Visit and remain clear at the Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

- Change from baseline in total wart area (sum of individual warts) at Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

- Change from baseline in the percent of total wart area (sum of individual warts) at Study Day 84 (EOT), and Follow-up Visits on Study Day 112 and Study Day 147 (EOS)

12.0 STATISTICAL METHODS

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.

Summaries of data from subjects enrolled in Part A will be pooled with corresponding subjects in Part B. For instance, if one of the two regimens selected for Part B is the 6-hour application of VP-102, then results from subjects who received the 6-hour application of VP-102 from Part A will be pooled with results from subjects who received the 6-hour application of VP-102 from Part B.

An additional set of tables will be generated that summarize subjects from Part A of the study who are not used in Part B of the study. Summary statistics for continuous variables and counts and percentages for categorial variables will be shown by treatment. However, due to the limited number of subjects for this set of tables (expected n=6), analyses to be carried out will only be descriptive in nature.

12.1 Analysis Populations

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

12.2 Analysis of Study Population and Subject Characteristics

Subject demographics, efficacy tables, and subject dropout rates will be tabulated at the Study Day 84 (EOT) Visit and the Study Day 147 (EOS) Visit. Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies, and

percentages for discrete variables. Corresponding by-subject data listings will be tabulated.

12.3 Efficacy Analyses

Efficacy will be evaluated in the ITT and PP Populations by treatment group.

At the end of the study, Part B tables will be generated that pool subjects from Part A and Part B. The regimens included in these tables will be VP-102 Regimen 1, VP-102 Regimen 2, Placebo Regimen 1, and Placebo Regimen 2 (Section 6.1.2). For the efficacy endpoints (Section 11.1), summary statistics for continuous variables and counts and percentages for categorical variables will be presented. In addition, statistical comparisons will be carried out to compare VP-102 Regimen 1 to Placebo Regimen 1 and VP-102 Regimen 2 to Placebo Regimen 2. Comparisons made within Regimen 1 (VP-102 vs Placebo) will be independent of comparisons made within Regimen 2. Comparisons may be carried across Regimens; however, no formal statistical testing will be carried out with comparisons being considered only observational.

An additional set of tables will be generated that summarize subjects from Part A of the study who are not used in Part B of the study. Summary statistics for continuous variables and counts and percentages for categorial variables will be shown by treatment. However, due to the limited number of subjects for this set of tables (expected n=6), analyses to be carried out will only be descriptive in nature.

12.4 Safety Analyses

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

Adverse events, including LSRs, will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.0. The number and percentage of subjects having TEAEs will be tabulated by system organ class and MedDRA preferred term with a breakdown by treatment group. 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 TEAEs and number of TEAEs will be summarized by treatment using frequency counts.

Any AE with an onset date after the EOS visit will be considered off study and will not be included in tables summaries (although they will appear in AE listings). Each AE will be counted only once for a given subject. If the same AE 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 AEs are reported as a unit, the individual terms will be reported as separate events.

Changes in vital signs (temperature and heart rate), from baseline to EOS, will be examined. Treatment-emergent changes from normal values to abnormal values will be identified.

12.5 Interim Analysis

No interim analysis is planned for this study.

12.6 Determination of Study Sample Size

Although no formal power calculations have been performed, it is expected that a sample size of 18 subjects in Part A and 90 subjects in Part B, evaluable at the Study Day 84 (–0/+8 days) EOT Visit, will be informative regarding wart clearance rates that can support assumptions in subsequent placebo-controlled trials.

12.7 Handling of Missing, Unused, and Spurious Data

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

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

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

12.8 Termination Criteria

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

12.9 Deviation Reporting

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

13.0 PROTECTION OF HUMAN SUBJECTS

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

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

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

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

14.0 INVESTIGATOR REQUIREMENTS

14.1 Investigator Information

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

14.2 Investigator's Study Files

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

14.3 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.

14.4 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.

14.5 Confidentiality

14.5.1 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).

14.5.2 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 ICF) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

14.6 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 ICF, the revised informed consent form prepared by the Investigator must also be approved by the Sponsor, Study Monitor, and the IRB before implementation.

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

14.7 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.

14.8 General Information

The Investigator should refer to the IB, Instructions For Use, and any other information provided about this investigational product and details of the procedures to be followed during this study.

15.0 DATA HANDLING AND RECORD KEEPING

The Investigator is required to prepare and maintain adequate and accurate source documents designed to record all observations and other data pertinent to the study for each study subject. Electronic case report forms (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. After the eCRFs are completed and source-verified, the Investigator must electronically sign all required pages in the eCRF, verifying the accuracy of all data contained in the eCRF.

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

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

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

16.0 QUALITY CONTROL AND QUALITY ASSURANCE

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

The purpose of monitoring is to verify that:

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

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

The purpose of an audit is to:

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

17.0 FINANCING AND INSURANCE

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

18.0 PUBLICATION POLICY

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

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APPENDICES

Appendix 1: Version History and Summary of Changes

SUMMARY OF PROTOCOL CHANGES: VP-102-104

Version history:

DOCUMENT	VERSION	DATE
Protocol VP-102-104	1	09 May 2019
Protocol VP-102-104	2	07 August 2019

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
Administrative Update Throughout Protocol	Updated Version to 2.0 and updated version date to 07 August 2019.
Title of Study (pg. 1) Protocol Synopsis: Title of Study (pg. 4)	The study title was updated to include "Cantharidin" and the study acronym of CARE-1 was added. CARE stands for **CA**ntharidin **R**egimen in **E**xternal Genital Warts.
Protocol Synopsis: Objectives (pg. 4) Section 5: Study Purpose and Objectives (pg. 41)	Added clarification that secondary and exploratory objectives will be applicable to both Part A and Part B of the study.
Protocol Synopsis: Exploratory Objectives (pg. 5) Section 5: Study Purpose and Objectives (pg. 41)	The change from baseline in total wart area and the percent change from baseline in total wart area were added as two new exploratory objectives. Removed reference to "Part B Only" as these will be applicable to both parts of the study.
Protocol Synopsis: Exploratory Efficacy Endpoints (pg. 13) Section 11.1: Efficacy Parameters (pg. 87-88)	The endpoints associated with the two new exploratory objectives evaluating the change from baseline in total wart area and the percent change from baseline in total wart area were added.
Section 8.2.2: Removal of Surgical Tape and Study Drug (pg. 56) Section 9.7.3: Removal of Surgical Tape (pg. 76)	The reference to "warm" water was removed, as it is not required for the water to be warm to remove the study drug.
Section 9.2: Screening Period (pg. 64) Section 9.3.1.1: Day 1 (Treatment Visit 1) (pg. 66)	Blood pressure was inadvertently referenced as part of the vital sign procedure, but instead should have said heart rate. All references to blood pressure have been replaced with heart rate to

SECTIONS/PAGES CHANGED	DESCRIPTION OF CHANGES
Administrative Update Throughout Protocol	Updated Version to 2.0 and updated version date to 07 August 2019.
Section 9.3.1.3: In-person Visit at 48 hours (±8 hours) after Study Drug Administration (Part A only) (pg. 67) Section 9.3.2.1: Day 1 (Treatment Visit 2, Treatment Visit 3, Treatment Visit 4) (pg. 68) Section 9.4: End-of-Treatment Visit: Study Day 84 (-0/+8 days) (pg. 71) Section 9.5: Follow-up Visits on Study Day 112 (±7 days) and Study Day 147 (±7 days) (End-of-Study) (pg. 73) Section 9.6: Unscheduled Visit (pg. 74)	match footnote 'h' in Table 1. Study Schedule of Assessments and Procedures (Part A and Part B)
Section 10.8: Risks for Women of Child-bearing Potential or During Pregnancy (pg. 86)	The definition of pregnancy was clarified to include any genetic contribution to a pregnancy by both male and female subjects.
Synopsis: Exclusion Criteria (pg. 10) Section 7.2: Subject Exclusion Criteria (pg. 50)	Removed reference to neoplasia in exclusion criteria #8, as it is already covered in exclusion criteria #15.
Section 14.1: Investigator Information (pg. 93)	Corrected reference to Manual of Operations to Investigator Brochure. The reference to a Manual of Operations was an oversight.
Section 14.2: Investigator's Study File (pg. 93)	Removed reference to Manual of Procedures, as there is not a need for this document for this protocol. The reference to a Manual of Procedures was an oversight.
Section 14.8: General Information (pg. 95)	Corrected reference to Manual of Operations to Instructions For Use. The reference to a Manual of Operations was an oversight.