CONFIDENTIAL

CLINICAL PROTOCOL

TITLE OF STUDY:

A Phase 2, Open-Label Study to Evaluate the Safety, Efficacy and Systemic Exposure of VP-102 Topical Film Forming Solution [0.7% (w/v) cantharidin] in Subjects (2 years and older) with Molluscum Contagiosum

Protocol VP-102-103

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Sponsor: **Verrica Pharmaceuticals, Inc.**
200 Garrett St # S
Charlottesville, VA 22902

Signatures of Approval of Protocol (Version 2.1)

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

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Acknowledgment of Responsibilities (Protocol Version 2.1)

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 written authorization 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

STUDY SYNOPSIS

Name of sponsor company: Verrica Pharmaceuticals, Inc.	
Name of finished product: VP-102 (0.7% w/v cantharidin delivered via a single-use applicator)	
Name(s) of active ingredient(s): Cantharidin	
Title of study: A Phase 2, Open-Label Study to Evaluate the Safety, Efficacy and Systemic Exposure of VP-102 Topical Film Forming Solution [0.7% (w/v) cantharidin] in Subjects (2 years and older) with Molluscum Contagiosum	
Number of sites: up to 5 sites in the United States	
Study period: 12 weeks	**Phase of development:** Phase 2

Objectives: The primary objective is to determine any potential systemic exposure to cantharidin from a single 24-hour dermal application of VP-102 topical film-forming solution [0.7% (w/v) cantharidin] (VP-102) when applied to molluscum contagiosum (molluscum) lesions on pediatric subjects 2 years old and older.

The secondary objectives are:

- to assess the safety of VP-102, when applied once every 21 days for up to 4 applications, to all treated molluscum lesions on subjects 2 years old and older by assessing adverse events, local skin reactions, physical examinations, and concomitant medications throughout the study as compared to baseline.
- to assess the efficacy of VP-102 in the treatment of molluscum lesions as assessed by clearance or reduction of treated molluscum lesions as compared to baseline.
- to assess the impact of VP-102 treatment on quality of life of patients as assessed via the administration of the Children's Dermatology Life Quality Index (CDLQI).

Methodology: This is a Phase 2, Open-Label Study to Evaluate the Safety, Efficacy and Systemic Exposure of VP-102 Topical Film Forming Solution [0.7% (w/v) cantharidin] in subjects 2 years and older with Molluscum Contagiosum. Up to 40 subjects will be enrolled in the study with the goal of 16 meeting criteria for, and completing all scheduled blood draws outlined in the exposure portion of the trial. Subjects that do not have enough molluscum lesions to participate in the exposure study but do meet all other criteria to participate in the study will be enrolled in the standard treatment group. No more than 16 subjects will complete exposure group activities; up to 16 subjects will be enrolled in the standard treatment group. The additional 8 subjects may be used for replacement patients. At least 3 patients in the exposure group will be from 2-5 years of age. All subjects will receive VP-102 containing 0.7% cantharidin to molluscum lesions every 21 days for a maximum of 4 sessions or until complete clearance. In the exposure group, blood samples for systemic exposure evaluation will be collected on Day 1, prior to the drug application, and 2 (± 30 minutes), 6 (± 1 hour) and 24 (±3 hours) hours post-application. A dermatologic examination will be performed by a qualified investigator quantifying molluscum lesion counts at every study visit. The CDLQI survey will be administered at each visit prior to VP-102 application and at the EOS visit. An assessment of local skin reactions (LSR) will be performed by the investigator or trained member of the research team at each treatment visit and at the EOS visit. Evaluations will also be provided by the patient or parent/guardian using a Patient Evaluation of Response to Investigational Treatment (PERIT) form, after every treatment. This form will be completed at home or, for those participating in the exposure blood sampling in the clinic, at approximately 24 hours after Study drug application. A follow-up phone call from the investigator or a designated member of the clinical research team will be conducted the following day after each treatment

STUDY SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals, Inc.

Name of finished product: VP-102 (0.7% w/v cantharidin delivered via a single-use applicator)

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

to allow parents/guardians to ask questions and report any concerns, confirm removal of Study drug and review the completion of the PERIT assessment. Adverse events and local skin reactions will be assessed at every study visit.

Each subject will be evaluated and treated as follows:

- Screening Period (Up to 14 days prior to first treatment).

- Standard Treatment Group (Day 1)
  - Pre-application: dermatologic exam
  - LSR and CDLQI assessments
  - VP-102 application
  - Removal of Study drug approximately 24 hours after application and PERIT assessment.

- Systemic Exposure Evaluation Period Group (Day 1)
  - Pre-application: dermatologic exam and blood collection
  - LSR and CDLQI assessments
  - VP-102 application
  - 2 hours (± 30 min) post-application: blood collection
  - 6 hours (± 1 hour) post-application: blood collection
  - 24 hours (± 3 hour) post-application: blood collection, removal of Study drug and completion of PERIT assessment.

- Safety and Efficacy Evaluation Period-Standard & Exposure Groups (visits targeted 21 days after prior visit)
  - Treatment 2: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessments, Study drug application. 24 hours post-application: removal of Study drug and PERIT assessment.
  - Treatment 3: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessment, Study drug application. 24 hours post-application: removal of Study drug and PERIT assessment.
  - Treatment 4: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessment, Study drug application. 24 hours post-application: removal of Study drug and PERIT assessment.
  - End of Study: dermatologic exam/lesion counts, LSR, CDLQI and Safety Monitoring assessments.

Study Duration: The study duration from treatment Day 1 through the end of study is approximately 84 days (12 weeks).

Subject Participation: Pre-study screening for eligibility (informed consent and assent when applicable, inclusion/exclusion criteria, physical exam and medical history) can occur up to 14 days before, or on the same day as Study drug application. Lesion count will be re-assessed on treatment Day 1 if Study drug is not applied at the initial Screening visit. Subjects that do not continue to meet

STUDY SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals, Inc.

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

criteria will be discontinued and treated per standard of care. Those subjects that continue to meet criteria will be treated with application of VP-102 topical solution to their molluscum lesions every 21 days until complete clearance or a maximum of 4 treatment sessions. The EOS study visit will be completed 21 days after treatment 4, (EOS; ~Day 84), or on the visit in which the investigator reports that molluscum lesions are 100% clear, whichever comes first. Subjects that are not assessed as 100% cleared at the EOS visit will be treated per standard of care at their physician's discretion and will have been deemed to have completed the study.

Systemic Exposure Subjects: Blood (2 mL) will be collected before the first application of VP-102 (Day 1) and 2 (± 30 min), 6 (± 1 hour), and 24 (± 3 hours) hours post-application. Blood will not be collected on consecutive applications of the study drug (Days 21, 42, and 63).

Method of sample analysis: Plasma will be evaluated by a GLP-compliant third party vendor for the presence of cantharidin using a validated GC/MS analytical method (MET012.v1). The unit of analysis is ng/ml with a limit of detection of 1ng/ml of plasma.

Inclusion criteria:
To qualify for inclusion in this study, subjects must:

1. Be healthy subjects ages 2 years and older.
2. Patients with 1-20 lesions may be enrolled and treated in the standard treatment group but are not eligible for the exposure study OR
   Patients with 21 or more lesions may only be enrolled in the exposure group. Subjects participating in the Exposure group must have at least 21 lesions treated at Day 1 to qualify.
3. Be otherwise medically healthy with no clinically significant medical history as determined by the investigator. Patients exhibiting active Atopic Dermatitis may be enrolled.
4. Refrain from application of all topical agents including alcohol-based sanitary products and sunscreens for a minimum of 4 hours before Study drug application. Topical agents including alcohol-based sanitary products and sunscreens may be used after application of the study drug so long as they are not applied to or near treated skin.
5. Refrain from swimming, bathing or prolonged immersion in water until the Study drug is removed.
6. Have the ability or have a guardian able to follow study instructions and be likely to complete all study requirements.
7. Provide assent in a manner approved by the institutional review board (IRB) and have a parent/guardian provide written informed consent as evidenced by signature on IRB approved assent/consent forms.
8. Provide written authorization for use and disclosure of protected health information.
9. Agree to allow photographs of all selected lesions to be taken and/or send photos via text or email to the study team for assessment at 24 hours post treatment. These images may be used on handouts in future trials, for training purposes, as part of the study data and/or marketing package. (*Photographs will be de-identified to those outside the research team. Effort will be made to ensure that no photos with identifiable features are obtained).*

STUDY SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals, Inc.

Name of finished product: VP-102 (0.7% w/v cantharidin delivered via a single-use applicator)

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

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 molluscum venereum (sexually transmitted molluscum).
3. Have active molluscum eczema.
4. Are systemically immunosuppressed or are receiving treatments such as chemotherapy or other non-topical immunosuppressive agents.
5. Have had any previous treatment of molluscum in the past 14 days including the use of cantharidin, antivirals, retinoids, curettage or freezing of lesions. Additional treatments for molluscum should not be implemented during the course of the study.
6. Have history of illness or any dermatologic disorder, which, in the opinion of the investigator will interfere with accurate counting of lesions or increase the risk of adverse events.
7. History or presence of clinically significant medical, psychiatric, or emotional condition or abnormality that in the opinion of the investigator would compromise the safety of the subject or the quality of the data.
8. Have a history or presence of hypersensitivity or an idiosyncratic reaction to the Study drug or related compounds, or drug product excipients (acetone, ethyl alcohol, nitrocellulose, castor oil, camphor, gentian violet, and denatonium benzoate).
9. Have a condition or situation that may interfere significantly with the subject's participation in the study (e.g., patients who required hospitalization in the 2 months prior to screening for an acute or chronic condition including alcohol or drug abuse), at the discretion of the investigator.
10. Have received another investigational product within 14 days prior to the first application of the Study drug.
11. Have been treated within 14 days with a product that contains cantharidin (topical or homeopathic preparations) for any reason prior to screening.
12. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods. Females that have reached menarche, must have a negative urine pregnancy test at screening and each visit prior to treatment with study medication.
13. Are pregnant or breastfeeding.

Test product, dose, and mode of administration: Study drug (VP-102) is contained within a single-use applicator. Topical administration results in approximately 5 to 10 µL of Study drug per molluscum lesion (approximately 1mm to 4mm in diameter). The VP-102 single-use applicator contains 450µl (3.15 mg) of 0.7% w/v cantharidin. Up to 2 applicators may be used per patient, but a second applicator may only be necessary if treating >50 lesions.

STUDY SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals, Inc.

Name of finished product: VP-102 (0.7% w/v cantharidin delivered via a single-use applicator)

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

Duration of treatment: The length of study participation from treatment Day 1 is up to approximately 84 days (12 weeks): Up to 4 applications of Study drug at approximately 21-day intervals, followed by a EOS visit approximately 21-days after the final treatment. Subjects are instructed to gently wash all treated lesions with soap and warm water the morning following application (24 hours after treatment or earlier if significant pain or significant blistering has occurred). If not inconvenient, the patient will target a 24-hour removal time point. Washing of intact blisters should be gentle and without use of a washcloth. Washing in a bath or shower is encouraged.

Criteria for evaluation

The primary objective of the exposure protocol group is to determine the presence or absence of systemic cantharidin. Due to sample size, power calculations will not be performed. 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: All subjects who meet the screening eligibility criteria for the study and enrolled in the study, will be evaluated for efficacy. Clinical response to treatment of molluscum lesions will be evaluated at each scheduled visit until EOS by counting all molluscum lesions. New or additional treated and untreated lesions will also be counted. LSR will be assessed at each study visit and the EOS visit by the Investigator or trained personnel with a protocol specific LSR form.

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

- Incidence of adverse events (AEs) throughout the study:
  - A subject-by-subject treatment-emergent AE (TEAE) data listing, including verbatim term, preferred term, treatment, severity, and relationship to the Study drug, will be provided.
  - The number of subjects experiencing AEs and number of AEs will be summarized by treatment using frequency counts.
  - AEs will not include expected local skin reactions such as: minor pain, small blisters, pruritus, erythema, and post-inflammatory pigment changes.
  - Reactions to drug administration will be considered an AE if:
    - Individual blisters develop that are greater than 20mm in diameter. An aggregated blister composed of a number of smaller blisters is not considered an AE.
    - Any medical intervention excluding administration of mild over-the-counter (OTC) pain relievers is required.
    - The event results in discontinuation from the study.

STUDY SYNOPSIS (continued)

Name of sponsor company: Verrica Pharmaceuticals, Inc.

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

- LSR will be assessed at each treatment visit and the EOS visit by the Investigator or trained personnel with a protocol specific LSR form.
- Subjects' parent or guardian will be asked to complete the PERIT assessment within approximately 24 hours of each treatment to assess the subject's perception of treatment response. A photo may also be sent to the research team for assessment.
- Medical history, vital signs, and physical examinations:
  - Medical history and a limited physical exam will be collected for each subject. A limited physical examination will be completed before the first treatment and at the EOS visit. Vital signs (temperature and heart rate) will be obtained before the treatment is applied at each visit and at the start of the EOS visit. Unscheduled physical examinations will be performed when clinically warranted (e.g., if a subject reports symptom classified as an AE and requires further evaluation).
- Subjects will be asked to complete a Safety Monitoring Questionnaire at each study visit.

Safety considerations: Subjects should confirm the Study drug is completely dry prior to touching furniture, putting on clothing and leaving the clinic. It is important to prevent transference of the Study drug to healthy areas of skin to minimize any potential unnecessary reactions. VP-102 is considered highly flammable, even after drying. Subjects should avoid fire, flame or smoking during treatment.

Cantharidin has been shown safe for topical use, but it is highly toxic and potentially fatal if administered orally or taken internally. To deter potential oral ingestion, a bitter compound has been added to the Study drug. Patients should refrain from touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for up to 24-hours after treatment or until the Study drug is removed.

Households where siblings or friends are also diagnosed with molluscum should make every effort to avoid close contact with those individuals to prevent development of new lesions, recurrence, or spread of the disease. Sharing of personal items such as towels, clothes, utensils or toys is strongly discouraged.

Statistical methods:
There will be up to 40 subjects enrolled with the goal of 16 completing all blood draws in the exposure group and a maximum of 16 will be enrolled in the standard treatment group. The additional 8 subjects may be used for replacement patients. Any subject in the exposure group who does not complete all blood draws may continue to receive treatment, but will be replaced. No more than 16 subjects will be considered as completed Exposure group participants. At least 3 patients in the exposure group will be from 2-5 years of age. Subjects will be considered enrolled once they have signed informed consent and received at least 1 treatment. The primary objective of the study is to determine the presence or absence of systemic cantharidin exposure from application of VP-102. Thus, power calculations will not be performed. 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.

Study Schedule of Assessments and Procedures

Activities	Screening Period[a]	Safety and Efficacy Evaluation Period (Continued until complete clearance)				
	Up to 14 days before Day 1	Treatment 1: Day 1[b]	Treatment 2: Day 21[b]	Treatment 3: Day 42[b]	Treatment 4: Day 63: EOT[b]	End of Study: Day 84: EOS[c]
Informed Consent and Authorization	X					
Inclusion/Exclusion Criteria[d]	X	X				
Demographics[e]	X					
Height/Weight	X					X
Prior Relevant Medical History (5 years)	X					
Molluscum History	X	X				
Prior and Concomitant Medications	X	X	X	X	X	X
Vital Signs (T,P) [f]	X	X	X	X	X	X
Physical Exam[g]	X	X				X
Dermatologic Exam/lesion count[h]	X	X	X	X	X	X
LSR Assessment[i]		X	X	X	X	X
CDLQI Assessment[j]	X	X	X	X	X	X
Urine Pregnancy Test[k]		X	X	X	X	X
Photographs[l]		X	X	X	X	X
Study Drug Application[m]		X	X	X	X	
PERIT Assessment & photos[n]		X	X	X	X	
Adverse Events		X	X	X	X	X
Safety Monitoring Questionnaire			X	X	X	X
Exposure Group Blood Draws[o]		X				
Patient Take Home Instructions[p]		X	X	X	X	
Applicator Assessment[q]		X	X	X	X	

CDLQI: children's dermatology life quality index; EOS = end of study; EOT = end of treatment; LSR = local skin reaction; PERIT: patient evaluation of response to treatment; T,P= temperature, pulse

a. Screening can occur up to 14 days prior to Study drug application on Day 1. Screening can occur on the same day as treatment Day 1/Study drug application. An IRB-approved ICF must be signed before any study specific procedures are performed.
b. Subjects may be scheduled 21+/- 4 days after treatment in the event of scheduling conflict. If possible the next treatment or study visit should be scheduled 21 days from the day of the subject's last study visit. The 24 hour follow-up may be conducted at +/- 3 hours. Study medication should be removed after the 24 hour draw is completed.
c. At end of the study (EOS, ~Day 84), all subjects with unresolved molluscum lesions or unresolved treatment-emergent AEs, will be treated by the investigator per local standard of care. Patients who clear all lesions at study visits prior to ~Day 84 will complete all study related assessments that were required at the EOS visit and will not need to return for further assessment. A study completion form will be completed on the day they are cleared.
d. Confirmation of eligibility criteria.
e. Demographics: date of birth, sex, race/ethnicity will be collected.
f. Vital signs (e.g., temperature & heart rate) will be obtained at screening and at each treatment prior to application of Study drug.
g. Limited physical examination. Symptom- or AE-directed physical examination may be performed if warranted. (See Source/CRF for further outline of assessment.)
h. Regional lesion counts (head/neck, trunk, upper/lower extremities) should be performed.
i. LSR assessment will be performed by the Investigator or trained personnel with a protocol-specific LSR form at each treatment visit and the EOS visit.
j. CDLQI assessment to be completed prior to Study drug application and at EOS visit. CDLQI must be repeated if the first treatment is not completed within 7 days.
k. To be performed prior to Study drug application and at EOS in any females of childbearing potential (females that are capable of menstruating).

l. Photography of molluscum lesions will occur at selected clinical sites only.
m. Study drug may be gently removed from individual lesions prior to 16 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. Study drug should not be removed from the remaining unproblematic lesions until the 24 hour time point is reached. Every effort should be made to complete the PERIT at 24 hours after application.
n. PERIT assessment and photos are to be completed by parent/guardian at approximately 24 hours post application of Study drug. Treatment may be removed prior to overnight application in the event of significant blistering, significant pain or if treatment emergent AEs are experienced; however, every effort should be made to complete the PERIT at 24 hours.
o. Blood samples will be obtained from subjects participating in the exposure group only. Samples will be obtained at 2, 6 and 24 hours post application of study medication. Subjects will return to the clinic at 24 hours for assessment and completion of the PERIT.(See protocol to confirm study windows.)
p. Subjects will be given take home instructions describing the normal local skin reactions and what to expect over the next 24 hours to several months. A 24-hour emergency number will also be provided. The next visit date and time is also indicated on the form. Polysporin will be dispensed with take home instructions for use as needed.
q. Research staff will complete an assessment of how the applicator performed after each subject is treated.

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LIST OF ABBREVIATIONS

AE	adverse event
AEs	adverse events
CDLQI	children's dermatology life quality index
CRF	case report form
EOS	end of study
EOT	end of treatment
EDC	electronic data capture
FDA	Food and Drug Administration
ICF	informed consent form
ICH	International Council for Harmonization
ID	identification
IRB	institutional review board
ml	milliliters
Molluscum	molluscum contagiosum
ng	nanograms
LSR	local skin reaction
SAE	serious adverse event
SOP	standard operating procedure
PERIT	patient evaluation of response to investigational treatment
T24	human bladder carcinoma cells
TSGH 8301	human urinary bladder carcinoma cell line
VP-102	Verrica Pharmaceuticals-102 (0.7% w/v cantharidin)
w/v	weight/volume

1.0 INTRODUCTION

1.1 MOLLUSCUM CONTAGIOSUM

The causative agent of molluscum contagiosum (molluscum) is the molluscum virus, a dermatotropic DNA poxvirus. Molluscum is common in the pediatric population and is prevalent worldwide. It produces small flesh-colored papules and papulovesicles, 1-4 mm in diameter, which typically have an umbilicated or dimpled center. There is often little inflammation associated with molluscum papules, and the presence of an inflammatory reaction to such papules often heralds resolution of the disease. Molluscum lesions are generally not painful, but they may itch or become irritated. Picking or scratching the bumps can lead to autoinoculation, secondary bacterial infection or scarring.

Molluscum is spread readily by autoinoculation and by person-to-person contact. The virus may also be transmitted by touching objects such as towels, clothing, or toys. Most immunocompetent individuals will spontaneously clear the disease in an average of 13 months, although 25% children still have the disease after 18 months.[3] Spread to siblings and friends, as well as the development of additional lesions in neighboring sites during this time causes parental angst, socialization challenges for the afflicted individuals[1, 2] and has been shown to negatively impact quality of life.[3] The highest incidence is in children up to 14 years of age, where the incidence rate ranges from 12 to 14 episodes per 1000 children per year.[4]

There is no approved product by the Food and Drug Administration (FDA) for the treatment of molluscum. Given that there are no approved options, physicians employ a variety of treatment approaches including (a) benign neglect; (b) curettage; (c) cryotherapy; (d) expressing the molluscum bodies; (e) retinoic acid creams; (f) caustic agents; (g) topical immunotherapeutics; and (h) non-standardized, compounded cantharidin products of various purity, formulations, and strengths.

1.2 CANTHARIDIN

Cantharidin (1,2-dimethyl-3,6-epoxyperhydrophthalic anhydride) is a lipophilic natural compound that can be isolated from the body fluids of the blister beetle, primarily of the family Meloidae. Blister beetles are found in many parts of the world, including the southern United States and Asia (*Mylabris Cichorii L* and *Mylabris*

phalerata). *Lytta vesicatoria*, a metallic green beetle, was primarily used as a source of cantharidin in the early 1900s, as it is endemic to the United States. Regardless of species of blister beetle, the structure of the cantharidin molecule is maintained with only variations in the quantity of compound that can be readily isolated. The *Mylabris* species of beetle contains a much greater concentration of cantharidin and is the primary type of beetle used in modern cantharidin preparations.

Cantharidin functions as a vesicant, weakening desmosomes in the epidermis when applied topically via a liquid film-forming formulation. Application to the skin causes the release of neutral serine proteases resulting in the destruction of intercellular desmosomes responsible for holding the layers of the skin together.[5] Intracellular tonofilaments are also weakened, the result being a fluid-filled, thin-walled epidermal vesicle. The superficial nature of the blisters is attributed to cantharidin's lesser effect on hemidesmosomes in the basal layer compared to the more superficial desmosomes. In almost all patients, this process does not cause a scar, as the underlying dermal layer of skin is undamaged. Cantharidin has no known direct antiviral effects.

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

Although cantharidin has been used extensively for decades in the treatment of several dermatologic conditions including molluscum and verruca vulgaris, specifications for the quality of active pharmaceutical ingredient or a standardized formulation have never been established. Furthermore, a lack of reliable and regulated vendors of the compounded drug increases the chance of the drug product being inappropriately prepared, tested, stored or applied, which in turn increases the potential for unintended or even dangerous consequences in the future. Most currently used cantharidin preparations are prepared as 0.7% w/v (weight/volume) solutions in an acetone solvent with a flexible-collodion base in a screw-top glass bottle at volumes intended for repeated use across multiple patients by the medical professional. This type of container closure system paired with highly volatile formulations presents multiple challenges. Current clinical practice, which reuses the same bottle on multiple patients,

increases the risk of cross-contamination and viral transmission. Furthermore, due to the presence of volatile solvents in the preparation, evaporation from multiple uses heightens the risk of increased concentration and viscosity of the cantharidin in solution and creates a scenario where highly-concentrated material may be applied to the patient's skin. Many formulations also lack formal stability studies and medical professionals often will just use the material until it is "too thick" to apply. As a consequence, many patients are likely receiving much more drug than is clinically necessary to treat their molluscum lesions. While this does provide evidence of the safety profile for the drug, it also introduces unnecessary risk to the patient. Further, the nature of the liquid product coupled with the traditional application strategy of using the wooden end of a cotton-tipped swab makes it difficult to apply the minimum amount of drug necessary to achieve the desired effect. Complete treatment of all lesions is further confounded by the fact that there is no visual indicator present in the formulation to clearly identify for physicians, patients and caregivers where the drug has already been applied during the treatment session.

To address these current shortfalls, Verrica Pharmaceuticals, Inc. has developed VP-102, a 0.7% w/v cantharidin formulation, consistent with the predominant concentration of cantharidin used by physicians. VP-102 is delivered in a single-use glass ampule stored within a single-use plastic applicator with integrated inline filter to remove any glass particles capable of breaking the skin to minimize cross-contamination and concentration changes during use. Each VP-102 applicator will be able to deliver up to 450 µL (microliters), with each VP-102 unit containing 3.15 mg of cantharidin. Gentian violet, a dye common in surgical markers, has also been included to facilitate physician recognition of treated vs. untreated molluscum lesions. Finally, to afford additional safety and deter potential oral ingestion of the drug by young patients, the oral deterrent denatonium benzoate has been included.

1.2.1 Nonclinical Studies with Cantharidin

Preclinical published data for cantharidin focuses primarily on its effect on epithelial cells, endothelial cells, various carcinoma cells, and myocardial cells. Data most germane to the current study are those examining the effect of cantharidin on epidermal cells, since it is absorbed through the lipid layer of the skin, inducing acantholysis and desmosome disruption of the epidermal cell layer leading to small blisters.

Cantharidin has shown potent in vitro chemotherapeutic activity against a number of human cancer cell types including human bladder cancer T24 cells[6] and human bladder cancer TSGH 8301 cells.[7] Pharmacodynamic drug-drug interaction studies of topical application of cantharidin on rat ears showed a decreased anti-inflammatory response from dexamethasone, hydrocortisone, and prednisolone.[8]

Previously, safety pharmacology studies have been conducted primarily following oral administration, rather than dermally, due to the limited anticipated systemic exposure following topical administration. One study, however, focused on cardiovascular and renal effects of ingested cantharidin in rats. This study showed that cantharidin did not affect heart rate for the experimental period of 24 hours but decreased urine volume.[9] In a rabbit study, intermediate (1.3 or 1.5 mg/kg) and high (1.9 mg/kg) doses of intravenous bolus injection of cantharidin led to cardiac arrest, but no effects were noted at lower doses (0.6 or 1.1 mg/kg).[10]

In vitro studies of cantharidin produced positive inotropic responses in guinea pig papillary muscle,[11] human myocardial tissue,[12, 13] and bovine coronary artery rings.[13] Cantharidin inhibits mobilization of synaptic vesicles and depresses calcium release from the sarcoplasmic reticulum, affecting motor function[14] and causing contraction of bovine smooth muscle.[15] In GLP-compliant genotoxicity studies, cantharidin could not be evaluated in the chromosomal aberration assay with human peripheral blood lymphocytes, and therefore no conclusions can be made about its clastogenic potential. Cantharidin was negative in GLP-complaint bacterial reverse mutation assays and does not possess mutagenic potential.

1.2.2 Clinical Studies with Cantharidin

Cantharidin has been used by healthcare providers for decades to treat molluscum. The following summarizes significant studies documenting safety and efficacy of this treatment modality.

An ongoing bridging study has been implemented under Investigator IND 114032 to confirm if VP-102 is similar in safety and efficacy to a 0.7% cantharidin compounded formulation of cantharidin studied previously. As of 1 April 2017, VP-102 appears to be safe and well tolerated. There were no treatment related adverse events reported during application to over 1,000 molluscum lesions in 14 subjects with a 6-hour exposure. In an ongoing second part of this study, there have been no treatment related

adverse events reported with application to nearly 250 lesions in 12 subjects with an overnight exposure. The ability of VP-102 to completely clear molluscum is not significantly different from a 0.7% cantharidin compounded formulation, and both the compounded and VP-102 perform significantly better than the best estimate of placebo. Thus, this bridging study is deemed to have met its primary objective in demonstrating that VP-102 appears to be safe and effective in the treatment of pediatric molluscum (IND 114032; NCT# 03017846).

Schairer et al.[16] published an interim analysis of a two phase, double-blind, placebo-controlled study with the first 52 subjects (2 to 17 years old) who were randomly assigned to receive two treatments with topical 0.7% w/v cantharidin or placebo (with and without occlusion) 3 weeks apart with lesion counts and adverse events assessed every 3 weeks. Most recently, Garelik et al. (unpublished manuscript; with the full analysis of the population treated in Schairer et al.) published the complete results of the Schairer study. Cantharidin or placebo vehicle was administered in a blinded manner at week 0 and week 3 to 94 subjects with a maximum of 50 lesions. At 6 weeks (2 applications spaced 3 weeks apart), a greater percentage of subjects achieved complete lesion clearance in the cantharidin versus placebo arms ($p < 0.05$). Subjects who did not have clearance at week 6 were crossed over to treatment with open-label cantharidin every 3 weeks until all lesions were resolved. In this 94-subject study, 78.4% of the participants achieved total lesion clearance in a median of three visits (range 2 to 9 visits). In the open label group, the median time to clearance was 9 weeks (3 additional treatments with cantharidin) with 87.8% of subjects achieving complete resolution. There were no reported treatment related adverse events demonstrating that cantharidin is an effective and safe treatment for molluscum when applied as an in-office treatment.[16]

In another exploratory double-blind, placebo-controlled study, 29 children, with no upper limit of lesion count, were treated every 10-14 days over a 2-month period for a maximum of 5 visits.[17] Only 1-2 lesions were treated on the first visit and up to 20 lesions were treated on subsequent visits. By visit 5, the median lesion count for the cantharidin group was 8 (a reduction of 41% from baseline) whereas the median count for the placebo group was 18 (a reduction of 8% from baseline). Complete clearance of lesions was seen in 15% (2 of 13) of cantharidin-treated subjects and 9% (1 of 16) of the placebo group.

Lastly, a prospective, four-arm, open-label, randomized study investigated the efficacy of four recognized treatments for molluscum (curettage, 0.7% cantharidin, salicylic acid and lactic acid, imiquimod).[18] For each subject in the cantharidin treatment group, 10 lesions were selectively treated, and the remaining lesions were removed by curettage. Efficacy was based on the number of visits needed for clearance, incidence of side effects, and parental and subject satisfaction. Following curettage, cantharidin had the best tolerability and efficacy profile in this single center study where the investigators were primarily experienced with curettage as the primary treatment modality. Adverse events (AEs) reported in these studies were limited to blistering and pain at the application site. Less frequently, redness, pruritus, and pigment changes have been reported with cantharidin use.

Results of prospective studies are supported by retrospective reports of treatment of molluscum with cantharidin. In a retrospective study of 62 cases of pediatric molluscum involving facial lesions, treatment with cantharidin resulted in the following incidence of side effects; 18% discoloration, 10% blistering greater than expected, and 10% pain. Pruritus, scarring, irritation, bleeding, and spreading of lesions were uncommonly cited. A satisfaction survey of parents following treatment found an average score of 8.7 out of 10. The authors concluded that cantharidin is a safe and effective first-line treatment for molluscum lesions on the face.[19]

Moye, et al.[20] performed a retrospective analysis of 405 molluscum subjects (aged 5 months to 20 years old) treated with 0.7% w/v cantharidin. The study involved 1,056 treatments to over 9,688 lesions with an average of 2.6 visits per patient. A parent satisfaction assessment found that 86% of parents were satisfied with the cantharidin treatment or would opt to use it again, while 1.2% of parents were dissatisfied, citing irritation and pain as the reasons. Less than 1% of parents preferred another therapeutic option. The most common AEs in the population were blistering (11%), pain at the treatment site(s) (7%), and severe blistering (2.5%). Less than 1% of patients experienced pruritus, possible mild infection, significant irritation, non-severe pain after treatment, and bleeding.

Cathcart, et al.[21] also reported on parental satisfaction, efficacy, and AEs in 54 children (aged 3 months to 13 years old) with molluscum after treatment with cantharidin. Parents reported 96% improvement post-treatment with a 78% satisfaction rating. Overall, 46% of patients experienced AEs, including pain, pruritus, secondary

infection, and temporary hypopigmentation while 9% experienced severe pain. The authors concluded that cantharidin "should be considered a potential frontline treatment" for molluscum.

Silverberg, et al.[22] conducted a retrospective study to determine the safety, efficacy and parental satisfaction in 300 children (mean aged 4.7 years old) with molluscum after treatment with 0.7% w/v cantharidin. 90% of patients experienced complete clearing, 8% experienced significant improvement and 2% reported that the therapy was ineffective. 92% of patients had blistering, 37% experienced erythema (which lasted up to 3 weeks), 14% had mild to moderate pain, and 8% had a change in pigmentation at the site of application. Importantly, no major side effects or secondary bacterial infections were noted. 95% of parents stated that they would proceed with cantharidin therapy again if necessary.

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

1.3 STUDY RATIONALE

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

On average, it takes over 13 months to naturally clear molluscum lesions. Unfortunately, one in four children with diagnosed molluscum experience persistent lesions even after 18 months. Subjects with more than 10 molluscum lesions experience a significant negative effect on their quality of life.[3]

The primary objective of this study is to determine the presence or absence of systemic cantharidin following VP-102 application. Plasma will be evaluated by a

GLP-compliant third party vendor for the presence of cantharidin using a validated GC/MS analytical method (MET012. v1). The unit of analysis is ng/ml with a limit of detection of 1ng/ml in plasma.

The secondary objectives will be to evaluate the safety, efficacy and impact on quality of life with dermal application of VP-102, when applied once every 21 days for up to 4 applications in subjects age 2 years or older. Safety of the treatment will be evaluated by assessing AEs, LSRs, physical examinations, and concomitant medications throughout the study (up until EOS; ~Day 84) compared to baseline. For patients that have completely cleared prior to EOS (~Day 84), all corresponding study related activities will be conducted and an EOS form will be completed.

1.4 DOSE RATIONALE

A 0.7% w/v cantharidin solution is the recognized therapeutic dose of cantharidin for molluscum treatment in dermatological clinical practice[17, 19-23]. A lower dose of 0.5% was found to be ineffective in the treatment of molluscum.[24] The 0.7% w/v dose was determined to be safe and effective in a recent double-blind Phase 2 study of 94 subjects for the treatment of childhood molluscum,[16] Garelik et al. (unpublished manuscript) and in an ongoing study of VP-102 (NCT# 03017846) with 26 patients treated as of 1 April 2017.

The anticipated VP-102 label will focus on treatment of patients with any number of molluscum lesions. Each lesion is typically about 1 mm to 4 mm (0.78 mm^2 to 12.56 mm^2) in diameter and Verrica estimates that approximately 5-10 µL of VP-102 is sufficient to cover each lesion. A single use applicator should be sufficient to treat up to approximately 50 molluscum lesions and up to 2 applicators may be used per treatment.

OBJECTIVES

1.5 PRIMARY OBJECTIVE

The primary objective of the study is to determine the presence or absence of systemic cantharidin exposure from a single 24-hour dermal application of VP-102 topical film-forming solution [0.7% (w/v) cantharidin] (VP-102) when applied to molluscum contagiosum (molluscum) lesions on pediatric subjects 2 years old and older.

1.6 SECONDARY OBJECTIVES

The secondary objectives are as follows:

- to assess the safety of VP-102, when applied once every 21 days for up to 4 applications, to treated molluscum lesions on subjects 2 years old and older by assessing adverse events, local skin reactions, physical examinations, and concomitant medications throughout the study compared to baseline.
- to assess the efficacy of VP-102 in the treatment of molluscum lesions as assessed by clearance or reduction of treated molluscum lesions compared to baseline.
- to assess the impact of VP-102 treatment on quality of life of patients as assessed via the administration of the Children's Dermatology Life Quality Index (CDLQI).

2.0 STUDY DESIGN

2.1 BASIC DESIGN CHARACTERISTICS

This is a Phase 2, study that will be conducted in the United States to determine the systemic exposure, efficacy, safety and impact on quality of life of VP-102 (0.7% cantharidin) following treatment of molluscum lesions for up to 4 treatments, 21 days apart, with VP-102 in up to 40 pediatric subjects (2 years or older). Duration of molluscum lesions prior to Day 1 will be recorded but will not be an inclusion/exclusion requirement.

Study drug, VP-102, will be supplied in single-use applicators, with one applicator sufficient to treat at least 50 molluscum lesions. If required due to the number and size of lesions, a second single-use applicator may be used. No more than 2 applicators will

be permitted per subject per treatment. The film-forming Study drug solution will be applied and left on the lesions for approximately 24 hours before the subject and/or parents/guardian washes the lesions with soap and warm water. Those in the Exposure group will remove the dried film after the 24-hour blood draw is obtained. Treatment may be removed prior to the 24-hour timepoint in the event significant blistering, significant pain or treatment emergent AEs are experienced.

Molluscum lesions will be treated without occlusion in all anatomic areas including the face, trunk, back, arms, legs, hands, feet, genital region and buttocks as long as the physician feels it is safe to do so. Subjects participating in the Exposure group must have at least 21 lesions treated at Day 1 treatment to qualify.

The study duration from Day 1 through the EOS visit is up to 12 weeks. Pre-study screening for eligibility (informed consent, inclusion/exclusion criteria and medical history) will occur up to 14 days before, or on Day 1/Study drug administration. Subjects will be treated with application to molluscum lesions every 21 days (± 4 days) for a maximum of 4 treatment sessions. Subjects that completely clear prior to ~Day 84 will complete their EOS visit on that day. In the event of scheduling conflicts in subsequent visits after the Day 1 treatment, subjects may be scheduled on 21 ± 4 days following their previous treatment. The next study visit should then be scheduled 21 days after the previous treatment.

Assessment of local skin reactions (LSR) will be performed by the investigator or trained member of the research team at each treatment visit and the EOS visit. LSRs are not considered AEs and are part of the normal and necessary response to treatment. The following clinical responses will be recorded: erythema (including associated swelling), flaking/scaling, dryness and scabbing/crusting during resolution). A Skin Quality Assessment will also be performed as part of the LSR and will assess pigmentation changes (hyperpigmentation or hypopigmentation) and degree of scarring, if applicable.

Parent/subject quality of life and measure of impact of skin disease will be assessed with the CDLQI prior to application of Study drug at each treatment session and at EOS visit. Subjects will also complete a Safety Monitoring Questionnaire at visits 2-5.

Subjects will be given a 24-hour phone number to call the investigator or a clinical research team member in the event of questions or AEs. Evaluations will also be provided by the subject or parent/guardian using the Patient Evaluation of Response to Investigational Treatment (PERIT) form the following day after Study drug application. Parents will also be asked to take and send photos via text or e-mail to the study team for assessment during the 24-hour follow-up call. All observed AEs, local skin reactions and parent-reported AEs will be recorded.

Parents or guardians must provide informed consent, and pediatric subjects older than 5 years must provide assent as required by the IRB before any study procedures are conducted. Subjects must meet all study eligibility criteria through a complete review of pertinent medical history, a symptom/sign evaluation, and limited physical examination. Full inclusion/exclusion criteria are provided in Section 2.2.

2.2 STUDY POPULATION

There will be up to 40 subjects enrolled with the goal of 16 completing all blood draws in the exposure group. A maximum of 16 will be enrolled in the standard treatment group. The additional 8 subjects may be used for replacement patients. Any subject in the exposure group who does not complete all blood draws may continue to receive treatment, but will be replaced. No more than 16 subjects will be considered as completed Exposure group participants. At least 3 patients in the exposure group will be from 2-5 years of age. Subjects will be considered enrolled when they have signed informed consent and have received at least 1 treatment.

Eligibility will be established by the investigator on the basis of the inclusion and exclusion criteria.

2.2.1 Inclusion Criteria

To qualify for inclusion in this study, subjects must:

1. Be healthy subjects, ages 2 years and older.

2. Patients with 1-20 lesions may be enrolled and treated in the ‘standard treatment’ group but are not eligible for the exposure study OR

Patients with 21 or more lesions may only be enrolled in the 'exposure group'. Subjects participating in the Exposure group must have at least 21 lesions treated at Day 1 to qualify.

3. Be otherwise medically healthy with no clinically significant medical history as determined by the investigator. *Patients exhibiting active Atopic Dermatitis may be enrolled.*

4. Refrain from application of all topical agents including alcohol-based sanitary products and sunscreens for a minimum of 4 hours before Study drug application. Topical agents including alcohol-based sanitary products and sunscreens may be used after application of the study drug so long as they are not applied to or near treated skin.

5. Refrain from swimming, bathing or prolonged immersion in water until the Study drug is removed.

6. Have the ability or have a guardian able to follow study instructions and be likely to complete all study requirements.

7. Provide assent in a manner approved by the institutional review board (IRB) and have a parent/guardian provide written informed consent as evidenced by signature on IRB approved assent/consent forms.

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

9. Agree to allow photographs of all selected lesions to be taken and/or send photos via text or email to the study team for assessment at 24 hours' post treatment. These images may be used on handouts in future trials, for training purposes, as part of the study data and/or marketing package. *Photographs will be de-identified to those outside the research team. Effort will be made to ensure that no photos with identifiable features are obtained.*

2.2.2 Exclusion Criteria

Candidates will be excluded from the study if they:

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

2. Have molluscum venereum (sexually transmitted molluscum).

3. Have active molluscum eczema.

4. Are systemically immunosuppressed or are receiving treatments such as chemotherapy or other non-topical immunosuppressive agents.

5. Have had any previous treatment of molluscum in the past 14 days including the use of cantharidin, antivirals, retinoids, curettage or freezing of lesions. Additional treatments should not be implemented during the course of the study.

6. Have history of illness or any dermatologic disorder, which, in the opinion of the investigator will interfere with accurate counting of lesions or increase the risk of adverse events.

7. History or presence of clinically significant medical, psychiatric, or emotional condition or abnormality that in the opinion of the investigator would compromise the safety of the subject or the quality of the data.

8. Have a history or presence of hypersensitivity or an idiosyncratic reaction to the Study drug or related compounds, or drug product excipients *(acetone, ethyl alcohol, nitrocellulose, castor oil, camphor, gentian violet, and denatonium benzoate).*

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

10. Have received another investigational product within 14 days prior to the first application of the Study drug.

11. Have been treated within 14 days with a product that contains cantharidin (topical or homeopathic preparations) for any reason prior to screening.

12. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods. Females that have reached menarche, must have a negative urine pregnancy test at screening and each visit prior to treatment with study medication.

13. Are pregnant or breastfeeding.

2.3 ENDPOINTS

Primary endpoint:

- The presence or absence of systemic exposure to cantharidin by the collection and analysis of plasma samples from patients with 21 or more molluscum lesions following treatment of VP-102.

Secondary endpoint:

- Proportion of subjects exhibiting complete clearance of all treated molluscum lesions (baseline and new) on or before Week 12 (EOS).

Exploratory endpoints:

- Proportion of subjects exhibiting a 90% or greater reduction of all treated molluscum lesions (baseline and new) at the EOS visit.
- Percent reduction of treated molluscum lesions from baseline at the EOS visit.
- Change from baseline in the number of treated molluscum lesions at the EOS visit.
- Change from baseline in quality of life and impact of skin disease as measured by the CDLQI assessment.

- Spread to siblings as measured by any new occurrence of molluscum in siblings of the subject.

2.3.1 Safety

The following safety parameters will be assessed:

- Subjects will be monitored for signs and symptoms of AEs throughout the study. All AEs will be reported on the case report form, including seriousness, severity, action taken, and relationship to the Study drug. If AEs should occur, the first concern will be the safety of the subject.

- Limited physical examinations will be performed by a qualified medical practitioner, at screening and at EOS. Height and weight will be recorded at screening, and weight will be recorded at EOS. Unscheduled physical examinations will be performed when clinically warranted (e.g., if a subject reports symptom requiring further evaluation).

- Vital signs (e.g., heart rate and temperature) will be obtained at screening and at all subsequent visits prior to treatment. A final assessment of vital signs will be obtained at the EOS visit.

- If the subject discontinues the study prematurely (after the first treatment) due to clearance of lesions, or for any reason, attempts will be made to encourage the subject/parent/guardian to complete the EOS assessments.

- Assessment of local skin reactions (LSR) will be performed by the investigator or trained member of the research team at each treatment visit and the EOS visit. LSRs are not considered AEs and are part of the normal and necessary response to treatment. The following clinical responses will be recorded: erythema (including associated swelling), flaking/scaling, dryness and scabbing/crusting during resolution). A Skin Quality Assessment will also be performed as part of the LSR and will evaluate pigmentation changes (hyperpigmentation or hypopigmentation) and degree of scarring, if applicable.

- Patient Evaluation of Response to Treatment (PERIT)

- Safety Monitoring Questionnaire

- Households where siblings or friends are diagnosed with molluscum should make every effort to avoid close contact with those individuals to prevent development of new lesions, recurrence, or spread of the disease. Sharing of personal items such as towels, clothes, utensils or toys is strongly discouraged.

2.3.2 Efficacy

Efficacy parameters will be recorded for all subjects that receive at least one application of Study drug. Clinical response to treatment will be evaluated at each scheduled visit and EOS with counts of all molluscum lesions present (treated and untreated).

2.4 REPLACEMENT OF DROPOUTS

Subjects participating in the exposure group that do not complete all required blood draws will be replaced. Subjects that do not complete the blood draws but wish to continue in the exposure group may be continued and will be evaluated for efficacy and safety after 4 treatments.

Those patients that do not complete the full treatment due to protocol adherence or request to be discontinued from the study will be not be replaced. Subjects who do not complete the safety and efficacy evaluation period will be considered dropouts. Dropouts will not be replaced. In the event a patient 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 not replaced.

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

3.0 DRUGS AND DOSAGES

3.1 IDENTIFICATION AND DESCRIPTION OF INVESTIGATIONAL PRODUCT

3.1.1 Investigational Product

VP-102 is a cantharidin solution [0.7% (w/v)] in a film-forming excipient formulation. Once applied to the skin, solvents in the Study drug evaporate leaving behind a thin, flexible and resilient film. The Study drug is light purple in color and has been manufactured under good manufacturing practices (GMP).

VP-102 is manufactured in a GMP facility. The cantharidin used in VP-102 is >99% pure and manufactured under GMP. VP-102 is stable for at least 180 days when stored at controlled room temperature in a dark location. VP-102 is undergoing a GMP stability study and the stability date of this product may be updated in accordance with current FDA guidelines with appropriate data. Study drug is delivered in a single-use glass ampule stored within a single-use plastic applicator with integrated inline filter to remove any glass particles capable of breaking the skin. The Study drug will be released after passing quality control measures for description, assay, identification, impurities and microbial limits.

The study will be initiated using applicators with the tip and cap made from prototype materials manufactured via sterolithography or injection molding. The tip will be attached to the tube either with a friction fit or ultrasonic weld. The primary glass ampule packaging, filter and tube will be with the commercial grade, to-be-marketed materials. Each lot of applicators will be released for clinical use after a subset has undergone applicator suitability testing and demonstrated that they can deliver at least 50 droplets of drug product in a controlled manner without leaking or spilling. A visual assessment will confirm that the delivered drug product is free from glass particles large enough to break the skin. Once the commercial tip and cap components have completed testing, the applicators used in this study may be exchanged for the full commercial grade applicators.

Similar packaging systems containing crushable glass ampules in plastic housings with attached filters and/or tips are used in FDA approved medical products for the application of medical adhesives like Dermabond® (PMA number P960052) and antiseptics like Chloraprep® (NDA 21-555) as well as in commonly used OTC

analgesics and antiseptics like Orajel® Singles and Medicaine®. The primary manufacturer for many of these applicators as well as the VP-102 applicator described herein is a FDA registered manufacturer of both drugs and medical devices. Many of the products they manufacturer are used directly by patients and others are used in an urgent care setting and applied to high-risk patient populations, including premature infants.

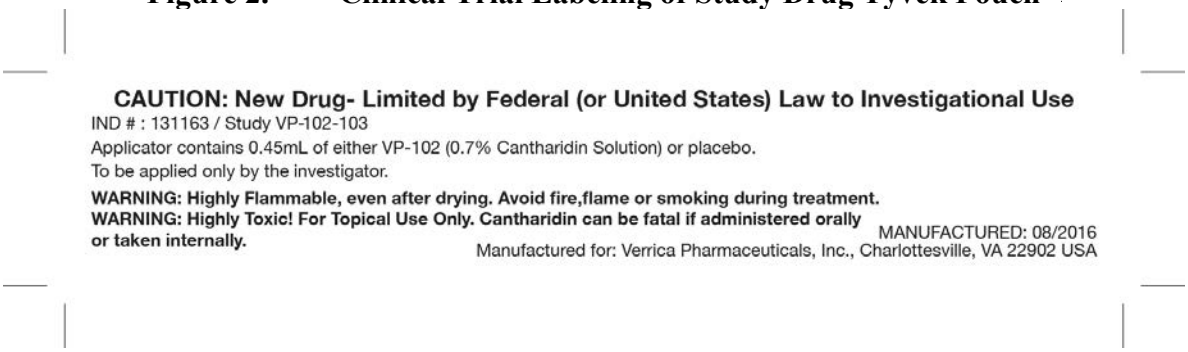
3.1.2 Labeling

An example of the label on Study drug single use applicator packaging is presented below in Figure 1. The applicator will also display the appropriate warnings including standard flammable and toxicity symbols. The applicator labels will be prenumbered from 001-107.

Figure 1. Clinical Trial Labeling of Study Drug Applicator

Each Study drug single use applicator will be wrapped in a Tyvek pouch for additional safety against leakage or other damage. These Tyvek pouches will also have a label which provides additional more detailed safety warnings about the flammability and toxicity of the study drug. An example of the label on the Tyvek pouch is presented in (Figure 2).

Figure 2. Clinical Trial Labeling of Study Drug Tyvek Pouch



3.2 DOSING INSTRUCTIONS AND SCHEDULE

Upon activation, clinical sites will be provided with an initial supply of single-use applicators that can deliver up to 450 µL of the Study drug (VP-102). Each applicator can treat at least 50 molluscum lesions.

Following examination, all subjects will receive application of Study drug to all active molluscum lesions approximately every 21 days for a maximum of 4 applications.

Be sure that you read, understand and follow the Instructions for Use in the Investigator's Brochure Appendix A before you use the Study Drug applicator.

.**Additional points to Consider:**

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

2. Observe subjects for 5 minutes after Study drug application or until the film is formed and totally dry. Strongly urge subjects and parents/guardians not to touch or wash the treated area for up to 24 hours. To remove the Study drug, the treated lesions should be washed with soap and warm water. VP-102 should be removed at 24 hours or shortly after provided there are no adverse events. Subjects and parents will be cautioned not to use washcloths, abrasive material or vigorous rubbing to remove the Study drug as this may cause temporary pain, opening of blisters, and slow the healing process. Washing in a bath or shower to remove study drug is encouraged.

3. Provide subjects and parents/guardians with both verbal and written follow-up instructions on potential side effects and complications, contact information of the study investigator/study coordinator for questions or concerns, and a copy of their signed informed consent (Screening Day and/or Day 1 only). The images included in the PERIT contain examples of expected or excessive blistering for assessing the subject's treated area. Subjects will be given a tube of Polysporin® (Manufactured by Pfizer) to apply to those lesions in which blisters have ruptured to minimize the

risk of secondary infection. Band-Aids may be used in the event there is oozing or leaking, at the discretion of the parent. After the treatment session, parents/guardians will be contacted by the investigator or clinical research team the next day to ensure that application sites have been washed, to discuss responses on the PERIT assessment, and to answer any questions or concerns. Participants will be given a 24-hour call number for any emergencies that may arise post-treatment and throughout the study.

All serious and/or severe AEs will be reported to the IRB and FDA per applicable guidelines and regulations.

3.3 STORAGE AND HANDLING OF INVESTIGATIONAL PRODUCT

Each applicator will be individually wrapped in a labeled Tyvek pouch. This Tyvek pouch should not be opened until the you are ready to initiate treatment. The applicator will be labeled with the Investigational New Drug application number and a study identification number. The label will also display the date of production manufacture and the statement "Caution: New Drug--Limited by Federal Law to Investigational Use." and "Warning: Flammable Liquid." The applicator will also display warnings appropriate to the characteristics of the Study drug the specifically appropriate yellow triangular flammable symbol sticker with the phrase "Warning: Flammable Liquid" and a yellow toxic chemical symbol with the phrase "Warning: Highly Toxic" as well. Applicators will be received in bulk supply and numbered in sequential order. Applicator numbers are used for accountability purposes only and are recorded on the accountability log as they are used. Applicators do not need to be used in sequential order. All used and unused study product is to be held until completion of the study.

Drug accountability will be reviewed and confirmed by the study monitor assigned by Verrica Pharmaceuticals, Inc., and instructions for destruction or return will be given at that time.

Study drug must be stored at controlled room temperature (68°-77°F; excursions of 59°-86°F are acceptable for short periods) in a secure, dry location with limited and controlled access, and out of direct sunlight. Extended exposure to extreme temperature conditions should be avoided (eg. Study drug should not be left in an unoccupied vehicle). Contact the study sponsor in the event you believe that any materials may have been exposed to such conditions for guidance. Study drug may be

administered only by the investigator or by a trained member of the clinical site staff specifically as authorized by the investigator.

3.4 CONCOMITANT MEDICATIONS

All medications taken within 14 days prior to the first dose of the Study drug will be classified as prior medication, while all medications used after the first dose of study will be classified as concomitant medications. Any anti-microbial, anti-viral, steroidal or topical drugs received within 30 days prior to Day 1 should also be recorded. Prior and current concomitant medications will be recorded on the CRF, along with the reasons for administration and duration of use.

Medications or treatments that can interfere with the evaluation of the study drug (e.g., topical steroids) should not be used 4 hours before treatment and should not be applied near or to treated skin for 24 hours following treatment. Particular attention will be paid to treatments (e.g., topical steroids) that can influence the intended effects or mask the side effects of the Study drug. Lotions and creams such as sunscreens should not be used for a minimum of 4 hours before treatment and should not be applied near or to treated skin for 24 hours following treatment.

4.0 EXPERIMENTAL PROCEDURES

4.1 OVERVIEW: SCHEDULE OF TIME AND EVENTS

Each subject will be evaluated and treated as follows:

1. Screening Period (Up to 14 days prior to visit Day 1).

2. Standard Treatment Group (Day 1)
   - Pre-application: dermatologic exam
   - VP-102 application

3. Systemic Exposure Group (Day 1)
   - Pre-application: dermatologic exam and blood collection
   - VP-102 application
   - 2 hours (± 30 min) post-application: blood collection
   - 6 hours (± 1 hour) post-application: blood collection
   - 24 hours (± 3 hour) post-application: blood collection, PERIT assessment

4. Day 1: Treatment 1

   - Confirm that subject still meets all criteria (Dermatologic exam/lesion count; can attend study visits).

5. Day 1 though Visit 4 Treatment activities

   - LSR and CDLQI assessments.

   - Study drug application/Complete Applicator Assessment Form for each applicator used

   - 24 hours post-application: removal of Study drug and PERIT assessment: Study drug should be removed by gentle washing after overnight (24 hours) application. (*Study drug may be gently removed from individual lesions prior to 24 hours of application in the event of significant blistering, significant pain or treatment emergent AEs. Study drug should not be removed from the remaining unproblematic lesions until the 24 hour time point is reached. Study drug should be removed as close to the 24 hour time point as possible. Every effort should be made to complete the PERIT at 24 hours after application)*

6. Study evaluation windows: *(Subjects may be scheduled 21+/- 4 days after treatment in the event of scheduling conflict. If possible the next treatment or study visit should be scheduled 21 days from the day the subject's last study visit.)*

   - Treatment 2: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessments, Study drug application. 24 hours post-application: removal of Study drug and PERIT assessment. Complete Applicator Assessment Form for each applicator used.

   - Treatment 3: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessments, Study drug application. 24 hours post-application: removal of Study drug and PERIT assessment. Complete Applicator Assessment Form for each applicator used.

   - Treatment 4: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessments, Study drug application. 24 hours post-application: removal of Study drug and PERIT assessment. Complete Applicator Assessment Form for each applicator used.

   - End of Study: dermatologic exam/lesion counts, LSR, CDLQI & Safety Monitoring assessments.

The Screening period permits screening up to 14 days prior to Day 1. An IRB-approved ICF will be signed before any study specific procedures are performed. The Safety Evaluation Period (Day 1) will begin with confirmation that the subject still meets study criteria (e.g., Dermatologic exam/lesion count; can attend study visits). Parent/subject impact on quality of life will be assessed using the CDLQI during each treatment visit, prior to the application of Study drug. PERIT assessment will be completed at approximately 24 hours after each Study drug application. Subjects may be scheduled 21 +/- 4 days after treatment in the event of scheduling conflict. If possible the next treatment or study visit should be scheduled 21 days from the day of the subject's last study visit. AEs will be assessed at every study visit.

4.2 MEASUREMENTS AND EVALUATIONS

4.2.1 Screening Period (Up to 14 days prior to Day 1 visit or on Day 1 visit)

Before the initiation of screening assessments, the subject and parent/guardian must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the subject and parent/guardian must sign and receive a copy of an informed consent form (ICF) (Section 7.3), an IRB-required assent form, and an authorization for use and disclosure of protected health information (Section 7.3) that was approved by the IRB. Once consent and assent is obtained, the Screening Period assessments will be performed, and the eligibility of the subject will be determined. Subjects will be screened within 14 days prior to or on Day 1 of the study. Following consent and assent, review and recording of any medical history will take place, and the following evaluations will be performed and recorded in the eCRF:

1. Confirmation that inclusion/exclusion criteria are met.
2. Demographics (date of birth, sex, race/ethnicity).
3. Height and weight
4. Prior relevant medical history
    a. All past significant illnesses within the past 5 years.
    b. All drugs used (including non-prescription and herbal [complementary medicine] products) within 14 days prior to screening procedures. Any anti-microbial, anti-viral, steroidal or topical drugs received within 30 days prior to Day 1.
    c. Any non-pharmacologic treatments (e.g., ice packs, heat packs, warm soaks) administered in the 72 hours prior to the application of the Study drug.
5. Molluscum contagiosum history (duration, previous treatments, siblings, classmates, or peers with molluscum). If treated with cantharidin, confirm date of last treatment.
6. Vital signs (heart rate and temperature) obtained prior to each treatment with Study drug.

7. Limited physical examination.

8. Dermatologic exam*: (This must be repeated on Day 1 to confirm eligibility)*

   a. Regional molluscum lesion count (head/neck, trunk, upper/lower extremities).

      - Patients with 1-20 lesions may be enrolled and treated in the 'standard treatment group' but are not eligible for the exposure study.

      - Patients with 21 or greater lesions will be enrolled in the 'exposure group'. At least 21 lesions must be treated on Day 1 in order to participate.

   b. Presence of any confounding dermatologic diseases such as atopic dermatitis.

4.2.2 Evaluations (Treatment Day 1)

Subjects will return to the clinical site for screening if it was not completed previously, and the following evaluations will be performed:

1. Confirmation of eligibility.

2. Medical history to assess any changes since screening (as described in Section 4.2.1).

3. Review and recording of any concomitant medications and non-pharmacologic treatments or procedures in the last 14 Days prior to enrollment and since the last study visit.

4. Vital signs (heart rate and temperature).

5. Limited physical examination.

6. Dermatologic exam (as described in Section 4.2.1).

7. CDLQI assessment.

8. LSR assessment.

9. Urine pregnancy test for females of child bearing potential, defined as capable of menstruating, to determine protocol eligibility.

10. Photographs taken before application of the Study drug (at selected sites only).

11. Application of Study drug.

12. Review and record any AEs and concomitant medications.

13. Completion of PERIT assessment by parent or guardian approximately 24 hours following application of the Study drug.

14. Depending on age of subject, subject or parent/guardian will wash off the Study drug 24 hours post application of Study drug or when convenient after the 24 hour time point is reached provided there are no adverse reactions. Patients/guardians may gently remove the Study drug from lesions without the use of a washcloth in problematic areas prior to the expected 24 hours if the lesions have already blistered or if the patient is experiencing unmanageable pain. Study drug should not be removed from the additional lesions, where possible, until the expected blistering occurs or the 24 hour time point is reached, whichever comes first.

15. A follow-up phone call from the investigator or a designated member of the clinical research team will be conducted the following day after each treatment to allow parents/guardians to ask questions and report any concerns, confirm removal of Study drug, and review the completion of the PERIT assessment.

4.2.3 Evaluations: (Treatments Day 21, 42 and 63):

1. Review and recording of any concomitant medications and non-pharmacologic treatments/procedures since previous visit.

2. Review and recording of any AEs (before and after Study drug application).

3. Vital signs (heart rate and temperature) before Study drug application.

4. Dermatologic exam (as described in Section 4.2.1) with counting of molluscum lesions.

5. CDLQI assessment.

6. LSR assessment.

7. Safety Monitoring Questionnaire.

8. Urine pregnancy test for females of child bearing potential to confirm continued protocol eligibility before application of study drug.

9. Photographs taken before application of the Study drug.

10. Administration of study drug to all lesions including those lesions that may be newly developed. If any new lesions are not treatable, this will be documented.

11. Completion of PERIT assessment by parent or guardian approximately 24 hours following application of the Study drug.

12. Depending on age of subject, subject or parent/guardian will wash off the Study drug 16-24 hours post application of Study drug. Patients/guardians may gently remove the Study drug from lesions without the use of a washcloth in problematic areas prior to the expected 16-24 hours if the lesions have already blistered or if the patient is experiencing unmanageable pain. Study drug should not be removed from the additional lesions, where possible, until the expected blistering occurs or the 16-24 hour time point is reached, whichever comes first. If possible patients/guardians should target Study drug removal at 24 hours.

13. A follow-up phone call from the investigator or a designated member of the clinical research team will be conducted the following day after each treatment to allow parents/guardians to ask questions and report any concerns, confirm removal of Study drug, and review the completion of the PERIT assessment. Photos will be text or e-mailed by the parent/guardian to the research team for review during the 24-hour phone call.

4.2.4 Evaluation Period / End of Study (~Day 84 or earlier if patient is completely clear of molluscum):

Subjects will return to the clinical site for:

1. Review and recording of any concomitant medications and non-pharmacologic treatments/procedures since previous visit.

2. Review and recording of any AEs.

3. Vital signs (heart rate and temperature) obtained at the beginning of visit.

4. Limited physical examination.

5. Dermatologic exam (as described in Section 4.2.1) and counts of treated and untreated lesions.

6. LSR, CDLQI and Safety Monitoring assessments.

7. Urine pregnancy test for females of childbearing potential.

8. Photographs

5.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

5.1 DEFINITION OF AN ADVERSE EVENT

The following definition of *adverse event* (AE) will be used for this study:

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

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

The following are examples of AEs:

- Exacerbation of a chronic or intermittent preexisting 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

Examples of AEs do not include the following:

- Medical procedures (The medical condition that led to the procedure as the AE should be reported.)
- Situations that are unwanted by the subject but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital
- Anticipated day-to-day fluctuations of a preexisting disease or condition (present or detected before enrollment) that does not worsen overall

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

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

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

All AEs judged to be clinically significant will be followed until the EOS visit or until they have stabilized. 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 5.3.

5.2 DEFINITION OF A SERIOUS ADVERSE EVENT

In this study, a *serious adverse event* is defined as an AE that meets any of the following criteria:

- Results in death
- Is life-threatening

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

- Requires hospitalization or a prolongation of an existing hospitalization

  In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs, but not necessarily SAEs. An occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatments of a preexisting condition that did not worsen from its original baseline level is not considered an SAE.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  This definition is not intended to include AEs of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Other important medical event

Medical or scientific judgment should be exercised when deciding whether reporting is appropriate for other important medical events that may not result in death, be

life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

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

5.3 RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

When an AE or SAE occurs, the investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relative to the event(s). The investigator will record all relevant information about any AE (including SAEs) on the AE page of the CRF. 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 CRF. 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 CRF 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.

5.4 ASSESSMENT OF INTENSITY

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

The classifications in Table 1 should be used in assigning intensity of each AE recorded in the eCRF.

Table 1. Classification of AEs by Intensity[a]

Intensity	Definition
Mild AE (Grade 1)	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
Moderate AE (Grade 2)	An event that is sufficiently discomforting to the extent of interfering with normal everyday activities
Severe AE (Grade 3)	An event that prevents the subject from performing normal everyday activities
Life-threatening or disabling AE (Grade 4)	An event that, at the time of occurrence, put the subject at risk of death or resulted in a persistent or significant disability or incapacity
Death related to AE (Grade 5)	An event that resulted in death

AE: adverse event.
a From Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Any AE that changes in intensity or grade 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 when it meets one of the predefined outcomes described in Section 5.2.

5.5 ASSESSMENT OF CAUSALITY

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

investigational product. The investigator will also consult the Investigator's Brochure or product label for marketed products in estimating the relationship.

Because of reporting timelines, the investigator might have minimal information to include in the initial SAE report. However, the investigator must always make an assessment of causality for every SAE before the transmission of the SAE report. The investigator may change his or her opinion of the causality in light of follow-up information, with subsequent amendment of the SAE report. Causality assessment is one of the criteria used to determine regulatory reporting requirements and should not be left blank in the SAE report. The same applies to AEs that are to be processed as SAEs. Some definitions to use in the assessment are provided in Table 2.

Table 2. 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.

5.6 EXPECTEDNESS OF SERIOUS ADVERSE EVENTS

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

5.7 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE occurring after the subject signs the informed consent form must be reported to the Sponsor by phone, or e-mail within 24 hours of the time the investigator becomes aware of the SAE (Table 3). Urgent reporting of SAEs is required for the following reasons:

1. To enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority

2. To facilitate discussion between the Sponsor and the investigator about appropriate follow-up measures (if necessary)

3. To facilitate the Sponsor's rapid dissemination of information about AEs to other investigators or sites in a multicenter study

4. To facilitate reporting unanticipated problems involving risk to subjects to the IRB

Table 3. Timeline for Reporting SAEs

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

SAE: serious adverse event.

The SAE report will 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

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 safety department of the SAE. The SAE report form will be updated by the investigator when additional information is received.

5.8 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

- The condition resolves.
- The condition stabilizes.
- The event is otherwise explained.
- The subject is lost to follow-up.
- 30-days after the end of study (EOS visit).

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

New or updated information will be recorded on a copy of the initial SAE report form, with all the changes signed and dated by the investigator or designee. The updated SAE report form will then be signed and dated by the investigator and resubmitted to the pharmacovigilance department.

5.9 PREGNANCY

When 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 there is an outcome, and the outcome is reported to the Sponsor.

6.0 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

6.1 SUBJECT DISCONTINUATION

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator will provide a written explanation of the reason for discontinuation in a source document and this information will be recorded on the appropriate CRF page. If a subject withdraws before completion, every effort should be made to complete the Day 84 assessments scheduled during the End of Study visit.

A subject may be removed from the study for the reasons described in Section 6.1.1 through Section 6.1.5.

6.1.1 Adverse Event

If a subject experiences an AE that, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the subject, the subject may be discontinued from the study.

6.1.2 Intercurrent Illness

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

6.1.3 Noncompliance

After the investigator, the medical monitor, 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 3.0
- Failure to comply with protocol requirements

6.1.4 Refusal of Investigational Product Administration

Any subject refusing clinical trial material for any reason will be discontinued from the study, and the reason(s) will be documented on the appropriate CRF 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 CRF page.

6.1.5 Withdrawal of Consent

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

6.2 PREMATURE STUDY OR SITE TERMINATION

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

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study

- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

A study conducted at a single site in a multicenter study may also warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate

- Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities

- Submission of knowingly false information from the site to the sponsor, study monitor, or appropriate regulatory authority

- Insufficient adherence to protocol requirements

Study termination and follow-up will comply with the conditions set forth in International Council for Harmonisation E6, Guideline for Good Clinical Practice.

7.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

7.1 DATA COLLECTION AND PROCESSING

Hard copy/paper CRF's will be used to capture study assessments and data. 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. The study coordinator or other delegated study personnel will enter data from source documents into the CRFs. A combination of both is also acceptable. All CRFs will be reviewed and source-verified by the study monitor centrally and during periodic site visits, and the study monitor will ensure that all data in the CRF are correct and complete. All information recorded on the CRFs 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 CRFs. Once the CRFs are completed and source-verified, the investigator must sign all required pages in the CRF, verifying the accuracy of all data contained in the CRF.

Training will be provided for CRF completion at the study initiation visit. All study personnel completing the forms 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 for those assigned to support the required study activities.

If electronic data systems 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 7.4.

7.2 STATISTICAL ANALYSIS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP may contain any modifications to the analysis plan described below. All statistical analyses will be performed with the SAS statistical software package (Version 9.3, SAS Institute Inc., Cary, NC).

7.2.1 General Overview

Subject disposition, demographics, baseline characteristics and Study drug exposure will be summarized by treatment group. 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. All data collected will also be presented in listings by subject and visit.

7.2.2 Sample Size

The primary objective of the study is to determine the presence or absence of systemic cantharidin exposure from application of VP-102. Thus, power calculations were not performed. 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. There will be up to 40 subjects enrolled with the goal of 16 completing all blood draws in the exposure group. A maximum of 16 will be enrolled in the standard treatment group. The additional 8 subjects may be used for replacement patients. Any subject in the exposure group who does not complete all blood draws may continue to receive treatment, but will be replaced. No more than 16 subjects will be considered as completed Exposure group participants. At least 3 patients in the exposure group will be from 2-5 years of age. The definition of an enrolled will be those subjects that have signed informed consent and have been treated with at least 1 treatment.

Analysis Populations

Exposure Population: The Exposure population will include all subjects who have valid blood samples measured to assess exposure. This population will be used for the exposure analysis.

Intent-to-Treat Population: The intent-to-treat population (ITT) will include all subjects who meet the screening eligibility criteria and are enrolled in the study. This population will be used for the efficacy analysis.

Safety Populations: The safety population will include subjects who meet the screening eligibility criteria for the study and receive at least one application of Study drug. This population will be used for the safety analysis.

7.2.3 Exposure Analysis

Blood samples that will be obtained from subjects participating in the exposure group only. Samples will be obtained prior to the first treatment and at 2, 6 and 24 hours post application of study medication. Exposure will be assessed by looking for the presence of cantharidin in the plasma with a validated analytical method with a limit of detection of 1 ng/ml.

7.2.4 Efficacy Analysis

The efficacy endpoints to be analyzed are:

- Proportion of subjects exhibiting complete clearance of all treated molluscum lesions (baseline and new) on or before Week 12 (EOS).
- Proportion of subjects exhibiting a 90% or greater reduction of all treated molluscum lesions (baseline and new) at the EOS visit.
- Percent reduction of treated molluscum lesions from baseline at the EOS visit.
- Change from baseline in the number of treated molluscum lesions at the EOS visit.

- Change from baseline in quality of life and impact of skin disease as measured by the CDLQI assessment.

- Spread to siblings as measured by any new occurrence of molluscum in siblings of subject.

Data will be summarized using descriptive statistics and 95% confidence intervals for the above endpoints using the Intent-to-Treat Population.

7.2.5 Safety Analysis

Adverse event data for the safety population will be listed individually, and the incidence of adverse events will be summarized by treatment, using frequency counts. When calculating the incidence of adverse events, each adverse event will be counted only once for a given subject. If the same adverse event occurs on multiple occasions for a subject, the occurrence with the highest severity and relationship to Study drug will be reported. If two or more adverse events are reported as a unit, the individual terms will be reported as separate events. The Medical Dictionary of Regulatory Activities (MedDRA) (Version 19.1 or higher) will be used for coding AEs. Changes in vital signs, from baseline to the end of the study will be examined. Treatment-emergent changes from normal values to abnormal values will be identified as described in Section 2.3.1.

7.2.6 Interim Analysis

No interim analysis is planned for this study.

7.2.7 Handling of Missing Data

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

7.3 INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Written assent and informed consent and authorization of use and disclosure of protected health information must be obtained from each subject (or the subject's legally acceptable representative) before performing any study-specific screening/baseline period evaluations. One copy of the signed informed consent form (and IRB-required assent form) and authorization for use and disclosure of protected health information form will be given to the subject, and the investigator will retain the original. The informed consent form and authorization for use and disclosure of protected health information, which is prepared by the investigator or the site, must have been reviewed and approved by the sponsor, the study monitor, and the investigator's IRB and privacy board (if separate from the IRB) before the initiation of the study. The informed consent form must contain the 20 elements of informed consent described in International Council for Harmonisation E6, Section 4.8. The authorization for use and disclosure of protected health information must contain the elements required by Title 45 of the Code of Federal Regulations, Section 164.508(b), and any local regulations for valid authorizations.

7.4 STUDY DOCUMENTATION

7.4.1 Investigator Information

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

7.4.2 Investigator's Study Files

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

7.4.3 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 CRF for each subject will be checked against source documents at the site by the site monitor, and a final copy of the CRF will be signed by the investigator.

7.4.4 Retention of Study Documents

According to International Council for Harmonisation 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.

7.5 CONFIDENTIALITY

7.5.1 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).

7.5.2 Subject Anonymity

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

7.6 PROTOCOL COMPLIANCE

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

Departures from the protocol are allowed only in situations that eliminate an immediate risk to a subject and that are deemed crucial for the safety and well-being of that subject. The investigator or the attending physician also will contact the medical monitor as soon as possible in the case 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 in the subject's CRF the reasons for the protocol deviation and the ensuing events.

7.7 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 International Council for Harmonisation E6 guidance.

7.8 GENERAL INFORMATION

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

8.0 REFERENCES

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8.1 UNPUBLISHED MANUSCRIPT

Garelik J, Schairer D, Hwang H, Viola K, Cohen S. Safety and efficacy of topical cantharidin for the treatment of pediatric molluscum contagiosum: a prospective, randomized, double-blind, placebo-controlled trial.