**CONFIDENTIAL**

# CLINICAL PROTOCOL

**TITLE OF STUDY:**

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Pivotal Study to Evaluate the Safety and Efficacy of VP-102 Topical Film-Forming Solution [0.7% (w/v) Cantharidin] in Subjects (2 years and older) with Molluscum Contagiosum

Protocol VP-102-102

**Date of issue: 24 February 2017**
**Version number: (5) 01 February 2018**

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

## Signatures of Approval of Protocol (Version 5)

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

| Affiliation | Name | Signature | Date: |
|---|---|---|---|
| Sponsor: | Cindy Willson, RN, BSN | | 01 Feb 2018 |
| Medical Monitor: | Laurie Dunn, MD | | 01 Feb 2018 |

Sponsor:

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

Sponsor contact:

Cindy Willson, RN, BSN
Clinical Operations Director
10 N. High Street, Suite 200
West Chester, PA 19380
Phone: (628) 400-7617
Email : cwillson@verrica.com

Medical monitor:

Laurie Dunn, MD
Medical Monitor
Paidion Research, Inc.
240 Leigh Farm Road, Suite 175
Durham, NC 27707
Phone: (919) 928-6780
Email: laurie.dunn@paidion.com

## Acknowledgment of Responsibilities (Protocol Version 5)

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

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

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

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

| Institution Name | Investigator Name | Signature | Date |
|---|---|---|---|
| | | | |

# STUDY SYNOPSIS

| | |
|---|---|
| **Name of sponsor company:** Verrica Pharmaceuticals, Inc. | |
| **Name of finished product:** VP-102 (0.7% w/v cantharidin) | |
| **Name(s) of active ingredient(s):** Cantharidin | |
| **Title of study:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Pivotal Study to Evaluate the Safety and Efficacy 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 15 sites in the United States- (additional sites may be added if needed) | |
| **Study period: 84 Days (**12 weeks) | **Phase of development:** Phase 3 |
| **Objectives:** The primary objective is to evaluate the efficacy of dermal application of VP-102 relative to placebo, when applied once every 21 Days for up to 4 applications, to treatable molluscum contagiosum (molluscum) lesions on subjects 2 years and older by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit.<br><br>The secondary objectives are:<br>• to assess the safety and tolerability of VP-102, when applied once every 21 days for up to 4 applications, to treatable molluscum lesions on subjects 2 years old and older by assessing adverse events including expected local skin reactions, physical examinations, and concomitant medications at End of Study compared to baseline.<br>• to evaluate the efficacy of VP-102 relative to placebo by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions at Visit 2. Separate assessments for clearance will be repeated for both Visit 3 and Visit 4. | |
| **Methodology:** This is a Phase 3, randomized, double-blind, placebo (vehicle)-controlled, pivotal study to evaluate the safety and efficacy of VP-102 in 250 subjects (2 years and older) with molluscum lesions. Up to 15 sites will participate in the study. Additional sites may be added if needed. Subjects will receive Study drug in a 3:2 ratio of VP-102 containing 0.7% cantharidin or placebo/vehicle. Lesion counts will be conducted by a blinded member of the research team (blinded assessor). The blinded assessor is not required to be the same person for each assessment.<br><br>A dermatologic examination will be performed by a qualified investigator, which will include an assessment of local skin reactions at Treatment Visits 1, 2, 3, and 4. A dermatologic examination will also take place at the Day 84 End of Study Visit (EOS). The CDLQI survey will be administered at Treatment Visits 1, 2, 3 and 4 prior to VP-102 or placebo (Study drug) application (if applied) and at the end of study (EOS) visit. In addition, subjects will return to the clinic for a 24-hour assessment of evaluation of response to treatment (ERT) by the investigator or trained member of the research team within 48 hours (+/- 1 day) after the initial treatment visit. All subjects will receive application of the Study drug (VP-102 or placebo) to all treatable molluscum lesions every 21 days until complete clearance, or a maximum of 4 applications. Subjects will be given take home instructions describing what they might expect throughout the course of the study as well as recommendations for wound care, when it is important to call their doctor, and instructions for who to contact in an emergency. In addition, a Local Skin Reaction Guide will be provided and reviewed in detail at the clinic with the subject/guardian so the subject/guardian will be able to convey skin reactions in the ERT after treatments 2-4. Additional ERT phone assessments will be conducted at 7 and 14 days after the initial treatment. Subsequent treatment visit follow-ups will include ERT phone assessments at 24 hours, 7 and 14 days after each treatment. An in-person ERT will also be conducted at every visit prior to Study drug | |

## STUDY SYNOPSIS (continued)

**Name of sponsor company:** Verrica Pharmaceuticals, Inc.

**Name of finished product:** VP-102 (0.7% w/v cantharidin)

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

application. Assessments will be recorded by a research team member on the ERT form. ERT visits may not be conducted by a blinded assessor. Phone assessments will not be conducted if there is no treatment administered. The ERT includes questions related to removal of study drug and records the intensity of any local skin reactions, adverse events and concomitant medications (ConMeds). The subject and/or guardians will have time to ask questions and review any concerns. Concerns and events will be assessed and in the event any adverse events present a safety concern, an unscheduled clinic visit will be scheduled.

Each subject will be evaluated and treated as follows:

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

- Safety Evaluation Period (Treatment Visit 1)
  - Confirm that subject still meets criteria (Dermatologic exam/lesion count; ability to attend study visits).
  - Lesion count and CDLQI assessment.
  - Study drug application.
  - Removal of Study drug 24 hours after application.
  - 24-hour, in-office ERT, within 48 hours (+/- 1 day) after treatment.
  - ERT phone calls at Days 7 and 14 after treatment.

- Safety and Efficacy Evaluation Period (visits targeted 21 days after prior visit)
  - Treatment Visit 2: Lesion count by blinded assessor, dermatologic exam, CDLQI assessment, ERT, and Study drug application (if subject has treatable lesions remaining). Removal of Study drug 24 hours after application. ERT phone calls at 24 hours and Days 7 and 14 after treatment (if treated).
  - Treatment Visit 3: Lesion count by blinded assessor, dermatologic exam, CDLQI assessment, ERT, and Study drug application (if subject has treatable lesions remaining). Removal of Study drug 24 hours after application. ERT phone calls at 24 hours and Days 7 and 14 after treatment (if treated).
  - Treatment Visit 4: Lesion count by blinded assessor, dermatologic exam, CDLQI assessment, ERT, and Study drug application (if subject has treatable lesions remaining). Removal of Study drug 24 hours after application. ERT phone calls at 24 hours and Days 7 and 14 after treatment (if treated).

- End of Study (targeted 21 days after Treatment Visit 4 )
  - Lesion count by blinded assessor, dermatologic exam, CDLQI and ERT.

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

**Subject Participation:** Pre-study screening for eligibility (informed consent and assent, [assent when applicable], demographics, physical exam, prior and concomitant medications and molluscum and

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medical history) can occur up to 14 days before, or on the same day as Study drug application. Subjects that do not continue to meet criteria at Treatment Visit 1 will be discontinued and treated per standard of care. All lesions must be treatable at the time of randomization or the subject is not eligible to participate. Those subjects that meet the enrollment criteria will be randomized and treated with application of VP-102 or placebo to all molluscum lesions at Treatment Visit 1. Treatment will continue every 21 days to all treatable molluscum lesions until complete clearance or a maximum of 4 treatment sessions. The EOS study visit will be completed 21 days after Treatment Visit 4, (EOS; Day 84). In the event of scheduling conflicts in subsequent treatment visits, subjects may be scheduled 21 ± 4 days following their previous treatment for their next Treatment Visit and for their EOS visit.

In the event subjects miss a treatment visit and are outside the 4-day study window, they may return and be treated at the next available opportunity with the subsequent visit scheduled 21 days after the actual treatment visit. No study visits will be conducted after Day 100.

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

1. Be healthy subjects, at least 2 years of age or older.
2. Consent to having all molluscum lesions treated and the physician must be willing to treat all molluscum lesions initially present. *Lesions within 10mm of the eyelid margins or the margin of any mucosal membrane should be evaluated carefully to ensure that they can be safely treated. Non-mucosal genital area lesions and inflamed lesions are considered treatable.*
3. Be otherwise medically healthy with no clinically significant medical history as determined by the investigator. *Subjects exhibiting active Atopic Dermatitis may be enrolled.*
4. On day of treatment 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 within 5cm of treated skin lesions.
5. Refrain from swimming, bathing or prolonged immersion in water or any liquids until the Study drug is removed.
6. Have the ability or have a guardian with the ability to follow study instructions and be likely to complete all study requirements.
7. Provide written informed consent or assent in a manner approved by the institutional review board (IRB) and/or have a parent/guardian provide written informed consent as evidenced by the signature on an IRB approved assent/consent form.
8. Provide written authorization for use and disclosure of protected health information.
9. Agree to allow photographs to be taken, (selected sites only) of selected lesions at every visit that will be used for training, publication and future marketing brochures. *Photographs will be de-identified to those outside the research team. Efforts 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)

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**Exclusion criteria:**
Candidates will be excluded from the study if they:

1. Are unable to cooperate with the requirements or visits of the study, as determined by the investigator.
2. Are systemically immunosuppressed or are receiving treatments such as chemotherapy or other non-topical immunosuppressive agents.
3. Have any lesions present at baseline in anatomic locations that the subject/parent/guardian or the physician is unwilling to treat.
4. Have had any previous treatment of molluscum including the use of cantharidin, antivirals, retinoids, curettage or freezing of lesions in the past 14 days. Additional treatments should not be implemented during the course of the study.
5. Have a 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.
6. 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.
7. Have a history or presence of hypersensitivity or an idiosyncratic reaction to the Study drug or related compounds, or drug product excipients (acetone, ethyl alcohol, nitrocellulose, hydroxypropyl cellulose, castor oil, camphor, gentian violet, and denatonium benzoate).
8. Have a condition or situation that may interfere significantly with the subject's participation in the study (e.g., subjects who required hospitalization in the 2 months prior to screening for an acute or chronic condition including alcohol or drug abuse), at the discretion of the investigator.
9. Have received another investigational product within 14 days prior to the first application of the Study drug.
10. Have been treated within 14 days with a product that contains cantharidin (topical or homeopathic preparations) for any reason prior to screening.
11. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods. (e.g., combination of condoms and foam, birth control pills, intrauterine device, patch, shot and vaginal ring, etc.). Withdrawal is not an acceptable method of birth control. Females that have reached menarche must have a negative urine pregnancy test at each visit prior to treatment with Study drug.
12. Are pregnant or breastfeeding.

**Test product, dose, and mode of administration:** Study drug (VP-102 or placebo) 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. The placebo single-use applicator contains 450µl of placebo solution with the same color and consistency as VP-102. Up to 2 applicators may be used per subject, but a second applicator may only be necessary if treating >50 lesions.

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**Duration of treatment:** The length of study participation from Treatment Visit 1 is 84 days (12 weeks). Up to 4 applications of Study drug at 21-day intervals will be followed by an EOS visit on Day 84. Subjects are instructed to wash all treated lesions with soap and warm water 24 hours after treatment. 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. Washing of intact blisters should be gentle and without use of a washcloth. Washing in a bath or shower is encouraged.

**Criteria for evaluation**

**Efficacy:** All randomized subjects (Intent-To-Treat) will be evaluated for efficacy. Clinical response to treatment of molluscum lesions will be evaluated at each scheduled visit until EOS by counting all treatable molluscum lesions.

Primary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit (EOS).

Secondary endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 63 visit.
- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 42 visit.
- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 21 visit.

Exploratory endpoints:

- Change from baseline of the composite score from the Children's Dermatology Life Quality Index (CDLQI) assessment at the EOS visit to measure the quality of life and impact of skin disease in the subset of subjects 4 -16 years of age.
- Percent reduction of all treatable molluscum lesions (baseline and new) from baseline at the EOS visit.
- Change from baseline in the number of treatable molluscum lesions (baseline and new) at the EOS visit.
- Proportion of subjects exhibiting a 75% or greater reduction of all treatable molluscum lesions (baseline and new) at the EOS visit.
- Proportion of subjects exhibiting a 90% or greater reduction of all treatable molluscum lesions (baseline and new) at the EOS visit.
- Subject reported spread to household members as measured by any new occurrence of molluscum in household members of subject.

**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:

## STUDY SYNOPSIS (continued)

**Name of sponsor company:** Verrica Pharmaceuticals, Inc.

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

- Local Skin Reactions (LSRs) of all previously treated areas will be assessed at each treatment visit using the protocol specific ERT form. Additional, 24-hour in-person assessments will be conducted within 48 hours (+/- 1 day) after the initial treatment and at the EOS visit by the Investigator or trained personnel with the ERT form.
  - Subjects will have reviewed and be given take home instructions describing the potential local skin reactions and what they might expect throughout the course of the study as well as recommendations for wound care, when it is important to call their doctor, and instructions for who to contact in an emergency.

- Sites will conduct ERT phone calls at 24 hours after Treatment Visits 2-4 as well as 7 and 14 days after Treatment Visits 1-4 to assess treatment response, document any local skin reactions and any medical interventions taken. ERT assessments will also be conducted 21 days after Treatment Visits 1-4 in-person prior to re-treatment.
  - A Local Skin Reaction Guide for subjects with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. Should a subject report experiencing excessive blistering or another adverse event needing physician assessment, they will be scheduled for an unplanned study visit and safety evaluation at the next available opportunity.

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

**Safety considerations:** Investigators should confirm the Study drug is completely dry (2-5 minutes) prior to the subject touching furniture with treated skin, 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 if ingested. To deter potential oral ingestion, a bitter compound has been added to the Study drug. Subjects should refrain from touching, licking, or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes, and anogenital area for up to 24-hours after treatment or until the Study drug is removed.

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Subjects should wash clothing, bedding and towels on a regular basis with hot water to minimize re-inoculation. Subjects are encouraged to wash their hands regularly with soap and water and discouraged from scratching or picking at lesions, which can spread disease.

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:** The primary objective of this study is to determine the efficacy of VP-102-treated subjects relative to placebo-treated subjects. The primary endpoint of this study is the proportion of subjects who achieve investigator assessed complete clearance of all treatable lesions on the Day 84 EOS visit.

The study is expected to enroll and randomize 250 subjects with molluscum lesions to test for treatment differences in the rates of complete clearance (primary endpoint). Subjects will be randomized and treated in a double-blind manner with either VP-102 or placebo in a 3:2 ratio (approximately 150 subjects on VP-102 to 100 subjects on placebo).

Study assumptions include the following:

- a 10% drop out rate
- a 20% clearance rate for subjects treated with placebo. This is based on reported placebo treated clearance rates for placebo controlled studies, such as Aldara (26% clearance at 18 weeks, extrapolated down to the 12 weeks treatment duration of this study) and several other placebo studies suggesting a similar clearance rate including Short 2006, Syed 1998, Dosal 2012, Burke 2004 and Theos 2004.
- a 44% clearance rate for subjects treated with VP-102. This is based on a calculated clearance rate of 44% (11 cleared out of 25 completed subjects in NCT03017846)

Using these assumptions, a sample size of 250 subjects with 3:2 stratification of active/placebo in each protocol based on a Pearson Chi-Square test with a two-sided significance level of 0.05 will provide >=95% power to detect treatment differences in clearance rates.

All statistical tests will be two-sided with a significance level of $\alpha = 0.05$, unless specified otherwise. Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) for continuous variables and frequencies and percentages for discrete variables. Corresponding by-subject data listings will be tabulated.

A Pearson Chi-Square test will be used to compare the treated and placebo groups for the primary efficacy endpoint. Other binary endpoints also will be analyzed with this method.

Continuous endpoints will be analyzed with an ANOVA model with a factor for treatment or an ANCOVA model with a factor for treatment and a covariate for number of baseline lesions. Further details of analyses of other endpoints will be provided in the statistical analysis plan.

## **STUDY SYNOPSIS** (continued)

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| **Name of sponsor company:** Verrica Pharmaceuticals, Inc. |
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| **Name(s) of active ingredient(s):** Cantharidin |
| Adverse events, including local skin reactions, will be coded with the MedDRA® dictionary. The number and percentage of subjects having treatment-emergent AEs will be tabulated by system, organ class and MedDRA preferred term with a breakdown by treatment group. |

## Table 1 Study Schedule of Assessments and Procedures

| Activities | Screening [a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Up to 14 days before Day 1 | Treatment 1: Day 1 [b] | 24-hour in-person Visit [m] | Day 7 Phone Call [m] | Day 14 Phone Call [m] | Treatment 2: Day 21 | 24hr Phone Call [m] | Day 7 Phone Call [m] | Day 14 Phone Call [m] | Treatment 3: Day 42 [b] | 24hr Phone Call [m] | Day 7 Phone Call [m] | Day 14 Phone Call [m] | Treatment 4: Day 63: EOT [b] | 24hr Phone Call [m] | Day 7 Phone Call [m] | Day 14 Phone Call [m] | End of Study: Day 84: [c] | Unscheduled Visit [h] |
| Informed Consent and Authorization | X | | | | | | | | | | | | | | | | | | |
| Inclusion/ Exclusion Criteria | | X | | | | | | | | | | | | | | | | | |
| Demographics [d] | X | | | | | | | | | | | | | | | | | | |
| Height/Weight | X | | | | | | | | | | | | | | | | | X | |
| Prior Relevant Medical History | X | X | | | | | | | | | | | | | | | | | |
| Molluscum History | X | X | | | | | | | | | | | | | | | | | |
| Prior and Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs (T,P) [e] | | X | | | | X | | | | X | | | | X | | | | X | X |
| Physical Exam [f] | X | | | | | | | | | | | | | | | | | X | |
| Lesion Count [g] | | X | | | | X | | | | X | | | | X | | | | X | |
| Dermatologic Examt [g] | | X | | | | X | | | | X | | | | X | | | | X | X |
| CDLQI Assessment [i] | | X | | | | X | | | | X | | | | X | | | | X | |
| Sibling Assessment | | X | | | | X | | | | X | | | | X | | | | X | |
| Urine Pregnancy Test [j] | | X | | | | X | | | | X | | | | X | | | | X | |
| Photographs [k] | | X | X | | | X | | | | X | | | | X | | | | X | |
| Study Drug Application [l] | | X | | | | X | | | | X | | | | X | | | | | |
| ERT Assessments [m] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Take Home Instructions, LSR guide/subject education [n] | | X | | | | X | | | | X | | | | X | | | | | |

CDLQI: children's dermatology life quality index; EOS = end of study; EOT = end of treatment; LSR = local skin reactions; ERT: 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/Assent must be signed before any study specific procedures are performed.
b. Out of Window Parameters: Subjects may be scheduled 21+/- 4 days after treatment in the event of scheduling conflict. If possible, the next treatment visit should be scheduled 21 days after the last treatment. The 24-hour onsite visit may be conducted within 48 hours of Treatment 1. The 24 hour phone contact may be conducted at +/- 4 hours. The Day 7 and Day 14 phone contact may be conducted at +/- 24 hours. If it is found during any treatment visit that all treatable molluscum lesions are cleared, the investigator will only conduct safety and ERT assessments and will not apply additional treatment.
c.. Subjects who clear all lesions at study visits prior to Day 84 will return to the office for each treatment visit (even if no treatment is applied) to complete all study related assessments. A final safety assessment and study completion form will be completed at the Day 84 (EOS) visit.
d. Demographics: date of birth, sex, race/ethnicity will be collected.
e. Vital signs (e.g., temperature & heart rate) will be obtained at each treatment prior to application of Study drug.
f. Limited physical examination. Symptom or AE-directed physical examination may be performed if warranted. (See Source/CRF for a more detailed description)
g. Regional lesion counts (head/neck, chest/abdomen, back/buttocks, groin, upper/lower extremities) should be performed. Lesion counts completed at Treatment Visits 2, 3, 4 and EOS should be performed prior to the dermatologic exam and ERT assessments and will be obtained by a blinded assessor. The blinded assessor does not have to be the same person at each visit.
h. Unscheduled visits may be completed when clinically warranted (e.g. if a subject reports signs or symptoms classified as a treatment emergent AE and requires further evaluation)
i. CDLQI assessment to be completed by the subject or guardian prior to Study drug application and each treatment visit regardless whether treatment was administered.
j. To be performed prior to Study drug application and at EOS in any females of childbearing potential (females that are capable of menstruating).
k. Photographs of molluscum lesions will be obtained by the research team at selected clinical sites only for every visit for every randomized subject. Photos of the 3 most severe areas will be obtained. If there are no lesions remaining, the same areas will be photographed until EOS regardless of whether lesions are present.
l. 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.
m. An Evaluation of Response to Treatment (ERT) in-person 24-hour assessment will be conducted within 48 hours (+/- 1 day) after the initial treatment application and after Study drug has been removed. Phone assessments will be conducted at 7 and 14 Days after Treatment Visit 1. Phone assessments will be conducted at 24 hours, 7 Days and 14 Days after Treatment Visits 2, 3 and 4. Phone assessments will not be conducted for those subjects that did not receive treatment on their last visit. Assessments will be recorded by the research team member on the Evaluation of Response to Treatment (ERT) form. All ERT safety assessments must be conducted by a qualified member of the research team who is not utilized as a blinded assessor during the subject's study participation. The blinded assessor may be utilized for a subject's initial screening and enrollment but no additional study related activities other than lesion counts. The blinded assessor does not have to be the same person at each visit.
n. Subjects will be given take-home instructions describing the possible local skin reactions and what to expect over the next 24 hours to several months. A 24-hour emergency number will also be provided. The next visit date/calls and time will be indicated on the form. A Local Skin Reaction Guide for subjects will be reviewed at the clinic with the subject /guardian by the research team with copies provided for home use in the required follow-up phone calls. Both take home instructions and LSR Guide will be provided and reviewed after each treatment to ensure understanding and confirm the education materials are available.

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# LIST OF ABBREVIATIONS

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| AE | adverse event |
| AMES | Genetic Toxicity Study: in vitro Bacterial Reverse Mutation |
| CDLQI | children's dermatology life quality index |
| cm | centimeter |
| eCRF | electronic case report form |
| EOS | end of study |
| EOT | end of treatment |
| EDC | electronic data capture |
| ERT | Evaluation of response to treatment |
| FDA | Food and Drug Administration |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| ID | identification |
| IFU | instructions for use |
| IRB | institutional review board |
| mg | milligrams |
| mm | millimeter |
| Molluscum | molluscum contagiosum |
| LSRs | local skin reactions |
| SAE | serious adverse event |
| SOP | standard operating procedure |
| TEAE | treatment emergent adverse event |
| T24 | human bladder carcinoma cells |
| TSGH 8301 | human urinary bladder carcinoma cell line |
| uL | units per liter |
| 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 1,000 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 subjects, this process does not cause a scar, as the underlying dermal layer of skin is undamaged. Cantharidin has no known direct antiviral effects.

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

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

increases the risk of cross-contamination and viral transmission. Furthermore, due to the presence of volatile solvents in the preparation, evaporation from multiple uses heightens the risk of increased concentration and viscosity of the cantharidin in solution and creates a scenario where highly-concentrated material may be applied to the patient's skin. Many formulations also lack formal stability studies and medical professionals often will just use the material until it is "too thick" to apply. As a consequence, 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. Study drug (VP-102 or placebo) will be administered with a single-use applicator to minimize cross-contamination and concentration changes during use. Each VP-102 applicator contains 450 µL (microliters) of drug product, with each VP-102 unit containing 3.15 mg of cantharidin. Gentian violet, a dye common in surgical markers, has also been included to facilitate physician recognition of treated vs. untreated molluscum lesions. Finally, to afford additional safety and deter potential oral ingestion of the drug by young subjects, the oral deterrent denatonium benzoate has been included.

### 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 topically applied cantharidin on rat ears showed a decreased anti-inflammatory response from dexamethasone, hydrocortisone, and prednisolone.[8]

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 vitro studies in cultured Chinese hamster cells[26] showed that cantharidin was not clastogenic at the doses tested, but a significant increase in chromosomal aberrations was noted only at the highest concentration tested (10% versus 1 – 2% in the vehicle group), a concentration that was considered cytotoxic, *i.e.* cell survival was 36.1%. Cantharidin at 1 µg/mL (100% survival) and 2 µg/mL (36.1% survival) induced endoreduplication (39% and 65% of the cells, respectively), an indication that this agent can interfere *in vitro* with the formation of the mitotic spindle apparatus and that it may be aneugenic.

Cantharidin was evaluated in several GLP-compliant genotoxicity studies. Cantharidin was negative in bacterial reverse mutation assays (AMES test) and does not possess mutagenic potential. Cantharidin was also evaluated in a chromosomal aberration assay with human peripheral blood lymphocytes, but due to assay limitations, no conclusions can be made about its clastogenic potential in human cells.

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 focused on the 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]

### 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.

*Prospective studies*

An ongoing pharmacokinetic study is being conducted to determine if subjects in the upper quartile of severity of molluscum infection (defined as having greater or equal to 21 lesions) who are treated with VP-102 have any systemic exposure to cantharidin in blood. As of 1 September 2017, plasma samples from 7 subjects with severe disease (greater than 21 lesions treated) have been evaluated (NCT03186378) with an application duration of 24 hours. Cantharidin was below the lower limit of quantification (1 ng/ml) in the plasma from these subjects at 2, 6 and 24 hours following application. This study is still ongoing with a goal of collecting plasma from 16 subjects. Thus far, the data support the conclusion that cantharidin plasma levels are below the lower limit of quantification following the treatment of molluscum with VP-102 and that VP-102 treatment presents no risk of systemic toxicity.

A recently completed bridging study was implemented to confirm that VP-102 is similar in safety and efficacy to a 0.7% cantharidin compounded formulation studied previously. In this study, VP-102 appeared to be safe and well tolerated, with no unexpected treatment related adverse events reported during its application to over 1,700 molluscum lesions in 30 subjects. 25 subjects completed the study and were evaluable for lesion clearance. The first cohort of subjects in this study was treated with a 6-hour application duration. The second cohort was treated with a 24-hour application duration. There was no significant safety difference between these treatment cohorts and both treatment durations were well tolerated with many subjects experiencing application site blistering and some experiencing transient mild pain and pruritus. The complete clearance rate within 12 weeks in the 6-hour cohort for subjects that completed the study (N=13) was 46.2% (6/13). The complete clearance rate within 12 weeks in the 24-hour cohort for subjects that completed the study (N=12) was 41.6% (5/12). In conclusion, the ability of VP-102 to completely clear molluscum has not been shown to be significantly different from the compounded 0.7% cantharidin formulation. In addition, both compounded cantharidin and VP-102 perform significantly better than the best estimate of placebo. Thus, this bridging study met its

primary objective in demonstrating that VP-102 appears to be safe and effective in the treatment of pediatric molluscum (NCT# 03017846).

Schairer et al.[16] published an interim analysis of a two phase, double-blind, placebo-controlled study of 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) administered 3 weeks apart. Lesion counts and adverse events were assessed every 3 weeks. Most recently, Garelik et al. (unpublished manuscript) provided a full analysis of the entire population treated in the Schairer et al., 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 (following 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 for a total of up to 5 overall) with 87.8% of subjects achieving complete resolution. There were no reported treatment related adverse events, demonstrating that cantharidin is an effective and safe modality 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 lesion 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 addressed 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.

*Retrospective studies*

Results of prospective studies are supported by retrospective reports of the 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 subject. 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 subjects 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 after-treatment with a 78% satisfaction rating. Overall, 46% of subjects 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 subjects experienced complete clearing, 8% experienced significant improvement and 2% reported that the therapy was ineffective. 92% of subjects 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 subjects 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 objectives of the current study will be to evaluate the safety and efficacy of dermal application of VP-102, when administered 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, physical examinations, Evaluation of Response to Treatment (ERT), and concomitant medications compared to baseline.

## 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 a recently completed study of VP-102 (NCT# 03017846) with 30 subjects treated.

The anticipated VP-102 label will focus on treatment of subjects with one or more treatable 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 no more than 2 applicators may be used per treatment on each subject.

OBJECTIVES

## 1.5 PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of dermal application of VP-102 relative to placebo, when applied once every 21 Days for up to 4 applications, to treatable molluscum contagiosum (molluscum) lesions on subjects 2 years and older by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 (EOS) visit.

## 1.6 SECONDARY OBJECTIVES

The secondary objectives are as follows:

- to assess the safety and tolerability of VP-102, when applied once every 21 days for up to 4 applications, to treatable molluscum lesions on subjects 2 years old or older by assessing adverse events, including local skin reactions, physical examinations, and concomitant medications at EOS compared to baseline.

- to evaluate the efficacy of VP-102 relative to placebo by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions at Visit

2. Separate assessments for clearance will be repeated for both Visit 3 and Visit 4.

# 2.0 STUDY DESIGN

## 2.1 BASIC DESIGN CHARACTERISTICS

This is a Phase 3, multi-center, randomized, double-blind, placebo (vehicle)-controlled, pivotal study that will be conducted in the United States to determine the efficacy and safety of VP-102 following treatment of molluscum lesions for up to 4 treatments, every 21 days, with VP-102/placebo in 250 pediatric subjects (2 years or older). Subjects will receive active 0.7% cantharidin VP-102 or placebo in a 3:2 ratio. Duration of molluscum lesions prior to Treatment Visit 1 will be recorded but will not be an inclusion/exclusion requirement.

Study drug (VP-102 or placebo) will be supplied in single-use applicators, with one applicator sufficient to treat up to approximately 50 molluscum lesions. If required, due to the number and size of lesions, a second single-use applicator may be used per subject. 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 24 hours before the subject/guardian washes the lesions with soap and warm water. Study drug may be removed prior to the 24-hour time point in the event significant blistering, significant pain or treatment-emergent AEs are experienced.

Molluscum lesions will be treated without occlusion in all anatomic areas including the face, trunk, back, arms, legs, hands, feet, anogenital region and buttocks. For study enrollment, the physician must be willing to treat all lesions initially present. Lesions that develop during the course of the study within 10mm of the eyelid margins or the margin of any mucosal surface should be evaluated carefully to ensure that they can be safely treated. Non-mucosal genital area lesions and inflamed lesions are considered treatable.

The study duration from Treatment Visit 1 through the Day 84 (EOS) visit is approximately 84 days (12 weeks). Pre-study screening for eligibility (informed consent, and assent (if assent is applicable), demographics, physical exam, prior and concomitant medications and molluscum and medical history) will occur up to 14 days before, or on Treatment Visit 1. Subjects who do not meet the inclusion criteria at Treatment Visit 1 will be discontinued and treated per standard of care. Those subjects

that continue to meet criteria will be randomized per IWRS and treated with application of VP-102 or placebo solution to all molluscum lesions every 21 days (± 4 days) for a maximum of 4 treatment sessions. Subjects who completely clear all treatable lesions prior to Day 84 will complete the remainder of the Treatment Visits in order to monitor safety. If new lesions appear on a previously cleared subject, they should be treated. In the event of scheduling conflicts in subsequent visits after the first 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. In the event a subject misses a treatment visit and is outside the 4-day study window, they may return and be treated at the next available opportunity with the subsequent treatment visit scheduled 21 days later to facilitate up to 4 treatments within 84 Days.

The final study visit assessment must be completed on or before Day 100. Should it become clear that the subject would be unable to complete the EOS on or before Day 100, the subject should be brought in for their EOS visit on or before Day 100, regardless of the number of days since their last Treatment Visit (eg., a missed treatment may cause the subject to fall outside this window of 16 days).

Subjects who are unable to attend the in-office EOS visit may have the option of an EOS home visit by a qualified member of the research team if this is within the site's standard of practice. Consent for Home Visit will be included in the initial consent process. Subjects who continue to require treatment outside the specified study windows must be treated allowing for EOS to occur before or on Day 100. Subjects who are not assessed as 100% cleared of all treatable lesions at the EOS visit will have completed the study and will be further treated per standard of care at their physician's discretion but may not be re-enrolled in this study.

Evaluation of Response to Treatment (ERT) will be performed by the investigator or trained member of the research team, who is not a blinded assessor for that subject, at each treatment visit. An additional 24-hour in-office assessment will be conducted within 48 hours (+1 day) after the first treatment and at the EOS visit. Qualified study personnel who are not blinded assessors for the subject, will conduct ERT phone calls at 7 and 14 days after Treatment Visits 1. In addition, ERT phone calls at 24-hours as well as 7 and 14 days after Treatment Visits 2, 3 and 4 will be performed to assess treatment response, document any local skin reactions and any medical interventions taken if treatment was administered. The following clinical responses will be recorded

as part of the Evaluation of Response to Treatment (ERT) with type and intensity recorded on the AE log: blistering, pain, pruritus, erythema, edema, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting, and pigmentation changes (hyperpigmentation or hypopigmentation). Scarring will be assessed at each treatment visit and the EOS visit by a qualified medical professional. Scarring information will not be collected as part of the phone assessment. Additional information related to AE's and ConMeds will also be collected during each assessment.

Subject quality of life and measure of impact of skin disease will be collected using the Children's Dermatology Life Quality Index Questionnaire. The CDLQI questionnaire is validated for use in children ages 4-16 years of age but will be administered to all study subjects and/or their guardians regardless of age. It should be handed to the subject who is asked to fill it in with the help of a parent/guardian as needed. The subject or guardian will be given completion instructions to evaluate their skin condition as it specifically relates to molluscum contagiosum. They will be guided to disregard the impact of any other concomitant skin conditions like atopic dermatitis during completion. The CDLQI should be scored by the site using the guidelines in Appendix 1.

Subjects will be given take-home instructions describing the potential local skin reactions and what they might expect throughout the course of the study. The instructions include recommendations for wound care, when it is important to call their doctor, who to contact in the event of emergency and a 24-hour emergency number. The additional scheduled visits and calls up through the next treatment visit, or EOS, will also be indicated on this form. Take-home instructions will be reviewed and provided at each treatment visit.

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

Subjects 18 and older must provide consent as required by the IRB before any study procedures are conducted. Parents or guardians must provide informed consent, and pediatric subjects older than 10 years must provide assent as required by the IRB before

any study procedures are conducted. Subjects must meet all study eligibility criteria through a complete review of pertinent medical history, a dermatologic exam/lesion count and limited physical examination. Full inclusion/exclusion criteria are provided in Section 2.2.

## 2.2 STUDY POPULATION

250 subjects are expected to be enrolled and randomized into the VP-102-102 protocol (approximately 150 receiving VP-102 and 100 receiving placebo). Eligibility to participate in the study will be determined by the investigator on the basis of the inclusion and exclusion criteria. A second identically designed study is also anticipated to be conducted.

### 2.2.1 Inclusion Criteria

To qualify for inclusion in this study, subjects must:

1. Be healthy subjects, 2 years of age or older.

2. Consent to having all molluscum lesions treated and the physician must be willing to treat all molluscum lesions initially present. *(e.g., lesions within 10mm of the eyelid margins or the margin of any mucosal membrane should be evaluated carefully to ensure that they can be safely treated. Non-mucosal genital area lesions and inflamed lesions are considered treatable).*

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

4. On day of treatment 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 within 5cm of treated skin lesions.
5. Refrain from swimming, bathing or prolonged immersion in water until the Study drug is removed.

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

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

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

9. Agree to allow photographs to be taken (selected sites only) of selected lesions at every visit that will be used for training, publications and marketing brochures. *Photographs will be de-identified to those outside the research team. Efforts will be made to ensure that no photographs 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. Are systemically immunosuppressed or are receiving treatments such as chemotherapy or other non-topical immunosuppressive agents.

3. Have any lesions present at baseline in anatomic locations that the subject/guardian or the physician is unwilling to treat.

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

5. 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.

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

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

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

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

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

11. Are sexually active or may become sexually active and are unwilling to practice responsible birth control methods (e.g., combination of condoms and foam, birth control pills, intrauterine device, patch, shot and vaginal ring, etc.) Withdrawal is not an acceptable method of birth control. Females who have reached menarche must have a negative urine pregnancy test at each visit prior to treatment with study drug.

12. Are pregnant or breastfeeding.

## 2.3 ENDPOINTS

Primary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit (EOS).

Secondary endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 63 visit.

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 42 visit.

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 21 visit.

Exploratory endpoints:

- Change from baseline of the composite score from the Children's Dermatology Life Quality Index (CDLQI) assessment at the EOS visit to measure the quality of life and impact of skin disease in the subset of subjects 4-16 years of age.

- Percent reduction of all treatable molluscum lesions (baseline and new) from baseline at the EOS visit.

- Change from baseline in the number of treatable molluscum lesions (baseline and new) at the EOS visit.

- Proportion of subjects exhibiting a 75% or greater reduction of all treatable molluscum lesions (baseline and new) at the EOS visit.

- Proportion of subjects exhibiting a 90% or greater reduction of all treatable molluscum lesions (baseline and new) at the EOS visit.

- Subject reported spread to household members as measured by any new occurrence of molluscum in household members of subject.

### 2.3.1 Safety

The following safety parameters will be assessed:

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

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

- If the subject discontinues the study prematurely (after the first treatment) for any reason, attempts will be made to encourage the subject/guardian to complete the EOS assessments. At home assessments by a trained member of the study team may be considered in order to complete the EOS assessment.

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

- Assessment of LSRs will be recorded at each Treatment Visit using the protocol specific ERT form. Additional assessments will be conducted at 24-hours as well as day 7 and 14 after treatment either in person or by phone contact using the ERT form. LSRs will be considered AEs even though some LSRs may be part of the normal response to treatment and correlated with efficacy. The following LSRs will be recorded: blistering, pain, pruritus, erythema, edema, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting, and pigmentation changes (hyperpigmentation or hypopigmentation). These responses will be queried for duration and intensity. Scarring will be evaluated in person by a qualified practitioner who is a trained member of the research team at in office treatment visits and the EOS visit.

- Medical interventions taken throughout the course of the study prior to initial treatment, at 24-48 hours and 7, 14 and 21 days after treatment.

### 2.3.2 Efficacy

Efficacy parameters will be recorded for all randomized subjects. Clinical response to treatment of molluscum lesions will be evaluated at each scheduled visit until EOS by counting all treatable molluscum lesions. Untreatable lesions will be tracked and recorded.

## 2.4 RANDOMIZATION AND BLINDING

Randomization through an interactive web response system (IWRS) will be used to assign treatment in a 3:2 ratio (expected 150 subjects treated with VP-102 to 100 subjects treated with placebo). Trial sites will have access to an internet-based randomization system. Randomization will be conducted in a centralized manner.

Subjects with molluscum lesions present from the same household may be enrolled in the study. For ethical and practical considerations, subjects in the same household will be assigned to the same treatment group. After a subject is randomized to a treatment, any other subject enrolled in the study from that household will be assigned the same randomization number and be given the same treatment. As a result, the unit of randomization is the household- not the subject. Randomizing by household at the site level could lead to strong differences from the desired treatment ratio at individual sites. Therefore, randomization by household will be carried out at the study level. Since randomization is not done by site, analyses will not be stratified by site.

If a medical emergency occurs and a decision about a subject's condition requires knowledge of the treatment assignment, the investigator will contact the study assigned medical monitor at (919) 928-6780 to discuss the need and procedure for unblinding. The study blind may be broken for that specific subject only. Any broken blind will be clearly justified and explained by a comment on the appropriate page of the case report form. In addition, the investigator will immediately notify the medical monitor of the situation.

In order to reduce possible functional unblinding and bias, blinded assessors will conduct lesion counts while separate trained members of the research team will conduct safety assessments and evaluations of response to treatment. A blinded assessor is a trained research team member that is not aware of a subject's ongoing response to treatment. The blinded assessor's role is to count and record the number of lesions at Treatment Visits 2, 3, 4 and EOS. It is not required that the blinded assessor be the same person for each subject study visit.

The Day 84 EOS visit will require a final assessment of ERT and confirmation of the presence or absence of molluscum lesions. Each investigator conducting this final lesion count, must be a qualified member of the research team and will asked to complete an attestation to determine if they remain blinded as to the subject's treatment group.

REPLACEMENT OF DROPOUTS

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

All randomized subjects will be evaluated in the intent-to-treat population. Those subjects who do not complete the full treatment due to lack of protocol adherence or who request to be discontinued from the study will be not be replaced. In the event a subject requests to be removed from the study due to study-related adverse experiences or additional spreading of disease, data will be collected and analyzed as a treatment failure and the subject will not be replaced. Further discussion of how treatment failure will be utilized in analysis will be provided in the statistical analysis plan.

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

# 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. The placebo contains all ingredients except cantharidin. Once applied to the skin, solvents in the Study drug evaporate leaving behind a thin, flexible and resilient film. The Study drug is light violet to dark purple in color and has been manufactured under good manufacturing practices (GMP).

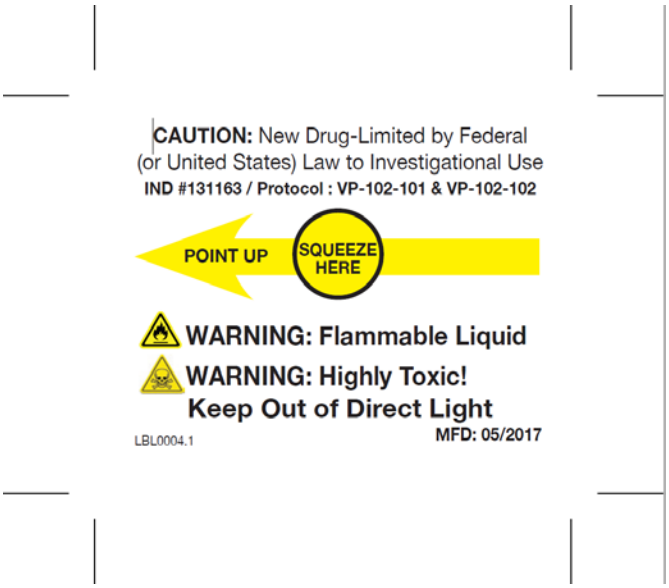
VP-102 is manufactured in a GMP facility. The cantharidin used in VP-102 is more than 99% pure and manufactured under GMP. VP-102 is stable for at least 180 days when stored at controlled room temperature and out of direct light. VP-102 is undergoing a GMP stability study and the stability date of this product may be updated in accordance with current FDA guidelines with appropriate data. The Study drug will be released after passing quality control measures for description, uniformity of fill content, viscosity, assay, identification, impurities and microbial limits. Study drug is delivered in a single-use glass ampule stored within a single-use plastic applicator with integrated in-line filter to remove any glass particles capable of breaking the skin. Each applicator is packaged in a tamper evident zip-top bag. There are 5 applicators in each carton. The IWRS system assigns one carton to each subject at the time of randomization. Should a subject require more than 1 kit, the site will notify the Sponsor so that an additional Study kit may be assigned and a replacement kit obtained or shipped per study kit replenishment procedures.

### 3.1.2 Labeling

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

**Figure 1. Clinical Trial Labeling of Study Drug**

Label on Applicator




Label on Bag Around Each Applicator

Label on Carton

**CAUTION: New Drug- Limited by Federal (or United States) Law to Investigational Use**

KIT NUMBER:

MANUFACTURED: 05/2017

IND #: 131163 / Protocol: VP-102-101 & VP-102-102

Patient Identifier: _____

Carton contains five (5) applicators.
Each applicator contains 0.45mL of
either VP-102 (0.7% Cantharidin Solution) or placebo

**To be applied only by the investigator.**

Store at 20°- 25°C (68° - 77°F) Excursions permitted to 15°-30°C (59-86°F)

**Keep Out of Direct Light and Away from Heat.**

*Do not destroy. Return packaging and any unused medication.*

**WARNINGS: Highly Flammable, even after drying. Avoid fire, flame or smoking during treatment. Highly Toxic! Avoid inhaling vapors. If product gets into the eyes, flush with water for 15 minutes. For Topical Use Only. Cantharidin can be fatal if administered orally or taken internally.**

LBL0005.2

Manufactured for Verrica Pharmaceuticals, Inc. Charlottesville, VA 22902 USA

## 3.2 DOSING INSTRUCTIONS AND SCHEDULE

Upon activation, clinical sites will be provided with an initial supply of single-use applicators that each contains 450 µL of the Study drug (VP-102). Each applicator can treat up to approximately 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.

Please see the Instructions for Use (IFU), located in the accompanied Investigational Brochure for step-by-step instructions.

**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. Subjects should confirm the study drug is completely dry prior to touching furniture with treated skin, 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 and unnecessary reactions. Subjects should refrain from touching, licking or biting treated skin or putting treated skin in or near any mucosal surface including the mouth, nostrils, eyes and anogenital area for up to 24 hours after treatment or until the Study drug is removed. Strongly urge subjects/guardians not to touch or wash the treated area for up to 24 hours.

3. To remove the Study drug, the treated lesions should be washed with soap and warm water. Subjects/guardians will be cautioned not to use washcloths, abrasive material or vigorous rubbing to remove the Study drug as this may cause temporary pain and damage to the external layer of the skin and slow the healing process. Removal in the bath or shower is recommended, as simply wiping the treated lesions might not be sufficient for removal of the study drug.

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

5. Subjects should wash clothing, bedding and towels on a regular basis with hot water to minimize re-inoculation. Subjects are encouraged to wash their hands regularly with soap and water and discouraged from scratching lesions, which can spread disease.

## 3.3 STORAGE AND HANDLING OF INVESTIGATIONAL PRODUCT

Study medication is packaged in subject-specific kits within cardboard boxes that contain 5 individually packaged applicators. Each applicator is individually contained in a labeled zip-top bag. The zip-top should not be opened until treatment is ready to be applied.

The applicator is labeled with the Investigational New Drug (IND) application number and an applicator/kit number, which will be assigned to a specific subject. The label also indicates the date of manufacture and "Caution: New Drug--Limited by Federal Law to Investigational Use" and "Warning: Flammable Liquid." The applicator warnings indicate characteristics of the Study drug including the required labeling "Warning: Flammable Liquid" and the yellow toxic chemical symbol with the phrase "Warning: Highly Toxic". Used applicators are not to be discarded after use but should be returned to their zip-top bags and stored in the subject-specific carton until the study monitor completes accountability at the monitoring visit. All used and unused study medication is to be discarded at the site in a sharps container, or per the site's SOP for disposal, after the study monitor has reviewed and confirmed accurate accountability. Those sites that are not allowed to dispose of the Study drug at their site will make arrangements with the Sponsor for return and destruction.

Study drug must be stored at controlled room temperature (68°-77°F; excursions of 59°-86°F are acceptable for short periods) in a secure, dry location with limited and controlled access, and out of direct light. Extended exposure to extreme temperature conditions or to direct light should be avoided (e.g. Study drug left in an unoccupied

vehicle in a hot or cold environment). Contact the study sponsor in the event you believe that any materials may have been exposed to such conditions for guidance. Study drug may be administered only by the investigator or by a trained member of the clinical site staff specifically as authorized by the investigator.

## 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 drug will be classified as concomitant medications. Prior and concomitant medications will be recorded in the eCRF, along with the reasons for administration and durations of use.

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

# 4.0 EXPERIMENTAL PROCEDURES

## 4.1 OVERVIEW: SCHEDULE OF TIME AND EVENTS

Each subject will be evaluated and treated as follows:

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

2. Safety Evaluation: (Day 1: Treatment Visit 1)

- Confirm that subject still meets all inclusion criteria and does not meet any exclusion criteria.

- Lesion count and CDLQI assessments.

- Study drug application.

- Removal of study drug 24 hours after application.

- 24-hour in-office ERT within 48 hours (+/- 1 day) after treatment and after medication has been removed. (AE's, ConMeds)

- ERT phone calls at 7 and 14 days after treatment. (AE's, ConMeds)

3. Safety and Efficacy Evaluation Period *(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 treatment.)*

- Treatment 2: Lesion count by blinded assessor, dermatologic exam, CDLQI, ERT assessments and Study drug application (if subject has treatable lesions remaining). Removal of study drug 24 hours after application. ERT phone calls at 24 hours and Days 7 and 14 after treatment.

- Treatment 3: Lesion count by blinded assessor, dermatologic exam, CDLQI, ERT assessments and Study drug application (if subject has treatable lesions remaining). Removal of study drug 24 hours after application. ERT phone calls at 24 hours and Days 7 and 14 after treatment.

- Treatment 4: Lesion count by blinded assessor, dermatologic exam, CDLQI, ERT assessments and Study drug application (if subject has treatable lesions

remaining). Removal of study drug 24 hours after application. ERT phone calls at 24 hours and Days 7 and 14 after treatment.

4. End of Study: (targeted 21 days after Treatment Visit 4)

- Lesion count by blinded assessor, dermatologic exam, CDLQI and ERT assessments.

The Screening period permits screening up to 14 days prior to Treatment Visit 1. An IRB-approved Informed Consent and Assent (assent when applicable) will be signed before any study specific procedures are performed. The Safety Evaluation Period (Treatment Visit 1) will begin with confirmation that the subject still meets study criteria (e.g., Dermatologic exam/lesion count; ability to attend study visits). After the screening/enrollment study activities have been completed, all safety assessments must be completed by a qualified member of the research team who is not utilized as a blinded assessor for an individual subject's efficacy assessments. Lesion counts will be performed at each treatment visit by a blinded assessor prior to each treatment application. It is not required that the blinded assessor be the same person for each study visit.

Subject impact on quality of life will be assessed using the CDLQI during each treatment visit, prior to the application of Study drug. ERT in-person safety assessments will be conducted during the initial treatment visit and within 48 hours after the initial treatment application (and must be after Study drug has been removed). Subsequent safety follow-ups will include ERT phone assessments at 24 hours, 7 and 14 days after each treatment. ERT will also be assessed at each 21-day in person visit prior to Study drug application. During the Safety and Efficacy Evaluation Period, subjects will be scheduled every 21 days (+/- 4 days); in the event that there are scheduling conflicts preventing a 21-day return visit, the next treatment will be scheduled at 21 days after the last treatment. In the event a subject misses a treatment visit and is outside the study window, they may return and be treated at the next available opportunity with the subsequent visit scheduled 21 days after treatment to facilitate up to 4 treatments within 84 Days. The final study visit assessment must be completed on or before Day 100. Subjects who are not assessed as 100% cleared of all treatable lesions at the EOS visit will have completed the study and will be further treated per standard of care at their physician's discretion. AEs will be assessed at every study visit.

## 4.2 MEASUREMENTS AND EVALUATIONS

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

Before the initiation of screening assessments, the subject/guardian must be given a complete explanation of the purpose and evaluations of the study. Subsequently and depending on the age of the subject, the subject/guardian must sign and receive a copy of an informed consent form (ICF) (Section 7.3), an IRB-required assent form (subjects 10 years or older), 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. Subjects will be screened within 14 days prior to or on Treatment Visit 1 of the study. Following consent and assent, review and recording of any medical history will take place, and the following evaluations will be performed and recorded in the electronic case report form (eCRF):

1. Demographics (date of birth, sex, ethnic origin).
2. Height and weight
3. Prior relevant medical history
    a. All past relevant illnesses with in 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, etc.) administered in the 72 hours prior to the application of the Study drug.
4. Molluscum contagiosum history (duration and previous treatments). If treated with cantharidin, confirm date of last treatment.
5. Limited physical examination.

### 4.2.2 Safety Evaluation Period (Treatment Visit 1)

Screening and Treatment Visit 1 may occur on the same day. The following evaluations will be performed and recorded in the electronic case report form (eCRF):

1. Confirmation that the inclusion/exclusion criteria are met.
2. Dermatologic exam:
    a. Regional molluscum lesion count (head/neck, chest/abdomen, back/buttocks, groin, and upper/lower extremities) including treated and untreated lesions.
    b. Presence of any confounding dermatologic diseases such as atopic dermatitis.
3. Medical history to assess any changes since screening (as described in Section 4.2.1).
4. 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.
5. The presence of household members with molluscum. If these household members are enrolled in the study and if so the household member's subject ID number.
6. Vital signs (heart rate and temperature).
7. Limited physical examination.
8. CDLQI assessment.
9. Urine pregnancy test for females of child-bearing potential, defined as capable of menstruating, to determine protocol eligibility.
10. ERT assessment (LSRs, AEs, ConMeds)-prior to treatment.
11. Photographs taken before application of the Study drug (at selected sites only).
12. Application of Study drug.

13. Subjects will be given take-home instructions describing potential local skin reactions and what they might expect throughout the course of the study, as well as recommendations for wound care, when it is important to call their doctor and instructions for who to contact in an emergency.

14. A local skin reaction guide for subjects with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. Should a subject report experiencing excessive blistering or another adverse event needing physician assessment, they will be scheduled for an unplanned study visit and safety evaluation at the next available opportunity.

15. Review and record any AEs and concomitant medications.

16. Depending on age of subject, subject or parent/guardian will wash off the Study drug with warm water at 24 hours after application of Study drug. Subjects/guardians may gently remove the Study drug from lesions without the use of a washcloth in problematic areas prior to the directed 24 hours if the lesions have already blistered or if the subject is experiencing significant pain. Study drug should not be removed from the additional lesions, where possible, unless significant blistering occurs or the 24-hour time point is reached, whichever comes first.

17. A 24-hour in-person follow-up visit will be conducted within 48 hours (+/- 1 day) following the initial treatment. Study drug must have been removed before the actual visit. Additional ERT assessments will be conducted over the phone at 7 and 14 days after treatment.

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

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

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

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

4. Dermatologic exam (as described in Section 4.2.1) with counting of molluscum lesions. Lesion counts must be conducted and documented by a blinded assessor who is not familiar with the subject's safety assessments or response to treatment.

5. CDLQI assessment.

6. ERT assessment (LSRs, AEs, ConMeds)-prior to treatment. (May not be conducted by a research team member who is utilized as the subject's blinded assessor)

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

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

9. 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 by the team member who is applying the treatment.

10. Subjects will be given take-home instructions describing the potential local skin reactions and what to expect over the next 24 hours to several months.

11. Post treatment safety evaluations will be conducted by the research team via phone calls at 24 hours and days 7 and 14 after every treatment application (ERT). The phone call will review questions related to removal of Study drug, and review and documentation of local skin reactions, adverse events and con-meds since the prior visit or call. Phone calls may not be conducted by a research team member utilized as the subject's blinded assessor.

12. Depending on the age of the subject, the subject/guardian will wash off the Study drug 24 hours after application of Study drug. Subjects/guardian may gently remove the Study drug from lesions without the use of a washcloth in problematic areas prior to the directed 24 hours if the lesions have already blistered or if the subject is experiencing significant 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.

### 4.2.4 End of Study (Day 84):

Subjects will return to the clinical site for:

1. Review and recording of any concomitant medications and non-pharmacologic treatments/procedures since previous visit.
2. Review and recording of any AEs.
3. Vital signs (heart rate and temperature) obtained at the beginning of visit.
4. Limited physical examination.
5. Lesions counted and recorded by blinded assessor.
6. CDLQI assessment
7. Dermatologic exam, ERT assessment (LSRs, AEs, ConMeds) (conducted by qualified member of the research team who is not utilized as a subject's blinded assessor.
8. Urine pregnancy test for females of childbearing potential.
9. Photographs (at selected sites only).

## 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 pre-existing condition, including an increase in frequency or intensity of the condition

- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study

- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product

- Local skin reactions (erythema, scaling/flaking/dryness, edema/swelling, small blisters, hyper- and hypopigmentation, scabbing/crusting, erosion/ulcerations, scarring)?

- Development of individual blisters that are greater than 20mm in diameter (the diameter of a dime). (An aggregated blister composed of a number of smaller blisters is not considered a severe blister)

- Blistering distal to the treatment site

- Scarring-(independent of any pigmentary changes; include depressed (atrophic) and elevated (hypertrophic)

- Secondary infection

The following are not examples of AEs:

- Medical procedures (The medical condition that led to the procedure as the AE should be reported.)

- Situations that are unwanted by the subject but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital

- Anticipated day-to-day fluctuations of a preexisting disease or condition (present or detected before enrollment) that does not worsen overall

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

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

The investigator is responsible for performing periodic and special assessments for AEs. The investigator and study personnel will note all AEs mentioned by the subject starting from the day the informed consent is signed until the end of study visit (~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 will receive appropriate treatment and medical supervision for any AE that occurs.

All unresolved AEs will be followed for 30 days after study completion. 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, etc.) relative to the event(s). The investigator will record all relevant information about any AE (including SAEs) on the AE page of the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of the properly completed AE or SAE pages of the eCRF. These documents should not be sent unless they are specifically requested by the designated Medical Monitor. If this request occurs, all subject identifiers and protected health information should be blinded on the copies of the medical records before submission to the Sponsor and to the appropriate authorities.

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

## 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 2 should be used in assigning intensity of each AE recorded in the eCRF.

**Table 2 Classification of AEs by Intensity**

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

AE: adverse event.

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

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an AE (such as mild, moderate, or severe myocardial infarction). However, the event itself may be of relatively minor medical significance, such as a severe headache. Both AEs and SAEs can be assessed as severe. An AE is considered serious (an SAE) when it meets one of the predefined outcomes described in Section 5.2.

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

## 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 3.

**Table 3 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 or designee by phone, or e-mail within 24 hours of the time the investigator becomes aware of the SAE (Table ). 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 4 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 must be completed as thoroughly as possible, including the following:

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

Within 24 hours of knowledge of a new SAE, the investigative site will enter the event as an SAE into the EDC system being used for this study and recorded into the safety module. The SAE report should include the essential elements.

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

New SAEs, or follow-up SAE information, may be reported to the Paidion Research Medical Monitor (Laurie Dunn, MD) by calling the SAE Hotline at (919) 928-6780. The SAE Hotline may be accessed 24 hours/day, 7 days/week. The Hotline is monitored 24 hours/day, 7 days/week. A call to the SAE Hotline is not required and does not alleviate the Investigator of the responsibility to report a new SAE in the EDC system within 24 hours of knowledge.

## 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 and/or stabilizes.
- The subject is lost to follow-up.
- 30-days after the end of study (EOS visit).

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

## 5.9 PREGNANCY

Should study personnel become aware of a subject's (or subject's partner's) pregnancy, the site personnel must report the pregnancy to the Sponsor's medical monitor within 24 hours by using the pregnancy notification form. The female subject will discontinue Study drug. The pregnancy will be followed until the outcome is known and will be reported to the Sponsor.

# 6.0 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

## 6.1 SUBJECT DISCONTINUATION

Subjects are encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator will provide a written explanation of the reason for discontinuation in a source document and this information will also be recorded on the appropriate eCRF page. If a subject withdraws before completion, every effort should be made to complete the Day 84 assessments scheduled during the End of Study visit. Should a subject be unable to complete the in-office EOS evaluation by Day 100, if available, they may be given the option of an in-home assessment by a qualified member of the research team.

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

- Failure to receive study medication or treatment as mandated by the specific instructions provided in Section 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) for their discontinuation will be documented on the appropriate eCRF page. Reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments after treatment discontinuation. These efforts should be documented on the appropriate eCRF page.

### 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 eCRF page. If subjects do not want their data that has already been submitted or specimens utilized they will need to submit a request in writing to the Investigator for removal of their information.

## 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. Data from all sites, including those that have been terminated for non-compliance or unsatisfactory enrollment will be evaluated and included in the interpretation of study findings. Subjects from sites that terminate early will be considered for analysis. If a subject does not complete the study, they will still be counted as a failure for the primary endpoint.

# 7.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

## 7.1 DATA COLLECTION AND PROCESSING

Electronic case report forms (eCRFs) 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 eCRFs. All eCRFs will be reviewed and source-verified by the study monitor during periodic site visits as well as via centralized monitoring, and the study monitor will ensure that all data in the eCRF are correct and complete. All information recorded on the eCRFs for this study must be consistent with the source documentation (i.e., medical records). Before or between visits, the medical monitor or study monitor may conduct a preliminary medical review of the eCRFs. Once the eCRFs are completed and source-verified, the investigator must electronically sign all required pages in the eCRF, verifying the accuracy of all data contained in the eCRF.

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

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

If electronic data systems other than those provided and maintained by the Sponsor are used for documentation and data capture, the investigator must ensure that the systems are validated and that data are backed up as described in Section 7.4.

## 7.2 STATISTICAL ANALYSIS

### 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. Data will also be listed as deemed appropriate. All statistical analyses will be performed and data appendices will be created by using SAS version 9.3 or higher. All statistical tests will be two-sided at the $\alpha = .05$ level.

### 7.2.2 Populations of Interest

The intent-to-treat population (ITT) will include all subjects randomized to either placebo or VP-102.

Subjects who receive all 4 planned treatments of VP-102/Placebo and have no major protocol violations will be included in the Per Protocol population. The following pre-determined reasons will exclude subjects from being included in the Per Protocol population:

- Subjects treated with the incorrect study drug.
- Subjects who do not come in for required treatment visits.
- Subjects who refuse to have all of their treatable lesions treated or investigators who refuse to treat all treatable lesions.
- Early removal of the study drug not associated with pain, blistering or other medically appropriate reason for early removal.
- Subjects with missing lesion counts or clearance assessments.
- Subjects who begin alternative treatments for their molluscum after starting the study.
- Subjects enrolled who did not meet the inclusion/exclusion criteria.
- Subjects whom have their blind broken as to their treatment group without following study procedures.

The safety population will include randomized subjects who meet the screening eligibility criteria for the study and receive at least one treatment of VP-102 or placebo.

### 7.2.3 Efficacy Analysis

Efficacy analysis using the ITT population will be considered the primary analysis. Analysis carried out on the per protocol population will be considered secondary in nature. Efficacy analysis carried out on the ITT and per protocol populations will be based on the treatment the subject was randomized to.

The primary endpoint of proportion of subjects exhibiting clearance of all treatable lesions (baseline and new) at the Day 84 (EOS) visit will be analyzed. Treatment difference in clearance rates will be tested with a Pearson Chi-Square test. Other binary endpoints, including clearance at Day 63, clearance at Day 42 and clearance at Day 21, spread to household members and 75% and 90% reduction of treatable lesion count, will also be analyzed with this method.

Continuous endpoints: percent change in treatable lesion count from baseline, change in treatable lesion count from baseline, change in CDLQI assessment from baseline will be analyzed with an ANCOVA model to test for treatment differences at EOS. For the ANCOVA model, the independent variable will include treatment. A covariate of baseline lesion count will be included. Further details of analyses of other endpoints will be provided in the statistical analysis plan.

Though the analysis will not be stratified by site, an assessment of the results across sites will be performed. A Breslow Day test will be performed to consider any potential site-to-site variability of study results. A site with a strong deviation in treatment effect from other sites will be further investigated to try to gain a better understanding of why differences at the site may exist.

Sequential testing will be used to control the overall study-wise alpha. If the primary endpoint is significant, testing of the secondary endpoints in the order specified in the statistical analysis plan will continue. If any hypothesis test fails to reach statistical significance, then testing will cease for confirmatory purposes.

### 7.2.4 Safety Analysis

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

Adverse event data for the safety population will be listed individually, and the incidence of adverse events will be summarized by treatment, System Organ Class, and Preferred Term using frequency counts. Local skin reactions will be included as part of the overall adverse event summaries. Adverse events will be tabulated by total rate of occurrence and rate of severe occurrences. When calculating the incidence of adverse events, only Treatment Emergent Adverse Events (TEAEs) will be considered. In addition, any adverse event with an onset date after the EOS visit will be considered off study and will not be included in tables summaries (though they will appear in adverse event listings). Each adverse event will be counted only once for a given subject. If the same adverse event occurs on multiple occasions for a subject, the occurrence with the highest severity and relationship to Study drug will be reported. If two or more adverse events are reported as a unit, the individual terms will be reported as separate events. Changes in vital signs, from baseline to the end of the study will be examined. Treatment-emergent changes from normal values to abnormal values will be identified as described in Section 2.3.1.

In addition, separate summaries of local skin reactions (LSRs) will be generated. Investigator and subject reported LSRs will be displayed by treatment, severity, causality, time (treatment visit) and body region.

### 7.2.5 Interim Analysis

No interim analysis is planned for this study.

### 7.2.6 Sample Size

The sample size for the study is calculated based on hypotheses of the primary efficacy endpoint. The primary endpoint for this study is the proportion of subjects with complete clearance of all treatable lesions (baseline and new) after treatment. The statistical hypotheses for the primary endpoint are:

$H_O$: The proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) at the EOS visit is equal when comparing the subjects treated with VP-102 vs. the subjects treated with placebo.

$H_a$: The proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) at the EOS visit is different when comparing the subjects treated with VP-102 vs. the subjects treated with placebo.

The study is expected to enroll and randomize 250 subjects in the VP-102-102 protocol with molluscum lesions to test for treatment differences in the rate of complete clearance. Subjects will be randomized and treated in a double-blind manner with either VP-102 or placebo in a 3:2 ratio (approximately 150 subjects on VP-102 to 100 subjects on placebo).

Study assumptions include the following:

- a 10% drop out rate.
- a 20% clearance rate for subjects treated with placebo. This is based on reported placebo treated clearance rates for placebo controlled studies, such as Aldara (26% clearance at 18 weeks, adjusted to Verrica's 12-week study) and several other placebo studies suggesting a similar clearance rate including Short, 2006, Syed 1995, Dosal 2012, Burke 2004 and Theos 2004.
- a 44% clearance rate for subjects treated with VP-102. This is based on a calculated clearance rate of 44% (11 cleared out of 25 completed subjects in NCT03017846.

Using these assumptions, a sample size of 250 subjects based on a Pearson Chi-Square test with a two-sided significance level of 0.05 will give >=95% power to detect treatment differences in clearance rates.

### 7.2.7 Handling of Missing Data

Clearance of all treatable lesions is to be assessed a maximum of four times during the study. Assessments are to be done at Day 21, Day 42, Day 63 and Day 84 (EOS). The assessment done at Day 84 is considered to be the primary efficacy endpoint.

Subjects who do not have an assessment of complete clearance of all treatable lesions at Day 84 will be considered to have missing data for the primary endpoint. The primary method to handle missing data will be to assign all subjects with missing

complete clearance data as not having achieved complete clearance. It is assumed that the proportion of subjects with missing data will be greater for subjects treated with VP-102 than subjects treated with placebo. This is because subjects treated with VP-102 are assumed to be more likely to clear prior to Day 84; meaning they will be less likely to return for their Day 84 (EOS) visit. Under this condition, one would expect there to be less chance to detect treatment differences (conservative approach). Rates of subjects with missing data of the primary endpoint will be compared by treatment group. Significant deviations in rates of subjects with missing data that may affect study conclusions will be included in the study report.

Sensitivity analyses of primary endpoint using the ITT population are based on ICH Guideline E9 [25] and will include the following:

- Analysis using only non-imputed data (complete case analysis);
- Analysis in which all subjects with missing data are assigned as having achieved complete clearance;
- Analysis in which subjects with missing data and treated with placebo are considered to have complete clearance; subjects with missing data and treated with VP-102 are considered to not have complete clearance (worst case analysis).

One additional set of analyses of the primary endpoint will be generated using the per protocol population.

The CDLQI assessment is validated for subjects 4 to 16 years and old. However, subjects 2 and 3 years old are allowed to be enrolled in the study as well as subjects older than 16. One planned set of sensitivity analysis for CDLQI will be to test for treatment differences of the composite CDLQI score using all subjects enrolled, rather than the subset of subjects 4-16 years of age. Results using all subjects enrolled will be compared to the exploratory endpoint using only those subjects 4-16 years of age.

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

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

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

## 7.4 STUDY DOCUMENTATION

### 7.4.1 Investigator Information

Investigator information is included in the Study Procedures Manual, 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, the study procedures manual and study logs, eCRFs, records of monitoring activities, and correspondence between sponsor or study monitor and the investigator. Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for source documentation.

### 7.4.3 Electronic Case Report Forms and Source Documentation

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

### 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.

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

## 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 eCRFs and other documents retrieved from the site or sent to the study monitor, Sponsor, regulatory agencies, analysis laboratories, or blinded reviewers. Documents that identify the subject (e.g., the signed informed consent form) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, or sponsor representatives.

## 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 and assent form, the revised informed consent and assent forms prepared by the investigator must also be approved by the sponsor, study monitor, and the IRB before implementation.

In instances where there is an immediate risk to a subject that is deemed crucial for the safety and well-being of that subject, the investigator or the attending physician will contact the medical monitor as soon as possible to make them aware of such a

departure. These departures do not require preapproval by the IRB; however, the IRB and medical monitor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document the reasons for the protocol deviation and the ensuing events in the subject's eCRF.

## 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.

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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.

# APPENDICES

# APPENDIX 1

# CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX SCORING INSTRUCTIONS

## APPENDIX 1

Children's Dermatology Life Quality Index Scoring Instructions [27]

Subjects and their guardians will be instructed to fill out the CDLQI as it relates to molluscum and not other concomitant skin diseases.

The scoring of each question of the CDLQI is as follows:

| | |
|---|---|
| Very much | scored 3 |
| Quite a lot | scored 2 |
| Only a little | scored 1 |
| Not at all | scored 0 |
| Question unanswered | scored 0 |
| Question 7: "Prevented school" | scored 3 |

The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

**Interpretation of incorrectly completed questionnaires:**

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.

2. If two or more questions are left unanswered the questionnaire is not scored.

3. If both parts of question 7 are completed the higher of the two scores should be counted.

## CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

**The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.**

| | | | |
|---|---|---|---|
| **1.** | Over the last week, how **itchy**, "**scratchy**", **sore** or **painful** has your skin been? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **2.** | Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **3.** | Over the last week, how much has your skin affected your **friendships**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **4.** | Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **5.** | Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **6.** | Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **7.** | <u>Last week</u>, was it **school time**?<br>**OR**<br>was it **holiday time**? | **If school time**: Over the last week, how much did your skin problem affect your **school work**?<br>**If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**? | Prevented school<br>Very much<br>Quite a lot<br>Only a little<br>Not at all<br>Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐<br>☐<br>☐<br>☐<br>☐<br>☐ |
| **8.** | Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **9.** | Over the last week, how much has your **sleep** been affected by your skin problem? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **10.** | Over the last week, how much of a problem has the **treatment** for your skin been? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |

**Please check that you have answered EVERY question. Thank you.**

# APPENDIX 2

# VERSION HISTORY AND SUMMARY OF CHANGES

# APPENDIX 2

Version history:

| DOCUMENT | VERSION | DATE |
|---|---|---|
| Protocol VP-102-102 | 1 | 24 February 2017 |
| Protocol VP-102-102 | 2 | 31 July 2017 |
| Protocol VP-102-102 | 3 | 29 September 2017 |
| Protocol VP-102-102 | 4 | 05 December 2017 |
| Protocol VP-102-102 | 5 | 01 February 2018 |

Summary of changes to Protocol VP-102-102 (revised 01 February 2018):

| SECTIONS/PAGES CHANGED | DESCRIPTION OF CHANGES |
|---|---|
| Cover pages: | Changes to Sponsor contact information and address. |
| Synopsis:<br>Objectives: Page 4<br><br>Main Protocol:<br>1.6 Secondary Objectives: Page 29, 30 | Secondary Objectives updated to remove 2 objectives and now reads as follows:<br>• to assess the safety and tolerability of VP-102, when applied once every 21 days for up to 4 applications, to treatable molluscum lesions on subjects 2 years old and older by assessing adverse events including expected local skin reactions, physical examinations, and concomitant medications at End of Study compared to baseline.<br>• to evaluate the efficacy of VP-102 relative to placebo by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions at Visit 2. Separate assessments for clearance will be repeated for both Visit 3 and Visit 4 |
| Synopsis:<br>Secondary and Exploratory Endpoints: Page 8<br><br>Main Protocol:<br>2.3 Endpoints: Page 36 | Updated to move the CDLQI from the secondary endpoints to the exploratory endpoints. |
| Main Protocol:<br>2.4 Randomization and Blinding: Page 38 | Randomization through an interactive web response system (IWRS) will be used to assign subjects treatment in a 3:2 ratio (expected 150 subjects treated with VP-102 to 100 subjects treated with placebo). Trial sites will have access to an internet-based randomization system. Randomization will be conducted in a centralized manner. Subjects with molluscum lesions present from the same household may be enrolled in the study. For ethical and practical considerations, subjects in the same household will be assigned to the same treatment group. After a subject is randomized to a treatment, any other subject enrolled in the study from that household will be assigned the same randomization number and be given the same treatment. As a result, the unit of randomization is the household- not the subject. |

| | |
|---|---|
| | Randomizing by household at the site level could lead to strong differences from the desired treatment ratio at individual sites. Therefore, randomization by household will be carried out at the study level. Since randomization is not done by site, analyses will not be stratified by site. |
| Synopsis:<br>Statistical Methods: Page 10, 11<br><br>Main Protocol:<br>7.2 Statistical Analysis: Page 67, 68 | Updated to reflect changes in types of analysis to be conducted. Updated to indicate that the Breslow Day test will be performed to consider any potential site-to-site variability of study results. |
| Main Protocol:<br>7.2.4 Safety Analysis: Page 68 | Updated to clarify that separate summaries of local skin reactions (LSRs) will be generated. Investigator and subject reported LSRs will be displayed by treatment, severity, causality, time (treatment visit) and body region. |