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

1.0 INTRODUCTION

1.1 MOLLUSCUM CONTAGIOSUM

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

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

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

1.2 CANTHARIDIN

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

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

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

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

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

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

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

2.3.1 Safety

The following safety parameters will be assessed:

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

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

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

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

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

- Patient Evaluation of Response to Treatment (PERIT)

- Safety Monitoring Questionnaire

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

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

3.3 STORAGE AND HANDLING OF INVESTIGATIONAL PRODUCT

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

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

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

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

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

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

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

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

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

7. Limited physical examination.

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

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

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

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

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

4.2.2 Evaluations (Treatment Day 1)

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

1. Confirmation of eligibility.

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

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

4. Vital signs (heart rate and temperature).

5. Limited physical examination.

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

7. CDLQI assessment.

8. LSR assessment.

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

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

11. Application of Study drug.

12. Review and record any AEs and concomitant medications.

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

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

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

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

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

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

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

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

5. CDLQI assessment.

6. LSR assessment.

7. Safety Monitoring Questionnaire.

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

9. Photographs taken before application of the Study drug.

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

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

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

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

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

Subjects will return to the clinical site for:

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

2. Review and recording of any AEs.

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

4. Limited physical examination.

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

6. LSR, CDLQI and Safety Monitoring assessments.

7. Urine pregnancy test for females of childbearing potential.

8. Photographs

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

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

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

All AEs judged to be clinically significant will be followed until the EOS visit or until they have stabilized. All AEs will be summarized in the annual report or more frequently if requested by the regulatory agency. SAEs require special reporting in addition to documentation in the eCRF as described in Section 5.3.

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

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

5.3 RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

5.4 ASSESSMENT OF INTENSITY

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

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

Table 1. Classification of AEs by Intensity[a]

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

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

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

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

5.5 ASSESSMENT OF CAUSALITY

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

5.7 REPORTING OF SERIOUS ADVERSE EVENTS

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

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

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

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

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

Table 3. Timeline for Reporting SAEs

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

SAE: serious adverse event.

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

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

The SAE report will be forwarded to the Sponsor within the designated time frames. If additional information to complete the SAE report form is needed, the investigator

will not wait before notifying the safety department of the SAE. The SAE report form will be updated by the investigator when additional information is received.

5.8 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

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

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

5.9 PREGNANCY

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

6.0 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

6.1 SUBJECT DISCONTINUATION

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

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

6.1.1 Adverse Event

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

6.1.2 Intercurrent Illness

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

6.1.3 Noncompliance

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

- Failure to receive study medication or treatment as mandated by the specific instructions provided in Section 3.0
- Failure to comply with protocol requirements

6.1.4 Refusal of Investigational Product Administration

Any subject refusing clinical trial material for any reason will be discontinued from the study, and the reason(s) will be documented on the appropriate CRF page. Reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments after treatment discontinuation. These efforts should be documented on the appropriate CRF page.

6.1.5 Withdrawal of Consent

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

6.2 PREMATURE STUDY OR SITE TERMINATION

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

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

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

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

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

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

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

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

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

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

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

2.2 STUDY POPULATION

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

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

2.2.1 Inclusion Criteria

To qualify for inclusion in this study, subjects must:

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

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

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

2.3.2 Efficacy

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

2.4 REPLACEMENT OF DROPOUTS

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

Those patients that do not complete the full treatment due to protocol adherence or request to be discontinued from the study will be not be replaced. Subjects who do not complete the safety and efficacy evaluation period will be considered dropouts. Dropouts will not be replaced. In the event a patient requests to be removed from the study due to study related adverse experiences or additional spreading of disease, data will be collected and analyzed as a treatment failure and not replaced.

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

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

3.4 CONCOMITANT MEDICATIONS

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

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

4.2 MEASUREMENTS AND EVALUATIONS

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

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

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

5.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

5.1 DEFINITION OF AN ADVERSE EVENT

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

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

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

The following are examples of AEs:

- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition
- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product

Examples of AEs do not include the following:

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

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

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

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

Table 2. Assessment of Causality of AEs

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

AE: adverse event.

5.6 EXPECTEDNESS OF SERIOUS ADVERSE EVENTS

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

- 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.