

Phase 2 Open-Label Extension Study Investigating the Safety and Efficacy of Topical Cantharidin, VP-102, for the Treatment of Molluscum Contagiosum

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1 INTRODUCTION

The objective of these open-label studies is to confirm the comparability of the efficacy and safety of a commercially viable 0.7% to 1.0% cantharidin formulation for the treatment of pediatric molluscum contagiosum (MC) to the 0.7% cantharidin formulation used in the initial study that investigated safety and efficacy of a compounded cantharidin formulation. An additional objective is to investigate potential systemic exposure under maximal use conditions. MC is a dermatologic disorder caused by a pox virus - molluscum contagiosum virus (MCV). The contagion manifests on any part of the body as small, pearly, dome-shaped papules with a dimpled center. While MC may be self-limiting, lasting anywhere from months to years, it can be unsightly and embarrassing. Patients and their parents often seek treatment for both cosmetic removal and to prevent the spread of MCV to close contacts. MCV is transmitted through close physical contact, such as bathing with siblings or the sharing of towels and even the use of public pools.

While treatment options do exist for MC, there is no standard of care. Dermatologists strive for treatment options in children, which in addition to being safe and effective are painless and non-traumatic. One such option is cantharidin, which is familiar to practicing dermatologists but does not have a U.S. Food and Drug Administration (FDA)-approved indication for MC. In our study, we will evaluate the efficacy of cantharidin 0.7% to 1.0% in the treatment of MC in a prospective, open-label study. The purpose of this study is to test the safety and efficacy of a commercially viable cantharidin 0.7% to 1.0% formulation. A 0.7% cantharidin concentration matches the dose we used in our previous study and is the most commonly used concentration for the treatment of molluscum. However, it has come to our attention that most practitioners reuse the same vial of cantharidin multiple times. Every time a vial is opened, solvent evaporates increasing the concentration of cantharidin. In reality, the concentration of cantharidin many patients receive is likely closer to 1.0%. Therefore, in order to more closely match historical concentrations, we would like to evaluate up to a 1.0% cantharidin concentration.

While most dermatologists who use cantharidin for the treatment of molluscum ask that patients wash off study material after 4-6 hours, some simply ask patients to wash the material off the next morning or when and if blistering has occurred. It has come to our attention that a significant portion of patients and their parents or guardians do not adhere to a 6-hour time point due to inconvenient timing and may wash study material off earlier in order to get ready for bed or later the next morning. Additionally, due to the lack of a colorant in historic formulations and the strong adherence of colloidion based formulation to skin, it is likely that many patients did not fully wash off study materials at the indicated time in past investigations. Therefore, in order get a better sense of what happens under more realistic conditions, we would like to explore what happens when patients are instructed to wash off the study material up to 24 hours after application or if blistering or pain is present rather than at 6 hours.

In support of the safety profile of VP-102, we will enroll an additional cohort of patients in an exposure cohort where we will also evaluate the level of systemic exposure that may occur. This study will enroll patients with at least 21 molluscum lesions so that the upper range of the expected exposure to VP-102 is assessed under maximal use conditions. Based on the low concentration and nature of the active pharmaceutical ingredient, the formulation of the drug product, and the lack of reported systemic exposure following dermal application, this study will enroll approximately 16 completed patients.

Specimens will be collected and stored at Montefiore Clinical Research Center at -80 degrees until ready to ship. Shipping supplies will be provided by the company and specimens shipped, at minimum, monthly to:

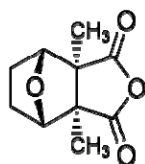
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510-964-9000 x2093

Results will be analyzed throughout the study but results will not be shared with the study staff or patients unless a safety concern arises.

The new formulation has a number of safety improvements over formulations previously used including: 1) the inclusion of an oral deterrent (denatonium benzoate); 2) inclusion of a colorant (gentian violet); 3) the removal of diethyl ether, a highly volatile and potentially explosive solvent; 4) use of a highly purified version of the active ingredient cantharidin (purity is now over 99.5%) that has been manufactured and released using Good Manufacturing Practice (GMP) protocols. 5) packaging in single use vials to ensure a consistent cantharidin concentration.

1.1 Investigational agent



Cantharidin is a topical vesicant. Its chemical name is 2,6-Dimethyl-4,10-dioxatricyclo-[5.2.1.0^{2,6}] decane-3,5-dione, and it is a type of terpenoid. The CAS registry number is [56-25-7]. Its molecular mass is 196.20 g/mol.

Cantharidin is the sole active ingredient in the investigational product.

Cantharidin 0.7% to 1.0% is prepared for topical administration of molluscum lesions. Treatment is applied in-office, by a trained dermatologist, using the non-cotton end of a wooden applicator stick or single use applicator. Systemic absorption through topical administration is minimal; therefore, all lesions may be treated concurrently in an outpatient office setting. There have been no reports of cantharidin toxicity caused by the reasonable application of cantharidin solution by a physician. One trial in MC treated a maximum of 20 lesions with no reports of systemic toxicity [Dosal. NCT#00667225]. Another trial treated a maximum of 10 lesions with no reports of systemic toxicity [Hanna, 2004]. In our most recent study at Montefiore Medical Center/Albert Einstein College of Medicine, we treated up to 50 lesions in 100 subjects with a very similar formulation to the one that will be used in this protocol and noted that the treatment was well-tolerated with no reports of systemic toxicity and no Severe Adverse Events (SAEs).

In the primary study, up to 40 patients will be enrolled in total. These 40 patients will be treated with VP-102 without occlusion. In the optional exposure study cohort, up to 24 additional patients will be enrolled with a goal of 16 patients completing all scheduled blood draws.

Study visits are scheduled for every 21 Days to a maximum of 4 treatments (5 office visits total).. Subjects enrolled will be treated at Visit 1 (Week 0), Visit 2 (Day 21), Visit 3 (Day 42) and Visit 4 (Day 63) with a follow-up evaluation at Visit 5 (Day 84, Week 12). Using the wooden end of a Q-tip, (or other application system that will deliver comparable volumes), application volume per lesion is estimated to be 0.005-0.01 ml. Application of 500ul of VP-102 0.7% (concentration of 7 mg/ml) would result in the topical administration of 3.5 mg. Patients are instructed to wash treatment off all lesions with soap and warm water the following morning (up to 24 hours after application) or earlier if unmanageable pain or significant blistering has occurred. Patients are to be cautioned not to use washcloths, abrasive material or vigorous rubbing to remove the medication as it might cause temporary pain and damage to the external layer of the skin and slow the healing process. There will be no occlusion arm in this study as our previous study suggested this did not improve outcomes. This is a twelve-week trial, with all patients set to receive up to four doses of the commercially viable formulation.

Any patients who have not completely resolved by Visit 5 (Day 84, Week 12) will be assessed and treated with what is in the best interest of the patient as determined by the principal investigator. All ongoing treatment and follow up at Visit 5 and thereafter will be at the physician's discretion. Patients who may

benefit from additional treatment with cantharidin will be treated with a compounded formulation identical to the one used in the previous study.

1.2 Overview of previous human experience

Cantharidin has a well-characterized history of safe use in the treatment of several dermatologic conditions, such as MC and verruca vulgaris. Few serious adverse event reports exist in the literature when applied topically. Oral administration is toxic, but concerns regarding systemic toxicity are minimized as in this protocol only a limited amount of cantharidin is applied topically by a trained professional in an office setting. The use of cantharidin by practitioners pre-dates the Food, Drug, and Cosmetic Act of 1938, and met the safety requirements therein. The FDA amended the Act in 1962 with the Drug Efficacy Study Implementation, which required manufacturers to submit efficacy data for products. When manufacturers did not submit efficacy data, cantharidin was removed from the US market. Following decades of calls from dermatologists for reconsideration of classification, cantharidin was reclassified under the FDA's "Bulk Substances List," which permits the compounding of bulk substances by a physician or pharmacist on a customized basis for individual patients.

Literature on the efficacy of cantharidin is lacking. Experience is cited primarily in anecdotal reports, retrospective reviews, or letters to the editor. Prospective studies are lacking. Dermatologists do, however, recognize the efficacy of this treatment. The American Association of Dermatology cited cantharidin as a 'Topic of Interest' for the 2012 Clinical Symposia, with a call for experience to Association members.

When ingested by humans, the oral Lethal Dose low (LD_{low}) is reported as 0.428 mg/kg (NLM Toxinet ChemID plus, 2016), with a lethal dose reported as low as 10 mg (Till et al, 1981). However, there have been cases of patients surviving doses up to 175 mg (Oaks et al 1960).

We recently completed a study of 0.7% cantharidin in molluscum patients under the same open IND. The full results of the study are in the process of being submitted for published. However, an abstract of the draft manuscript shown below demonstrates the safety of this investigational agent.

Abstract

Importance: Molluscum contagiosum (MC) is a common viral infection of the skin primarily affecting children. It is typically uncomfortable, disfiguring, and contagious. Since, there are no FDA-approved therapies, the need for a safe and effective remedy is essential.

Objective To determine the efficacy and safety of topical cantharidin 0.7% compared to placebo in the treatment of pediatric MC.

Design Double-blind, placebo-controlled trial followed by open label extension. Data was analyzed with an intention-to-treat and last-observation-carried-forward model.

Setting Participants were recruited from general and pediatric dermatology clinics at an academic medical center in Bronx, New York.

Participants Ninety-four participants aged 2 to 17 years with less than 50 MC lesions were enrolled in a two-phase trial from August 2012 through November 2015. Follow-up was completed by January 2016.

Interventions Participants were randomized blindly to four treatment groups: cantharidin 0.7% topical, cantharidin 0.7% topical with occlusion, placebo, and placebo with occlusion. Treatments were applied every three weeks. After week 6, participants were treated with open-label, cantharidin 0.7% without occlusion until all MC resolved.

Main Outcome and Measures The primary endpoint was total clearance. Secondary endpoints included lesion count, time to total clearance, adverse events and patient-reported side effects.

Results The 94 participants enrolled had a mean of 22.2 (SD 12.9) lesions at baseline. After 6 weeks, total clearance was significantly higher in the cantharidin (30.4%) and cantharidin with occlusion (41.7%) groups compared to those in the placebo (13.6%) and placebo with occlusion groups (8.0%) ($\chi^2(3, N=94) = 9.58, p < 0.05$). Furthermore, lesion counts were significantly lower in the groups receiving cantharidin compared to placebo ($F(1.513, 136.1) = 12.06, p < 0.0005$). In the open-label phase, the median time to clearance was 9 weeks and 85.9% of the participants had complete resolution. While parents reported varying degrees of inflammation immediately following treatment, there were no adverse reactions otherwise documented in the blinded or open label extension phases of this study.

Conclusions and Relevance For treatment of molluscum contagiosum, topical cantharidin resulted in greater lesion clearance compared to placebo without significant adverse events. These findings demonstrate that cantharidin is an effective and safe treatment for MC when applied in-office by a health care professional.

Trial Registration: clinicaltrials.gov Identifier: NCT02665260

1.3 Overview of preclinical data

Preclinical data of cantharidin focuses primarily on cantharidin's 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. Cantharidin is absorbed through the lipid layer of the skin, inducing acantholysis and desmosome disruption of the epidermal cell layer. The result is a small blister, which typically heals in 2-3 days without scarring.

2 GENERAL INVESTIGATIONAL PLAN

2.1 Research rationale and objectives

Cantharidin is cited in the dermatology and pediatric literature as a valuable treatment option. Treatment is often available in private practice offices, where a prescribing physician may offer a non-FDA approved treatment on an individualized basis. The situation is different in many hospital and academic settings, such as our own for example, where the formulary is defined through a FDA-approved indication. The absence of an indication precludes its addition to many hospital formularies, thus limiting the options available to a prescribing physician and denying patient access to a treatment offered in the private practice setting. An indication and formulary status require controlled clinical trials on the safety and efficacy of cantharidin in MC. The objective of this trial is to see if this commercially-viable cantharidin formulation has a comparable safety and efficacy profile as formulations previously studied under conditions which most closely match the what has been historically done in the clinic.

This study will enroll patients with at least 21 molluscum lesions so that the upper range of the expected exposure to VP-102 is assessed. Due to the fact that patients with more than 50 molluscum lesions have the highest likelihood of systemic exposure, those patients, who are currently excluded from the primary study will now be eligible for the exposure cohort of the study where potential exposure can be better monitored. Based on the low concentration and nature of the active pharmaceutical ingredient, the formulation of the drug product, and the lack of reported systemic exposure following dermal application, this study will enroll approximately 16 completed patients.

2.2 Proposed clinical research protocol

The proposed study will examine the efficacy and safety of a commercially-viable cantharidin formulation produced under GMP for the treatment of MC. The primary efficacy outcome measure will compare the percent of patients totally cleared following four treatments of either cantharidin. Secondary efficacy outcome measures will include: patient-reported outcomes, time from treatment to resolution, durability of cantharidin treatment response, partial clearance by the treatment and a comparison to data generated in our previous study (NCT02665260).

An additional, optional cohort of patients will be added to this study where the primary objective is to evaluate the possible systemic exposure to cantharidin from a single dermal application of VP-102 topical film-forming solution over the course of approximately 24 hours. Patients will be required to have at least 21 molluscum lesions on the day of treatment in order to participate in this exposure option.

Blood samples for systemic exposure analysis will be collected. In order to obtain a minimum of 1 mL, of plasma for assessment, approximately 2 mL of blood will be collected before the first application of VP-102 (Day 1) and at 2 (\pm 30 minutes), 6 (\pm 1 hour) and 24 (\pm 3 hours) hours post-application. Blood will not be collected on subsequent applications of the study drug (Days 21, 42, and 63). Patients will be asked to return to the clinic within approximately 24 hours of treatment for assessment and to obtain an additional blood sample. A 24-hour phone number is provided for patients to call where they will receive guidance on how to manage any adverse experiences that may arise.

Study population

This is a study in the pediatric population, aged 2-17, for whom MC is a common condition seen in dermatology practice.

Inclusion Criteria:

- Age 2 - 17
- Diagnosis of MC by the Principal Investigator.
- Execution of Informed Consent and or assent forms
- Subjects will be recruited from Montefiore Medical Center/Albert Einstein College of Medicine Division of Dermatology's Pediatric Dermatology clinics and the surrounding area.

- Patients with 1-20 lesions can only be included in the primary study,
- Patients with 21-50 lesions can be included in either the primary study or the exposure option.
- Patients with 51 or more lesions can only be included in the exposure cohort.
- All molluscum lesions present must be treated (eg, if facial lesions, they should not be close enough to the eyes or mouth that treatment is not practical or medically safe in the opinion of the investigator).
- Refrain from swimming, bathing, prolonged immersion in water, and application of all topical agents including alcohol-based sanitary products and sunscreens for a minimum of 6 hours before and 24 hours after application of the study drug. (*Topical agents may be used after 24 hours but avoid applying to the treated lesions*).

Exclusion criteria

- Patients with immunosuppression, including organ transplantation, HIV infection.
- Patients utilizing immunosuppressive agents (including oral corticosteroids) will be excluded except for patients using inhaled corticosteroids, such as those utilized for asthma or allergic rhinitis.
- Females who have reached menarche and are sexually active as well as pregnant patients will be excluded as the effects of this drug have not been evaluated in pregnancy. (*For females that are menstruating, a urine pregnancy test will be obtained at screening and each visit prior to treatment with study medication*)
- Patients who have greater than 50 MC lesions will also be excluded from the study unless they are participating in the exposure cohort.
- Any previous treatment of MC including the use of cantharidin, antivirals or freezing of lesions in the past 14 days. (Requires 14 day washout to participate). Additional treatments should not be implemented during the course of the study.
- Have 'inflamed' molluscum lesions at baseline of $\geq 10\%$ of total lesions.
- 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.
- Have history of illness or any dermatologic disorder (including molluscum eczema), which, in the opinion of the investigator will interfere with accurate counting of lesions or increase the risk of adverse events.

Primary Study Design

Up to 40 patients will be enrolled in total. Visits are scheduled for every 21 Days, with an allowance of scheduling at Day 18-30 in the event there is a scheduling conflict. Each treatment visit should be scheduled at 21 Days post the last treatment. Patients will be treated at Visit 1 (Week 0), Visit 2 (Day 21, Week 3), Visit 3 (Day 42, Week 6), and Visit 4 (Day 64, Week 9) if needed with a final, follow-up evaluation at Visit 5 (Day 84, Week 12). Using the wooden end of a Q-tip (or other application system that will deliver comparable volumes), application volume per lesion is estimated to be 0.005-0.01 ml. Application of cantharidin 0.7% to 1.0% (concentration of 7 mg/ml) to 50 lesions would result in topical administration of 3.5 mg - 5.0 mg. Patients are instructed to wash treatment off all lesions with soap and warm water the morning following application (up to 24 hours after application) or earlier if pain becomes unmanageable or significant blistering has occurred. Please see safety monitoring plan with detailed patient safety issues.

All patients who have not had full clearing of lesions will be treated as the Principal Investigator/Sub-Investigator deems appropriate following their completion of the last study visit Visit 5/Day 84. This additional treatment will not be a part of our primary endpoint data and a compounded formulation will be used for treatment rather than VP-102. Full enrollment is anticipated to take 7-9 months based upon the frequency of MC seen in the pediatric clinic population.

Exposure Cohort Design

Up to 24 patients will be enrolled in total with a goal of 16 whom complete all scheduled blood draws in the study. Due to scheduling considerations, the screening period for this cohort permits screening up to 14 days prior to Day 1 (baseline treatment). Patient's eligibility will be reassessed prior to treatment. In the event the patient no longer wishes to participate in this cohort or they no longer qualify due to lesion count, they may be continued in the main study. For this study, up to 2 mL of blood for plasma will be collected on Visit Day 1, before application of VP-102 (baseline) and at 2(\pm 30 minutes) and 6 hours (\pm 1 hour) post-application. In addition, patients will be asked to return within 24 hours (\pm 3 hours) the next day for an assessment and blood draw. Subjects will remain in the clinic for up to 8 hours in order to complete all study-related activities; age appropriate entertainment is available as needed. Blood will not be collected following subsequent applications with the study drug (Day 21, 42, and 63) or on the End of Study visit, Day 84. In order to evaluate exposure under maximal use conditions we would like to understand what the possible exposure is in younger patients and will therefore aim to collect plasma from at least 3 patients at 2-5 years of age. Enrollment will be open to all comers meeting criteria while tracking age ranges to ensure various age groups are included.

On their first visit, patients will be asked to remove the study drug before the 24-hour clinic visit. Subsequent treatment visits will be managed as in the primary study design as described above.

Primary Endpoint of Primary Study

The primary endpoint is the percentage of subjects who achieve total clearance, as defined as 100% reduction in baseline MC count by week six (Day 42) and twelve (Day 84) of the study. In order to appropriately track the outcome of the treated molluscum lesions, all will be documented as follows at each visit: 1) photographs of the most severely affected area(s); 2) plotting of those most notable on a body map; and 3) recording the number of lesion(s) in each anatomic location: head/neck, trunk, upper extremity (left, right), lower extremity (left, right) (attached Case Report Form). Additionally, a questionnaire will be utilized to record safety and efficacy measures for each visit. Secondary endpoints include the percentage of subjects who achieve a clearance of at least 90% of their molluscum lesions, the change in the Children's Dermatology Life Quality Index (CDLQI) (attached) given Visit 1 prior to the first treatment and on Visit 5 (or the last visit) and a comparison to the efficacy data obtained in our previous study (NCT02665260) after 2 treatments (a comparison will be made to both the VP-102 without occlusion

Primary Endpoint of Exposure Cohort

The primary endpoint of the exposure study will be the assessed systemic exposure levels of cantharidin following dermal application of VP-102 on 21 or greater molluscum lesions. All additional endpoints and methods of analysis from the Primary Study will apply to the patients in the exposure arm as described above.

Method of Analysis

Eligible patients enrolled in our study will receive the investigational drug. The primary endpoint is the percentage of patients who achieve total clearance, as defined as 100% reduction in baseline MC count.

The unit of analysis is clearance. Data will be summarized using descriptive characteristics for subject and lesion variables. A bivariate comparison between the independent variable (lesion clearance) and the independent variables (age, gender, race and/or ethnicity, lesion location, will be performed using Chi-square analysis. All statistical analyses will be performed with the SAS statistical software package (Version 9.2, SAS Institute Inc., Cary, NC).

The unit of analysis is procedure. A bivariate comparison between our dependent variable and our independent variables (age, gender, race, location of lesion, and region of country) will be performed using chi-square analysis. A Mantel-Haenszel analysis will be used to address possible confounding and effect modification. All statistical analyses will be performed with the SAS statistical software package (Version 9.2, SAS Institute Inc., Cary, NC).

Similar analyses will be done to investigate the secondary endpoints.

Subject data will be maintained on a protected database with restricted access to only those indicated in the informed consent documentation.

Method of Analysis of Exposure Arm:

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

2.3 Anticipated risks from study drug

When used appropriately, side effects of VP-102, topical cantharidin, are rare. Anticipated risks from topical application consist of local site skin reactions. A few hours after application, there may be some mild to moderate pain, pruritus, transient burning sensation, and/or temporary erythema. Post-inflammatory hypo- or hyper-pigmentation is a potential temporary side effect. The key common side effects for patient and family members to take notice of are pain and blistering (topical). Unexpected, but rarely reported side effects are as follows: There has been one case report of toxic shock syndrome following compounded cantharidin treatment for MC when a treated area came in contact with normal skin, resulting in a large blister that became secondarily infected with a toxin-producing bacteria. There have been two case reports of lymphangitis and one case of subsequent lymphedema after using cantharidin in the treatment of plantar warts (Stazzone et al, 1998, Dilaimy et al, 1975). However, since these cases of lymphangitis occurred when cantharidin was used for a different indication (plantar warts) and in a different protocol, these cases of lymphangitis were not disclosed in the consent forms in order to avoid patient confusion.

Safety monitoring

At each follow-up visit, the patient will be interviewed and asked to fill out a safety-monitoring questionnaire before treatment. Questions will include:

1. Have you noticed any changes in your condition (including lesion resolution/development) since your last VP-102 cantharidin treatment?
2. Have there been any changes in your overall health (including illnesses or injuries) since your last visit?
3. Did you experience any side effects while on the VP-102 cantharidin?
4. Are you taking any new medications?
5. Do you have any other comments/concerns about this treatment (VP-102, cantharidin)?

An active assessment of systemic drug safety will be assessed at every visit, including past medical history, vital signs and a thorough review of systems (attached Case Report Form Worksheets for Study Visits). Subjects will be monitored closely for both common and rare side effects. The most commonly reported side effects of topical administration are irritant dermatitis, dermal bullae, and post-inflammatory pigmentation. Patients or their parent/guardian will be asked to fill out a questionnaire, Patient Evaluation of Response to Investigational Treatment (PERIT), at home to evaluate the effect of VP-102, cantharidin on the treated site(s) 24 hours post-treatment. While systemic absorption via topical administration is believed to be negligible, signs and symptoms of systemic toxicity will be monitored. Systemic toxicity includes neurologic (ataxia, seizures), cardiovascular (hypotension, sinus tachycardia), renal (lumbar pain, polyuria, dysuria, hematuria), and gastrointestinal (vomiting, hematemesis, diarrhea, hematochezia, tenesmus) findings. [Medtext (registered) Database. Cantharidin. Accessed on 11 December 2011]. At each visit, patients will also fill out a patient evaluation of response to treatment form (attached).

Safety Monitoring Plan

Subjects and parents will be educated on the investigational product as well as the follow-up. A teach-back method will be demonstrated by the Principal Investigator/Sub-Investigator, in which he/she will show subjects/ family members how to wash off the area with mild soap and water. Patients will be monitored following treatment to ensure optimal drying of the investigational product (usually 1-2 minutes) and prevention of accidental oral ingestion prior to drying as this age group may unknowingly try to place hands in mouth, etc. Parents will be given both verbal and written follow-up instructions on potential side

effects and complications, key contact numbers, and the e-mail address of the study doctor/study coordinator for questions or concerns, and a copy of their signed informed consent. Parents of the subjects will receive a follow-up phone call within 24 hours post treatment to collect information to confirm the product was removed and any questions or adverse events that may have occurred since the product was applied. Patients are given a 24-hour phone number, which will connect them to the Dermatologist on call where they may discuss any concerns that may arise prior to the phone call. All Dermatologists have been trained and are familiar with the protocol. All severe adverse events will be reported to the IRB and FDA per FDA guidelines. A formal safety-monitoring questionnaire will be given at each study visit.

In addition, for female patients that have reached menarche, a urine pregnancy test will be conducted at screening and at each visit prior to the application of study medication. In the event a patient becomes pregnant during the treatment phase, treatment will be stopped and the patient will be followed until delivery. The pregnancy and any adverse events will be reported per HRPP/IRB and FDA reporting guidelines.

Subject stopping criteria

Patients may withdraw their consent at any time and no longer participate in the trial. Patients will be withdrawn from the study if they have poor tolerance to treatment, start using new medications for other conditions that prescribe the use of any of the agents used in the study, or major side effects, including:

- Severe allergic responses to any of the ingredients of the agents used in treatment
- Serious secondary infection at the treated site
- Other serious symptoms, which may be associated with the treatment from any of the agents used in the study; or anytime the medical provider or the patient feel that it is in the best interest of the patient to discontinue participation in the study.

3 Investigational Product

Cantharidin, a type of terpenoid, is derived from blister beetles of the *Meloidae* family. Its chemical name is 2,6-Dimethyl-4,10-dioxatricyclo-[5.2.1.0^{2,6}]decane-3,5-dione. Its molecular mass is 196.20 g/mol, and its density is 1.41 g/cm³. Its melting point is above 216-218°C. The Material Safety Data Sheet lists the Oral Lethal Dose 50 as 0.43 mg/kg [human].

Cantharidin is an odorless and colorless crystal. It is poorly soluble in water, and slightly soluble in alcohol, acetone, ether, and fats. It forms a water-soluble salt when it reacts with alkali.

Drug Product Manufacturer:
Sterling Pharmaceutical Services
109 South 2nd Street
Dupo IL 62239

Sterling Pharmaceutical Services is obtaining VP-102 (GMP cantharidin) from the manufacturer listed below.

API Manufacturer:
Albany Molecular Research Institute (AMRI)
21 Corporate Circle
Albany, NY 12203

AMRI has manufactured cantharidin to >99% purity under GMP conditions.

Sterling Pharmaceutical Sciences and Albany Molecular Research Institute are FDA-registered drug manufacturing establishments, which operate under current Good Manufacturing Practices. A MSDS for the API is attached.

3.1 General method of preparation and packaging

Cantharidin drug product will be made by Sterling Pharmaceutical Services, a GMP manufacturer of FDA approved drugs. Sterling Pharmaceutical Services will obtain cantharidin from AMRI. The investigational products VP-102 will be made in accordance with USP 795 guidelines for compounded drug products. Cantharidin and its vehicle are stable for 180 days from the compounding date at room temperature. This investigational product 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 final preparation will be in single-use 4 mL glass bottles with a black phenolic polyvinyl lined caps or in single-use glass ampules stored within in a single use plastic applicators with integrated inline filter to remove any glass particles capable of breaking the skin. The drug product, VP-102, will be released after passing quality control measures, such as visual inspection for physical appearance (color, uniformity) and physical stability (discoloration, changes in viscosity) according to USP guidelines. The final preparation will be stored at United States Pharmacopeia (USP) controlled room temperature (59-86°F) in a dark locked cabinet in the Division of Dermatology's Clinical Trials Unit at Montefiore Medical Center/Albert Einstein College of Medicine.

3.2 Drug components and drug product

Formula for 10 ml of Cantharidin 0.7% to 1.0% Topical Solution:

Compound	0.7% First Trial Formulation	0.7% Formulation for this Extension Trial	1.0% Formulation for this Extension Trial
Cantharidin (g)	0.070000	0.070000	0.100000
Acetone (ml)	5.300000	8.250000	8.250000
Ethanol (ml)	1.175000	1.750000	1.750000
Ether (ml)	3.525000	0.000000	0.000000
Castor Oil (g)	0.109800	0.109800	0.109800
Nitrocellulose (g)	0.139080	0.139080	0.139080
Hydroxypropyl Cellulose (g)	0.070000	0.070000	0.070000
Camphor (g)	0.073200	0.073200	0.073200
Denatonium Benzoate (g)	0.000000	0.000474	0.000474
Gentian Violet (g)	0.000000	0.000395	0.000395

All excipients listed above are United States Pharmacopeia (USP) or National Formulary (NF) grade. All drug components will be included in the final drug product.

Note: Our previous formulation was made using Collodion Flexible USP at a compounding pharmacy. Flexible Collodion is a mixture of diethyl ether, ethanol, nitrocellulose, camphor and castor oil.

3.3 Labeling

Each vial or applicator will be labeled with a study patient identification number or tracking number.. The label will also display the date of production and the statement **“Caution: New Drug--Limited by Federal Law to Investigational Use” and “Warning: Flammable Liquid.” The vial or applicator will display the appropriate yellow triangular flammable sticker as well.** There will be no placebo product made as this in an open-label study. All used and unused study product is to be held until completion of the study.

It is expected that patients enrolled in the *Primary* cohort will not need more than 6 vials of study medication to complete the study. Therefore, the site will continue to use the current study kits for patient numbers 001-031. In the event patients require more than 6 vials for treatment due to error or broken vials, the company must be notified prior to using vials from other kits or bulk supply. A specific plan will be outlined for each patient on a case-by-case basis.

Patients enrolled in the Exposure cohort will be treated with an additional bulk supply shipment of applicators numbered 001-120. Exposure cohort patients will be numbered in sequential order as E001-E024. This will allow for the intended goal of 16 patients to be treated. Vial numbers are used for accountability purposes only and are recorded on the accountability log as they are used. Vials do not need to be used in sequential order.

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.

3.4 Environmental analysis requirements

There is no available information on pollution hazards for cantharidin, but it is unlikely to cause environmental damage. A laboratory study evaluated the effect of cantharidin in blister beetles on the health of livestock. Results showed that blister beetles crushed in the fields and subsequently ingested by livestock were a greater health risk than cantharidin-contaminated hay free of blister beetles (Blodgett et al, 1992). The investigators request categorical exclusion from any environmental analysis requirements.

4 PHARMACOLOGY AND TOXICOLOGY

Cantharidin 0.7% to 1.0% Exposure Limits (route, species)

LD50: 1mg/kg (IPR, mouse)

LD50: 1710 Ug/kg (IPR, mammal)

LDLo: 0.428 mg/kg (oral, human)

Toxicology Data:

Inhalation: Exposure to vapors may cause irritation or dizziness

Skin/eye contact (localized irritation): Highly irritating to skin and eyes. Following contact with skin, it may cause blisters, prickling, and a burning sensation.

Ingestion (systemic): Poison; potentially fatal if ingested.

Extremely hazardous in the case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Very hazardous in the case of skin contact (permeator). Hazardous in the case of skin contact (corrosive). Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

(PCCA Cantharidin Material Data Safety Sheet, Revised June 2011. PCCA, Inc.)

Given the topical use of cantharidin in this investigation and the minimal number of reports of adverse events with topical application, the investigators have concluded that it is reasonably safe to conduct the proposed clinical investigation. A trained medical professional will apply cantharidin in a controlled manner. There has only been one reported case of a serious side effect after topical administration of cantharidin, which was due to a bacterial superinfection causing toxic shock syndrome. All other reported side effects are local irritation. Serious skin side effects are usually due to improper application onto normal skin or from using more than the recommended dose.

Toxicology Data on Excipients:

Acetone: Acetone is a naturally occurring chemical found both at low levels in the human body and in many FDA approved prescription and OTC drug products. Products with labels claiming 100% acetone are available for topical use in products such as nail-polish remover. Acetone has been used in FDA approved topical drug products at concentrations up to 12.69%, according to the FDA IID (2016). A dose of 0.2 mL (which is approximately equal to 157mg/20g or 7,850mg/KG) is recorded as a No Observed Adverse Event Level (NOAEL) value in murine chronic exposure studies. In this study, we estimate the maximum possible exposure at ~412mg (or 34.3mg/kg when scaled to the average 12kg 2-year old girl), or more than 200 times less than the NOAEL level when scaled to the youngest patients who can enroll in the study.

Ethanol: Ethanol has been previously approved for use in topical drug products in amounts up to 91.07% according to the FDA Inactive Ingredient Database (IID) (2016).

Castor Oil: Castor Oil has been previously approved for use in topical drug products in amounts up to 14.9%, according to the FDA IID (2016).

Nitrocellulose: When combined with an appropriate solvent, nitrocellulose is a film-forming mixture that is found in many FDA approved OTC drug products. Corn, callus, and wart removing drug products are often found in collodion-like vehicles comprised of solvents, nitrocellulose, and plasticizers and are generally recognized as safe and effective by FDA for topical application as over-the counter (OTC) products (21 CFR 358.503).

Hydroxypropyl Cellulose: Hydroxypropyl Cellulose has been previously approved for use in topical drug products in amounts up to 4%, according to the FDA IID (2016).

Camphor: Historically, camphor has been used as an active ingredient for its analgesic effect and has been found by the FDA Advisory Review Panel on OTC Topical Analgesic Drug Products to be safe at

concentrations up to 11% (44 FR 69802; December 4, 1979). In this formulation, camphor is being used as a plasticizer in order to increase the flexibility and resiliency of the nitrocellulose film. This is a historic use of camphor, where it makes up one component of what is known as flexible collodion, frequently utilized in over-the-counter products and currently used formulations of cantharidin.

Denatonium Benzoate: Denatonium benzoate has been used in FDA approved topical drug products at concentrations up to 0.0003% according to the FDA IID (2016). However, a 0.0003% solution of denatonium benzoate in the VP-100 vehicle is not sufficiently bitter to serve as an oral deterrent as its solubility is quite limited in the resulting film. The maximum possible dermal exposure to denatonium benzoate in the proposed formulation is 0.03mg, well below the reported no-observed-adverse-effect-level (NOAEL). (United States Consumer Product Safety Commission Final Report on Aversive Agents, 1992)

Gentian Violet: Gentian violet has been used as a medical dye for over 100 years, is found OTC drug products for the treatment of fungal, helminthic and bacterial infections and is also used as a colorant in numerous models of pre-surgical skin marking pens. In the investigational agent, gentian violet is used as a dye in order to visualize where the drug product has been applied. According to the USP, gentian violet is used as either a 1% (w/v) solution or a 1.6% (w/w) cream. The FDA has previously evaluated gentian violet as an OTC topical agent and determined that “Locally, when applied to the mucous membranes and skin, gentian violet is nontoxic”. Federal Register Vol. 47 No 101, Tuesday May 25th 1982 22874.

4.1 Pharmacodynamics

4.1.1 Primary pharmacodynamics

Cantharidin, a known protein phosphatase inhibitor, is absorbed by the lipid layers of epidermal cell membranes and results in the release of neutral serine proteases that cause degeneration of the desmosomal plaque, leading to detachment of tonofilaments from desmosomes. This process results in acantholysis and the formation of an intra-epidermal blister. Since the lesions are intra-epidermal, they heal without scarring (Moed et al, 2001).

Cantharidin does not have a direct effect on the MCV, but it is thought to induce an inflammatory response that speeds recovery.

4.2 Safety pharmacology

For this protocol, VP-102, (investigational product) will be applied topically. No amount of investigational product will be given to the subjects (i.e. no subject will have possession of the investigational product as it will be applied in the office by trained medical personnel).

Effects of topical administration:

- Reported effects of topical cantharidin application include mild irritation and inflammation to burns, blistering, and ulceration. Temporary post-inflammatory hyperpigmentation may occur with topical cantharidin treatment (Silverberg et al, 2000). Cantharidin is absorbed through the lipid layer of the epidermal cell membranes, and it is possible that with extensive cutaneous exposure (likely greater than 1ml), it may cause systemic toxicity with diaphoresis, tachycardia, hematuria, and oliguria. (MEDITEXT® Medical Managements. Cantharidin. Accessed 11 Dec 2011) When used in the treatment of warts, annular warts occasionally develop at the site of cantharidin administration (Fund et al, 1979).
- Allergic reactions to certain cantharidin formulations have occurred, consisting of inflammation, tenderness, edema, and ulceration with secondary lymphatic responses, such as lymphangitis and lymphedema (MEDITEXT® Medical Managements. Cantharidin. Accessed 11 Dec 2011)

Effects of oral administration:

- Neurological effects – generalized seizures, ataxia, and increased deep tendon reflexes have been reported in cantharidin poisoning, although this appears to be unusual (Karras et al, 1996).
- Cardiovascular effects – the most common cardiac effect noted in cantharidin poisoning by ingestion is sinus tachycardia. Hypotension has been reported with the ingestion of large amounts of cantharidin. Autopsy studies have revealed pericardial and subendocardial hemorrhages, particularly in the intraventricular septum. Controlled human studies have found dose-related myofibril degeneration and mitochondrial swelling. ECG abnormalities related to cantharidin ingestion have been reported and include ST segment elevation in inferior limb leads and anterior precordial leads, as well as transient T wave inversions. Ventricular ectopy, asystole, ventricular tachycardia and fibrillation have also been reported (Karras et al, 1996).
- Pulmonary effects – lung injury is an infrequent cause of morbidity in cantharidin poisoning and is usually not permanent. There have been reports of gross pulmonary edema, bronchial hemorrhage, and subpleural hemorrhages in cases of fatal cantharidin poisoning. Hyperventilation has also been noted (Karras et al, 1996).
- Renal effects – cantharidin is excreted by glomerular filtration, and its life-threatening effects are secondary to its renal toxicity. Symptoms include lumbar pain, polyuria, dysuria, urinary frequency, and hematuria, which may persist for up to 15 days. Acute tubular necrosis may occur, causing death. Gross pathology of cantharidin poisoning show renal engorgement with hemorrhage into the renal pelvis. Microscopy shows edema of Bowman's capsule and basement membrane with sloughed epithelial cells packing the capsular space. The lower genitourinary tract shows multiple petechial hemorrhages. Hemorrhagic bullae have been found in the bladder (Karras et al, 1996).
- Gastrointestinal (GI) effects – when ingested, cantharidin has a vesicant effect on the upper GI tract. It induces burning and blistering of the mouth, tongue, oropharynx, dysphagia, abdominal cramping, vomiting, and hematemesis. If cantharidin passes into the lower GI tract, it can induce diarrhea, hematochezia, and tenesmus. It may also induce fatal GI hemorrhage. The presence of lipids in the stomach enhances toxin absorption. Fatty changes and parenchymatous degeneration of the liver may be seen in severe cases (Karras et al, 1996).
- Abuse liability – when not applied in the office, it may be improperly used, causing large blisters or burns. Cantharidin has been known for its aphrodisiac potential when ingested, and cases of severe poisoning have been reported when used for this purpose. However there is no data on abuse or dependence potential
- Other effects – Priapism in men and vascular engorgement in women have been noted in cantharidin poisoning (Moed, 2001). There is one report of low-grade disseminated intravascular coagulation associated with cantharidin poisoning (Karras et al, 1996).

4.3 Pharmacokinetics

- 4.3.1 Absorption** – Cantharidin is absorbed through the lipid layer of the epidermal cell membrane. Ingestion results in systemic absorption through the GI tract. Onset may be as soon as 10 minutes with large doses or take several hours. Oral absorption is enhanced by fats, oils, and lipids.
- 4.3.2 Distribution** – When ingested, circulating cantharidin binds to albumin.
- 4.3.3 Metabolism** – Unknown.
- 4.3.4 Excretion** – When ingested, cantharidin is eliminated slowly by the kidneys.

4.4 Pharmacology summary

Topical application of cantharidin results in intra-epidermal blister formation due to acantholysis and disruption of the desmosome complex in the epidermis. Cantharidin is known to be a protein phosphatase inhibitor but its mechanism of action in MC is unknown.

4.5 Pharmacology conclusions

Cantharidin is postulated to speed the recovery in MC through local irritation and induction of the body's inflammatory immune response.

4.6 Toxicology

Karras DJ et al. Poisoning from "Spanish Fly" (Cantharidin). *Am J Emerg Med* 1996;14(5):478-483.

Key findings: A case series of four young adults who ingested cantharidin as an aphrodisiac. Cantharidin was mixed at an unknown concentration into a pitcher of Kool-Aid, by varying reports as either a prank or as an aphrodisiac for a girlfriend. All 4 patients had dysuria. Three patients reported abdominal pain, one had flank pain, and one woman had vaginal bleeding. Three had hematuria, and two had occult rectal bleeding. Two patients had low-grade disseminated intravascular coagulation. Management was supportive. All patients survived. The authors also review the literature on cantharidin poisoning.

Avery JS. A case of acute cantharides poisoning. *Lancet* 1908;2: 800.

Key findings: A man was treated with cantharidin for an undisclosed pulmonary issue. A 1:2 dilution of cantharidin liquor was painted on a large confluent area at base of lung (7x2 ¾ cm patch). [Note: For this protocol, cantharidin is only applied to the tip of molluscum lesions, which are small 1-5 mm papules.] The patient developed hematuria, tachycardia, profuse sweating, urgency, penis pain, dysuria, oliguria. The patient recovered.

Dilaimy M. Lymphangitis caused by cantharidin. *Arch Dermatol* 1975;111:1073.

Key findings: Lymphangitis occurring after patient treated with cantharidin for plantar warts.

Stazzone AM et al. Lymphangitis and refractory lymphedema after treatment with topical cantharidin. *Arch Dermatol* 1998;134:104-196.

Key findings: A 39 year old woman who developed swelling, pain, blistering, and ulceration several hours after using cantharidin to treat 7 plantar warts (0.5-1.5 cm). Three days later, the necrotic warts were excised under local anesthesia and the base was treated with phenol and povidone-iodine. Acute inflammation subsided after several days, but the patient's legs continued to swell for 9 months with progressive induration. The authors implicated cantharidin in the development of lymphangitis and refractory lymphedema.

Langley JM et al. Case report: Molluscum contagiosum. Toxic shock syndrome following cantharidin treatment. *Canadian Family Physician* 2003, July, Vol 49:887-9.

Key findings: Toxic shock syndrome developed within 24 hours of topical application in a 4-year-old boy treated for MC. He had 20 lesions on his chest wall treated and then covered with occlusive waterproof surgical tape. It is believed that the occlusive tape allowed cantharidin to spread to normal skin, thus inducing large blisters and increasing the risk of bacterial superinfection.

Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: Experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol* 2000;43:503-507.

Key findings: Retrospective chart review of 537 patients treated with cantharidin for MC. The investigators phoned 300 patients for results. Blisters occurred at sites of application in 92% of patients. Temporary burning, pain, erythema, or pruritus was reported in 6% to 37% of patients. No major side effects or secondary bacterial infections were reported. 95% of parents reported they would use cantharidin again.

Coskey RJ. Treatment of plantar warts in children with a salicylic acid-podophyllin-cantharidin product. *Pediatric Dermatology* 1984;2(1):71-73.

Key findings: 121 children with plantar warts were treated with the above preparation and had their warts occluded with a Band-Aid for 24 hours. One week later the bulla was debrided and silver nitrate applied. Efficacy found in 81 cases. Four patients developed cellulitis.

Tagwireyi D, Ball DE, Loga PJ, Moyo S. Cantharidin poisoning due to “Blister beetle” ingestion. *Toxicon* 2000;38:1865-1869.

Key findings: A 4-year-old girl mistakenly ingested a blister beetle, and presented with abdominal pain, oliguria, and hematuria. She was lethargic, tachycardic, tachypneic, hyponatremic, hyperkalemic, with slight generalized edema. She survived with supportive care, while her elder brother died on presentation to the hospital after also ingesting a blister beetle.

Nicholls DS, Teare D. Poisoning by cantharidin. *Br Med J* 1954;2:1384.

Key findings: Case report of a 43-year-old man who died after mixing 65 mg of cantharidin in water. The patient was using the mixture to soak fish bait to make the bait more ‘attractive to fish.’ The mixture got on his thumb, which he subsequently pricked with a fishhook, and sucked in palliation. He died shortly thereafter.

Fish HP, Reutter Fw, Gloor F. Lesions of the kidney and the efferent urinary tract due to cantharidine. *Schweiz Med Wochenschr* 1978;108:1664-1667. Reports 5 cases of cantharidin toxicity following use as an aphrodisiac or abortifacient.

Key findings: All patients had urinary tract symptoms, 4 had gross hematuria, and 1 had non-oliguric renal failure. All patients recovered.

Rabkin SW, Friesen JM, Ferris JA. A model of cardiac arrhythmias and sudden death: cantharidin induced cardiomyopathy. *J Pharmacol Exp Ther* 1979;210:43-50.

Key findings: Found to have a dose-related mitochondrial swelling with disruption of the cristae, appearance of intramitochondrial inclusion bodies and myofibril degeneration.

Oaks WM, Ditunno JF, Maganni T. Cantharidin poisoning. *Arch Intern Med* 1960;105:574.

Key findings: Ecchymotic areas of the medulla, cerebellum, and pia were found in cantharidin poisoning. Showed edematous and fatty changes of the brain.

Rosin RD. Cantharides Intoxication. *BMJ* 1967;4:33.

Key findings: Describes case of cantharidin poisoning after ingestion as an aphrodisiac. The patient survived but experienced severe dysuria, gross hematuria, priapism, and abdominal pain.

4.7 Genetic toxicology

There is currently no publically available data on the mutagenic or genotoxic potential of cantharidin. However, the sponsor has conducted a GLP mutagenesis study and cantharidin was found to be non-mutagenic. Cantharidin was not evaluable for clastogenic potential according to ICH guidelines in an *in vitro* micronucleus assay.

4.8 Carcinogenicity

IARC Carcinogen Rating 3. Cantharidin is not yet classifiable regarding carcinogenicity to humans. There are no studies on the potential carcinogenicity in humans. Cantharidin acted as a weak but complete carcinogen in mice following topical application; however, carcinomas did not appear before 16 months of observation (Laerum et al, 1972).

4.9 Reproductive and developmental toxicology

There were no studies found on possible reproductive effects of cantharidin in humans or experimental animals. However, various cantharidin-containing preparations have been used orally to induce abortion (Cheng et al, 1990, Moed et al, 2001). There is no data available about cantharidin's effect on breastfeeding. It is Pregnancy Class C (no reproductive data found).

4.10 Special toxicology studies

No special toxicology studies have been published to date.

4.11 Toxicology summary

Cantharidin is described as being toxic to the gastrointestinal tract and the kidneys when ingested, due to its phosphodiesterase inhibition. When used improperly, topical application can result in the formation of severe blisters and cutaneous burns. There has been one case of toxic shock syndrome after a cantharidin-induced blister developed a secondary bacterial infection. There have been two cases of lymphangitis with the use of cantharidin for plantar warts.

4.12 Toxicology conclusions

When ingested, cantharidin is highly toxic to multiple organ systems. When applied topically in a controlled manner in the treatment of MC, side effects are minimal and if present, typically consist of those expected from the drug action such as local skin reactions including irritation, inflammation, and non-scarring intra-epidermal blisters.

5 PREVIOUS HUMAN EXPERIENCE WITH THE INVESTIGATIONAL AGENT

5.1 *Marketed experience*

Cantharidin has a well-characterized history of safe use in the treatment of several dermatologic conditions, such as MC and verruca vulgaris. Few serious adverse event reports exist in the literature when applied topically; oral administration is toxic, but concerns regarding systemic toxicity are minimized by its use only within an office setting by a trained professional. The use of cantharidin by practitioners pre-dates the Food, Drug, and Cosmetic Act of 1938, and met the safety requirements there in. The FDA amended the Act in 1962 with the Drug Efficacy Study Implementation, which required manufacturers to submit efficacy data for products. When manufacturers did not submit efficacy data, cantharidin was removed from the US market. Following decades of calls from dermatologists for reconsideration of classification, cantharidin was reclassified under the FDA's "Bulk Substances List," which permits the compounding of bulk substances by a physician or pharmacist on a customized basis for individual patients.

Cantharidin is available in Canada under the trade name Canthacur. Canthacur is indicated for the topical use of removal of benign epithelial growths, such as periungual warts (verruca vulgaris) or MC.

5.2 *Prior clinical research experience*

Hanna et al. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatric Dermatology*. 2006;23(6):574-579. 124 children, aged 1-18 years were randomized to one of four groups. Ten molluscum lesions in each subject were treated with one of the four treatments. The rest of the molluscum lesions were treated with curettage in all patients. Efficacy was measured by the number of visits needed to treat molluscum. The authors reported that 36.7% of subjects treated with cantharidin needed one visit to treat their molluscum, 43.3% needed 2 visits, and 20.0% needed 3 visits. 60% of patients and parents were satisfied with cantharidin treatment. Reported an 18.6% rate of adverse effects in the cantharidin group, but did not disclose specifics about the adverse effects.

Maglio D, Nightingale CH, Nicolau DP. Production and resolution of cantharidin-induced inflammatory blisters. *International Journal of Antimicrobial Agents* 2003;22:77-80. Set out to characterize blister healing induced by 0.25% cantharidin ointment made from cantharidin powder. The ointment stayed on the skin for 12-14 hours. All volunteers had blister areas return to baseline without scarring, though resolution time varied with skin type.

Dosal et al. Efficacy of Cantharidin in Molluscum Contagiosum: A Pilot, Double-Blinded, Placebo-Controlled Trial. NCT#00667225. Submitted to *Pediatric Dermatology* in September 2011.

Abstract: A prospective, double-blinded, placebo-controlled, randomized clinical trial to evaluate the safety and efficacy of topical cantharidin for treatment of pediatric MC. 29 children aged 5-10 with the diagnosis of MC were enrolled. The performance of cantharidin treatment over approximately 2 months was not substantially better than the performance of placebo; however, the study was not adequately powered to detect a difference due to under-enrollment. Subjects experienced minimal side effects when treated with cantharidin.

Flygare RA. A clinical trial examining the efficacy of treatment of cutaneous verruca vulgaris in adult patients with combined liquid nitrogen cryotherapy and topical cantharidin versus liquid nitrogen and placebo. Copyright 2008 by ProQuest, LLC. UMI# 3328112. NCT# 1084824.

Abstract The objective of the study was to determine if cantharidin is more effective if it is used alone, or in combination with liquid nitrogen in the topical treatment of verruca vulgaris. Primary outcome was the complete clinical resolution of the warts studied, by the end of the course of treatment at 12 weeks. Although underpowered, the results of the study support combination therapy with these two agents (liquid nitrogen and topical cantharidin) as a viable alternative to those adult patients with warts who desire treatment more aggressive than standard monotherapy.

Our group recently completed a double-blind placebo controlled study in 94 patients under IND 114032. The Trial Registration: clinicaltrials.gov Identifier is NCT02665260. The interim results were presented in a poster at the 41st Society of Pediatric Dermatology meeting. A full manuscript is in the process of being submitted for publication, but the abstract of the draft manuscript is below:

Abstract

Importance: Molluscum contagiosum (MC) is a common viral infection of the skin primarily affecting children. It is typically uncomfortable, disfiguring, and contagious. Since, there are no FDA-approved therapies, the need for a safe and effective remedy is essential.

Objective To determine the efficacy and safety of topical cantharidin 0.7% compared to placebo in the treatment of pediatric MC.

Design Double-blind, placebo-controlled trial followed by open label extension. Data was analyzed with an intention-to-treat and last-observation-carried-forward model.

Setting Participants were recruited from general and pediatric dermatology clinics at an academic medical center in Bronx, New York.

Participants Ninety-four participants aged 2 to 17 years with less than 50 MC lesions were enrolled in a two-phase trial from August 2012 through November 2015. Follow-up was completed by January 2016.

Interventions Participants were randomized blindly to four treatment groups: cantharidin 0.7% topical, cantharidin 0.7% topical with occlusion, placebo, and placebo with occlusion. Treatments were applied every three weeks. After week 6, participants were treated with open-label, cantharidin 0.7% without occlusion until all MC resolved.

Main Outcome and Measures The primary endpoint was total clearance. Secondary endpoints included lesion count, time to total clearance, adverse events and patient-reported side effects.

Results The 94 participants enrolled had a mean of 22.2 (SD 12.9) lesions at baseline. After 6 weeks, total clearance was significantly higher in the cantharidin (30.4%) and cantharidin with occlusion (41.7%) groups compared to those in the placebo (13.6%) and placebo with occlusion groups (8.0%) ($\chi^2(3, N=94) = 9.58, p < 0.05$). Furthermore, lesion counts were significantly lower in the groups receiving cantharidin compared to placebo ($F(1.513, 136.1) = 12.06, p < 0.0005$). In the open-label phase, the median time to clearance was 9 weeks and 85.9% of the participants had complete resolution. While parents reported varying degrees of inflammation immediately following treatment, there were no adverse reactions otherwise documented in the blinded or open label extension phases of this study.

Conclusions and Relevance For treatment of molluscum contagiosum, topical cantharidin resulted in greater lesion clearance compared to placebo without significant adverse events. These findings demonstrate that cantharidin is an effective and safe treatment for MC when applied in-office by a health care professional.

5.3 Clinical care experience

Funt TR, Mehr KA. Cantharidin: A valuable office treatment of molluscum contagiosum. *Southern Med J* 1972;72:1019.

Description: A clinical brief in which authors report their 17-year history of successful use of cantharidin in pediatric patients with MC. The authors report a case of a severe, painful, bullous eruption after improper home application with cantharidin.

Silverberg NB. Pediatric molluscum contagiosum: Optimal treatment strategies. *Pediatr Drugs* 2003;5(8):505-512.

Description: This review article discusses the molluscum contagiosum virus, including its transmission, clinical appearance, and treatment. Cantharidin is one of the treatments discussed. Discussion of cantharidin treatment includes proper application, prognosis, contraindication, and safety monitoring.

Brown J, Janniger CK, Schwartz RA, Silverberg NB. Childhood molluscum contagiosum. *Int J Dermatol* 2006;45:93-99.

Description: Cantharidin is cited as a treatment of choice for young children. Discussion of use includes use in clinical practice, including safety monitoring.

Epstein E. Cantharidin therapy for molluscum contagiosum in children. [Letter] J Am Acad Dermatol 2001;45(4):638.

Description: Author references a Journal of the American Academy of Dermatology article [2000;43:503-7], describing their 25 years of experience with cantharidin as a safe and effective therapy for molluscum contagiosum. The letter includes administration tips and monitoring. The author reported no side effects with use.

6 ADDITIONAL INFORMATION

6.1 *Pediatric studies*

Any pediatric studies have already been discussed in previous subsections.

7 REFERENCES

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8 ATTACHMENTS

The following lists the attachments to this IRB application:

- FDA Form 1571
- FDA Form 1572
- IND “Study May Proceed” (official letter from FDA)
- Principal Investigator Curriculum Vitae
- Cantharidin Certificate of Analysis
- Cantharidin Material Safety Data Sheet
- Case Report Form Worksheets for Study Visits
- Patient Safety Monitoring Questionnaire
- Patient Evaluation of Response to Treatment Form
- Children’s Dermatology Life Quality Index (CDLQI)
- Study Event Flow Chart (Updated)
- USP <795> Pharmaceutical Compounding
- Manual of Operations for Specimen Collection-Exposure Cohort