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A Phase 2 Open-Label Study to Evaluate VP-102 for the Treatment of Molluscum Contagiosum

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ABSTRACT

Background: This Phase 2, open-label study evaluated the safety, efficacy, systemic exposure, and impact on quality of life (QoL) with treatment using VP-102, a drug-device combination containing cantharidin (0.7% w/v) in subjects with molluscum contagiosum (MC).

Study Design: Pediatric subjects with MC (2–15 years of age) were eligible to enroll in this 12-week study. MC lesions were treated topically with VP-102 every 21 days until clearance (maximum of 4 treatments). Adverse events (AEs) and QoL outcomes (using the Children's Quality of Life Index, CDLQI) were documented at each visit. Rate of complete clearance and the percent reduction in lesions were measured at each visit on days 21, 42, 63, and 84 (end of study [EOS] visit). A group of 17 subjects with at least 21 MC lesions was evaluated for systemic cantharidin exposure via plasma samples obtained before the first application of VP-102, and at 2 hours, 6 hours, and 24 hours post-application.

Results: A total of 33 subjects enrolled in the study (n=17 systemic exposure group, n=16 standard group). There were an equal number of male and female subjects. Subject mean (SD, range) age was 6.7 (3.3, 2–15) years, with a mean lesion count of 30 (26.1, 3–113). Complete lesion clearance was achieved in 48.5% of subjects, with a 90.4% reduction in lesions from baseline to the EOS visit. Mean CDLQI score decreased from 2.6 at baseline to 0.38 at the EOS visit. AEs were mild to moderate in severity and expected due to the pharmacodynamic action of cantharidin. There were no serious treatment-related adverse events and no study discontinuations due to treatment. In the systemic exposure group plasma cantharidin levels were below the lower limit of quantitation (LLOQ, 2.5 ng/mL) in 65 of 66 samples.

Conclusions: VP-102 treatment resulted in a reduction in lesion counts and improved QoL. Treated subjects had a 48.5% rate of complete clearance of molluscum lesions. Negligible systemic cantharidin exposure was observed in the systemic exposure group. This data demonstrates safety and efficacy of treatment with VP-102 in MC; a widespread viral infection that does not have any current FDA-approved treatments.

Significant Finding: Treatment of subjects with MC using VP-102 resulted in negligible systemic cantharidin exposure, as well as a reduction in lesion counts, improved QoL, and a demonstrated efficacy in clearance of new and baseline MC lesions.

Meaning: Results of this Phase 2 study demonstrate efficacy and safety outcomes in using VP-102 in MC subjects, and large randomized clinical trials are warranted to compare topical VP-102 with a vehicle control in order to fully evaluate the use of the medication.

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INTRODUCTION

Molluscum contagiosum (MC) is one of the 50 most prevalent diseases worldwide.[1] This common cutaneous infection mainly affects children, with the greatest incidence occurring in individuals aged 1–14 years.[2,3] The MC virus is most commonly transmitted through skin-to-skin contact with infected skin, contaminated objects (eg, bath towels, toys, and clothing), autoinoculation,[4] and sexual transmission.[3]

MC lesions can cause pain, pruritus, may become infected, and have been shown to negatively impact quality of life (QoL).[5] One study found that in untreated immunocompetent children, MC infections lasted an average of 13 months, and persisted in 30% of children after 18 months, and in 13% of children after 24 months.[6] MC is likely to have a substantial effect on the QoL on 10% of children with the infection, and a moderate effect has been documented in 17.3% of patients.[5]

Currently there are no approved treatments for MC in the United States (US). Although a variety of topical therapies, physical modalities, and destructive approaches are used to treat MC, no single therapeutic approach has been shown to be consistently

effective in large-scale clinical trials.[7] While some clinicians may choose not to treat and rely on spontaneous resolution of lesions, there is a growing body of literature in support of active treatment.[4,7,8] In a survey of 95 pediatric dermatologists, compounded cantharidin was identified as one of the most frequently used approaches and 92% of respondents were satisfied with the efficacy of this agent.[9]

Cantharidin is a terpenoid blistering agent secreted from many species of blister beetles (family Meloidae, *Lytta vesicatoria*). It has been used in Eastern medicine for 2000 years and has been documented as a treatment for MC and verrucae vulgaris in the US since the 1950s.[10] Once applied, acantholysis occurs through detachment of the desmosomes from tonofilaments, followed by formation of a superficial blister.[11]

Although normally used topically, compounded cantharidin has shown toxic effects following oral ingestion including ulceration of the gastrointestinal and genitourinary tracts, and electrolyte and renal function disturbance in humans (LD50 is 0.0.3–0.5 mg/kg). While systemic toxicity is not expected with topical cantharidin, systemic exposure studies have yet to be completed. Several small retrospective and prospective clinical studies using compounded cantharidin formulations have demonstrated effectiveness in subjects with MC using a variety of application durations and dosing regimens.[12-15]

There are caveats to consider when using cantharidin. Changes in concentration can occur with compounded formulations when exposed to air. Raw cantharidin and its formulations differ based on the source of the active ingredient, formulation components, or methods used by the pharmacy compounding the drug. The formulation is commonly applied using rudimentary tools (eg, cotton-tipped wooden swabs or toothpicks), which can lead to unintended side effects, treating of unaffected skin, and cross-contamination.[16] These inconsistencies in source material, formulations, and methods of application, along with the lack of large-scale randomized controlled trials, result in a lack of robust evidence in support of cantharidin as a treatment for MC.[16]

Herein we report the results of an open-label Phase 2 clinical study utilizing VP-102, a proprietary, drug-device combination product containing a topical formulation of 0.7% (w/v) cantharidin administered with a single-use applicator device for the treatment of MC in pediatric subjects. The standardized drug formulation and precision applicator combination of VP-102, with an established application duration and dosing schedule, were designed to overcome the limitations of compounded cantharidin formulation and application concerns.

Pharmacokinetic testing of blood samples was completed to evaluate the systemic exposure of cantharidin in pediatric subjects who had higher lesion counts (≥21 lesions). QoL was assessed using the Children's Dermatology Quality of Life Index (CDLQI) to determine the impact of the disease at baseline and after treatment with VP-102.

METHODS

Study Subjects and Treatment Procedures

The Phase 2, single-site, open-label study evaluated the potential systemic exposure, safety, and efficacy of topical application of VP-102 in children 2–15 years of age. The study was registered in the US (NCT03186378). Eligible participants with MC were enrolled. All subjects participated in the protocol as outlined below, with a subset of subjects with 21 or more MC lesions at baseline undergoing blood sampling for systemic exposure (exposure group). Any subject in the exposure group who did not complete all blood draws could continue to receive treatment but could be replaced. The protocol and consent forms were approved by an independent ethics committee. Assent and written informed consent were obtained from subjects or their parents/guardians.

VP-102 Treatment Methods

The study included a screening period of up to 14 days for an eligibility assessment. Physical exams, medical histories, and MC lesion counts were completed prior to treatment. Wash-out of any prior MC treatment agent occurred before the first treatment application on day 1. Additional applications of VP-102 to all treatable (baseline and new) lesions were completed once every 21 days (days 21, 42, 63) if lesions were present, for a maximum of four applications. No more than two applicators were permitted per subject per treatment. The subject or their parent/guardian was instructed to wash off the study drug 24 hours after treatment, or earlier, if significant blistering or pain occurred. The EOS assessments of complete clearance and safety were completed on day 84 or, in the case of subjects achieving complete clearance on or before Treatment 4, at the same visit at which subjects exhibited complete clearance. For subjects with complete clearance prior to Treatment 4, no further visits were required.

Subjects in the exposure group were required to have ≥21 lesions, and at least 3 subjects were required to be between 2 and 5 years of age. MC lesions were treated in all anatomical areas at the discretion of the investigator in the interest of subject safety.

Systemic Exposure Methods (Exposure Group)

Blood was collected prior to the first application of VP-102 on day 1 and then at 2 (± 30 min), 6 (± 1 hr), and 24 (± 3 hrs) hours thereafter, for a total of 4 blood samples (2 mL each). No samples were collected at other treatment visits. The presence of cantharidin in plasma was determined by a GLP-compliant independent laboratory (Pacific BioLabs, Hercules, CA) using

a validated gas chromatography/mass spectrometry analytical method. The unit of analysis was ng/mL, with an analysis sensitivity lower limit of quantitation (LLOQ) of 2.5 ng/mL of cantharidin in plasma.

Assessments

The primary objective was to assess the systemic absorption of cantharidin via plasma testing over a 24-hour exposure period after a single topical application of VP-102 to subjects with at least 21 MC lesions as outlined above. The secondary objectives included safety of VP-102, as well as measures of efficacy, and QoL prior to and throughout treatment.

Efficacy was assessed by the proportion of VP-102-treated subjects achieving complete clearance of all treatable MC lesions (baseline and new) on EOS/Day 84. Additional efficacy endpoints included the proportion of subjects achieving total clearance at days 21, 42, and 63, and percent reduction of MC lesions from baseline to each time point. Lesion counts were performed by a study investigator prior to each treatment application and at EOS.

The impact of VP-102 treatment on QoL was evaluated using the CDLQI completed by the subject, parent, or caregiver at baseline, and on visit days 21, 42, 63, and the EOS visit (day 84).

Safety and tolerability were assessed by determination of adverse events (AEs) and through parent/guardian reporting on the appearance of the skin, the presence of erythema, and/or blistering within 24 hours after each drug application via the Patient Evaluation of Response to Investigational Treatment (PERIT) form. Local skin reactions (LSRs) were only reported as AEs if they were outside of the expected response to treatment with cantharidin in the opinion of the investigator. Treatment-emergent AEs (TEAEs) were defined as AEs that occurred at or after the first treatment application.

Investigational Agent

This study introduced the first clinical use of VP-102; a drug-device combination with a topical solution packaged in a single-use applicator. The active pharmaceutical ingredient of VP-102 is a controlled, highly pure, standardized, viscous topical solution containing 0.7% (w/v) cantharidin manufactured under Good Manufacturing Practices. The film-forming solution also contains gentian violet (a surgical dye to facilitate physician recognition of treated vs untreated lesions) and denatonium benzoate (a bittering agent included to deter potential oral ingestion of the drug). Upon applying the solution via the applicator, the solution dries leaving a thin film that is then washed off up to 24 hours later.

Statistical Methods

Subject disposition, baseline characteristics, MC medical history, and study drug exposure are summarized using descriptive statistics for continuous variables and frequencies and percentages of discrete variables. Adverse event data for the safety population are listed individually and the incidence of AEs is summarized using frequency counts. Analyses included all subjects that entered the study (intent to treat, or ITT group).

RESULTS

A total of 33 subjects were enrolled at a single site in the US, 16 in the VP-102 standard population group and 17 in the exposure group. Baseline demographics including age (median 5 years; range, 2–15), gender, race distribution, and body mass index were similar in both groups (Table 1). Subjects in the standard group had a median of 13.5 lesions (range, 3–21) and a median duration of 33 days since clinical diagnosis. Participants in the exposure group had a median lesion count of 35 (range, 25–113) and median duration of 61 days since clinical diagnosis. A total of 97% (32/33) of subjects completed the study; one subject in the exposure group was lost to follow-up after the first treatment visit and was replaced. This subject had blood drawn prior to application and at the 2-hour post-application collection.

Systemic Exposure Results

Plasma drug levels of cantharidin were below the LLOQ in 65 of 66 samples at all timepoints in the exposure group. One subject (2-year-old white male, weight 13.4 kg, with 32 treated lesions) had a single cantharidin result above the LLOQ with a reading of 3.4 ng/mL at the 2-hour post-application blood draw. Readings from the 6- and 24-hour samples in this subject were below the LLOQ. The subject did not experience any systemic AEs indicative of cantharidin absorption.

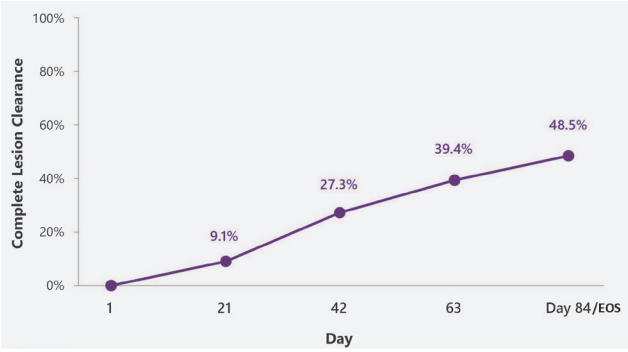
Efficacy

The percentage of subjects with complete clearance for the ITT population (all subjects that started the study) was 9.1% on day 21, 27.3% on day 42, 39.4% on day 63, and 48.5% on day 84/EOS visit (Figure 1). At day 84/EOS, MC lesion counts had decreased by a mean of 90.4% for the ITT population (Figure 2).

Safety Evaluations

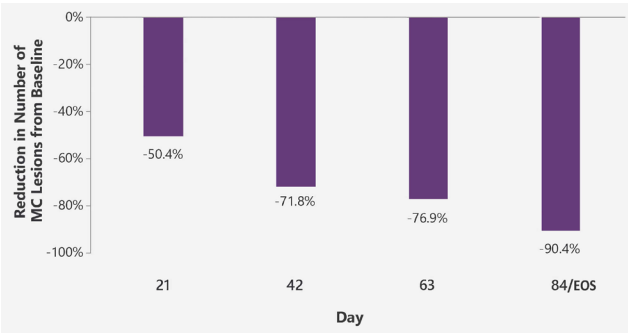
No subjects in either group experienced a severe or serious TEAE or exhibited symptoms indicative of cantharidin absorption. There were no discontinuations due to TEAEs (Table 2A). The three most commonly reported AEs for both groups were pain (19 subjects, 57.6%), cough (6 subjects, 18.2%), and headache (5 subjects, 15.2%). Only pain was considered related to treatment. The PERIT indicated that 93.9% (31/33) of subjects experienced blistering after the first treatment (Day 1). AEs at the application site not expected by the investigators were all mild to moderate in severity (Table 2B). No excessive blistering beyond investigator expectation at or beyond the application site was reported.

FIGURE 1. Percentage of VP-102-treated subjects (N=33) achieving complete clearance of MC lesions at each time point.



EOS = end of study visit

FIGURE 2. Percentage change in MC lesions from baseline at each time point.



EOS = end of study visit

TABLE 2A.

Treatment Emergent Adverse Events Reported During or After the First Application of VP-102 (safety population). Characteristics of Each Subject Group

	Exposure Group (N=17)*	Standard Group (N=16)	Overall (N = 33)
Number of TEAEs reported	53	35	88
Subjects with at least one – No. (%)			
TEAE related to study drug	13 (76.5)	8 (50.0)	21 (63.6)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Local skin reaction TEAE	12 (70.6)	8 (50.0)	20 (60.6)
TEAEs reported in 2 or more subjects in any treatment group – No. (%)			
Pain**	11 (64.7)	8 (50.0)	19 (57.6)
Cough	3 (17.6)	3 (18.8)	6 (18.2)
Scar	3 (17.6)	1 (6.3)	4 (12.1)
Headache	2 (11.8)	3 (18.8)	5 (15.2)
Rhinorrhea	2 (11.8)	1 (6.3)	3 (9.1)
Diarrhea	1 (5.9)	1 (6.3)	2 (6.1)
Oropharyngeal pain	1 (5.9)	2 (12.5)	3 (9.1)
Vomiting	1 (5.9)	3 (18.8)	4 (12.1)

*As per the protocol, subjects in the exposure population were required to have 21 or more molluscum lesions present at baseline
**Considered related to treatment by the investigator
***Popped blisters. Application site vesicles were an expected adverse event and were not tracked in this study, unless unexpected reactions occurred.

TABLE 1.

Baseline Demographics and MC Characteristics of Each Subject Group

	Exposure Group* (N = 17)	Standard Group (N = 16)	Overall (N = 33)
Demographics			
Age – years			
Mean (SD)	6.6 (3.5)	6.8 (3.2)	6.7 (3.3)
Median	5.0	6.0	5.0
Range	2–15	3–12	2–15
Gender – no. (%)			
Female	7 (41.2)	8 (50.0)	15 (45.5)
Male	10 (58.8)	8 (50.0)	18 (54.5)
Race or ethnic group – no. (%)			
White	16 (94.1)	14 (87.5)	30 (90.9)
Black or African American	1 (5.9)	2 (12.5)	3 (9.1)
Physical Characteristics			
Height (cm)			
Mean (SD)	119.6 (19.1)	123.7 (19.9)	121.6 (19.3)
Median	116.8	122.5	118.1
Range	89–169	95–161	89–169
Weight (kg)			
Mean (SD)	26.3 (15.7)	27.2 (10.9)	26.7 (13.4)
Median	21.4	25.2	22.7
Range	12–79	14–49	12–79
BMI (kg/m2)			
Mean (SD)	17.1 (3.5)	17.0 (1.6)	17.0 (2.7)
Median	15.7	16.9	16.6
Range	14-28	14-19	14-28
Baseline Disease Characteristics			
Time since clinical diagnosis (days)			
Mean (SD)	93.8 (102.8)	90.2 (133.0)	92.0 (116.5)
Median	61.0	33.0	36.0
Range	0–326	0–423	0–423
Age at diagnosis – years			
Mean (SD)	6.3 (3.4)	6.4 (3.3)	6.3 (3.3)
Median	5.0	6.0	5.0
Range	2–15	2–12	2–15
Previous treatment for molluscum – no. (%)			
Yes	7 (41.2)	6 (37.5)	13 (39.4)
Previous treatment with			
Cantharidin	3 (17.6)	1 (6.3)	4 (12.1)
Any other agent	5 (29.4)	6 (37.5)	11 (33.3)
Baseline lesion count			
Mean (SD)	47.4 (25.7)	11.6 (6.3)	30.0 (26.1)
Median	35.0	13.5	25.0
Range	25–113	3–21	3–113

SD=Standard deviation.
*As per the protocol, subjects in the exposure group were required to have 21 or more molluscum lesions present at baseline.

TABLE 2B.

Treatment Emergent Adverse Events Reported During or After the First Application of VP-102 (safety population). Characteristics of Each Subject Group									
	Exposure Treatment (N=17)*			Standard Treatment (N=16)			Overall (N=33)		
Local Skin Reactions by Severity – No (%)	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Application Site Pain	10 (58.8)	0 (0.0)	0 (0.0)	8 (50.0)	0 (0.0)	0 (0.0)	18 (54.5)	0 (0.0)	0 (0.0)
Application Site Scar	2 (11.8)	1 (5.9)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	3 (9.1)	1 (3.0)	0 (0.0)
Application Site Vesicles*	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)
Application Site Burning Sensation	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Popped blisters. Application site vesicles were an expected adverse event and were not tracked in this study, unless unexpected reactions occurred.

Quality of Life

For all subjects the composite CDQLI score decreased from 2.58 at baseline (mild effect on QoL) to 0.38 (no effect on QoL) at the EOS/day 84 visit.

DISCUSSION

This study represents the first clinical evaluation of VP-102, a propriety drug-device combination product containing 0.7% cantharidin (w/v), for the topical treatment of MC. While there are no approved treatments for this common skin infection in the US, compounded cantharidin has been used to treat MC and warts for more than 60 years.[17] There are several limitations to the use of cantharidin for treatment of MC. Cantharidin's access is limited due to restriction mandated by federal law, thus requiring physicians to obtain it outside the US or through compounding pharmacies. In addition, there are no data to support an optimized formulation or dosing regimen. Finally, the application and treatment schedule vary by practitioner, are inconsistent in previous studies, and the safety and efficacy of its use in MC has not been proven in large trials.[16]

The clinical development of VP-102 addresses these issues by seeking FDA approval of a standardized, shelf-stable formulation of cantharidin delivered via a proprietary, single-use applicator. The small tip of the applicator is designed to improve safety and efficacy by targeting MC lesions and sparing surrounding healthy skin, while the gentian violet surgical dye in the solution may assist in reducing duplicative dosing of individual lesions in a single treatment. The single-use applicator may also reduce the potential for cross-contamination, as direct contact with the skin is not necessary for application, and the applicator is not to be used across multiple patients.

Systemic exposure to cantharidin was negligible in this pediatric patient population, as evidenced by 65/66 plasma samples being below the LLOQ. These findings and the incidence of AEs support the safety of VP-102 to treat MC in the pediatric population. Complete clearance of MC lesions was observed in 48.5% of all VP-102-treated subjects and VP-102 treatment reduced the number of lesions by an average of 90.4% at the EOS/day 84 visit compared to baseline. On the CDLQI, subjects showed an improvement in QoL from a mild effect of disease at baseline to no effect at the end of the study.

CONCLUSION

In conclusion, the results of this Phase 2 study suggest that large randomized clinical trials are warranted to compare topical VP-102 with a vehicle control in a diverse population of subjects with MC in order to fully evaluate the safety and efficacy of VP-102.

DISCLOSURES

The trial and was sponsored by Verrica Pharmaceuticals Inc. Drafting of the manuscript and creation of the figures were funded by Verrica Pharmaceuticals. Drs. Niazi, Brabec, and Anschutz served as clinical study investigators on the trial and received funding to complete the study. Dr. Davidson, Dr. Burnett, and Ms. Willson were employees and stockholders with Verrica Pharmaceuticals Inc. at the time of the study. Dr. Davidson holds the following patents related to the study: WO2018226894A1, WO2018232277A1, WO2016100732A3, WO2016118633A1, WO2015027111A1, W02014308690.

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