CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212905Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

CLINICAL REVIEW

NDA #:	212905, Class 2 resubmission
Submission Date:	23 January 2023
Study Name:	VP-102
Brand Name:	Ycanth (conditionally approved)
Generic Name:	cantharidin
Dosage Form:	Topical solution
Dosage Strength:	0.7%
Reviewer:	Mary Kim, M.D.
Team Leader:	Amy Woitach, D.O., M.S.
Division Director:	Shari Targum, M.D.
Regulatory Project Manager:	Qianyiren Song, PharmD
Center:	Center for Drug Evaluation and Research
Office:	Office of New Drugs, Office of Immunology and Inflammation
Division:	Division of Dermatology and Dentistry
Sponsor:	Verrica Pharmaceuticals Inc
Submission Type:	Response to a Complete Response Action
Indication Sought:	For the treatment of Molluscum contagiosum in patients 2 years and older
Subject:	Clinical Review of NDA 212905 Third Resubmission after Third Complete Response
Date in DARRTS:	*** *** 2023

Background:

NDA 212905 for VP-102 for the topical application to treat molluscum contagiosum was submitted on 13 September 2019 under the 505(b)(1) regulatory pathway. Reference is made to the NDA multidisciplinary review completed on 09 July 2020. Per the review, the submitted evidence had met the evidentiary standard for providing substantial evidence of effectiveness. However, although cantharidin solution, 0.7% itself appeared safe in clinical trials per the review, the applicator at the time of the NDA submission had inherent flaws with the potential for medical errors once marketed. A Complete Response (CR) Letter was provided by the FDA on 13 July 2020 due to deficiencies of the device design, drug product, and manufacturing aspects adversely impacting the final combination product generating an unfavorable overall benefit/risk assessment. Refer to the CR letter dated 13 July 2020 and the Clinical Labeling Review dated 14 September 2021 for details regarding the contents of the original CR letter.

Regarding the CMC issues, the CR letter dated 13 July 2020 states:

> PRODUCT QUALITY
>
> 1) The proposed drug product specification does not include test to assure the drug product can be safety and accurately expelled onto the lesion area and avoid the adjacent healthy skin. The specification for the final assembled drug product should be revised to include the following:
>
> a. A test for the crushing force of the glass ampule.

b. A leakage test after ampule crushing to assure there is no drug leakage at release and during shelf-life.
c. A droplet test to demonstrate that the users are capable of dispensing various amount of drug product as needed to the affected skin area while avoiding the adjacent healthy skin.
2) The extraction solutions, [redacted] used in the extractable/leachable study are considered inadequate because:
a. [redacted]
b. Leachable compounds were detected during drug product testing for related substances that were not detected in the extractable studies. Extractable/leachable studies you have committed to in the amendment dated January 23, 2020 should be conducted and the results of these studies should be submitted to the application.
3) The drug product quality is not assured and the expiration dating period cannot be established because the registration drug product batches provided in the application were not fully assembled [redacted]. In order to assure the drug product quality and established expiration dating period for the drug product, at least 3 months of long-term and accelerated stability data from three batches of fully assembled [redacted] drug product with at least 3 times-points post manufacture (at initial, 1 months, 2 months, and 3 months) should be submitted to the application.

FACILITIES
4) Our field investigator could not complete inspection of the manufacturing facility [redacted] because the facility was not ready for inspection. Satisfactory inspection is required before this NDA can be approved. Please notify us in writing when this facility is ready for inspection.
5) We have not completed our inspection of your [redacted] manufacturing facility due to travel restrictions associated with COVID-19 pandemic. An inspection of [redacted] facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

PROCESS
[redacted]

The applicant submitted a response to the complete response action on 23 December 2020.

Chemistry, Manufacturing, and Control (CMC) concluded that the applicant had provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance, cantharidin and the drug product, cantharidin solution, 0.7% (w/v) for topical use with the resubmission dated 23 December 2020.

However, a recommendation for a CR for the resubmission dated 23 December 2020 was made from a CMC perspective due to a determination by the Office of Pharmaceutical Manufacturing Assessment (OPMA) facility inspection as inadequate-major (withhold). A CR letter dated 16 September 2021 was issued for:

> FACILITY INSPECTIONS
> During a recent inspection of the (b) (4) for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Regarding the issues identified by the Division of Medication Error and Prevention and Analysis (DMEPA), a separate general advice letter was sent on 22 September 2021 to address the results of the human factors (HF) validation study which had identified use errors with critical tasks. In the general advice letter, the Agency provided recommendations from DMEPA (refer to the DMEPA review dated 15 September 2021) to improve the proposed user interface to further mitigate the residual risk in order to ensure safe and effective use of the product.

The applicant submitted a response to the second complete response action on 24 November 2021. On 14 December 2021, the applicant submitted a response to the Agency's general advice

letter dated 22 September 2021. The submission included the implemented label and labeling changes and a supplemental HF validation study.

A recommendation for a CR for the resubmission dated 24 November 2021 was made from a CMC/OPMA perspective due to a determination by the OPMA facility inspection as inadequate-major (withhold). A CR letter dated 23 May 2022 was issued for:

> FACILITY INSPECTIONS
> During a recent inspection of the (b) (4) for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Regarding the issues identified by DMEPA, DMEPA reviewed the supplemental human factors (HF) validation study report submitted by the applicant on 14 December 2021 under NDA 212905 for Ycanth (cantharidin) as a response to the Agency's general advice letter dated 22 September 2021 (refer to the DMEPA memorandum dated 4 March 2022 and DMEPA review by Oluwamurewa Oguntimein, PhD, MHS, CPH, MCHES, dated 11 April 2022). DMEPA noted that the HF validation study showed no use errors, (e.g. failures, difficulties, or close call) with non-critical tasks. DMEPA concluded that the results of the HF validation study demonstrate that representative users can use the product, as designed, safely and effectively. DMEPA evaluation of the proposed packaging, label and labeling did not identify areas of vulnerability that may lead to medication errors. DMEPA found the proposed packaging, proposed labels and labeling (pending final agreed upon labeling), and the results of the human factors (HF) validation study acceptable. DMEPA had no additional recommendations regarding the applicant's response submitted on 14 December 2021 to the Agency's general advice letter dated 22 September 2021.

The applicant submitted a response to the third complete response action on 23 January 2023.

CMC/OPMA findings:
A recommendation for approval for the resubmission dated 23 January 2023 was made from CMC/OPMA perspective as it was determined that "the applicant provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance, cantharidin and the drug product, Trade Name (cantharidin) Solution, 0.7% (w/v) for topical use. OPMA made the overall recommendation of adequate regarding the facilities involved in this application." Refer to CMC/OPMA review by Dr. Hamid R Shafiei dated 06 June 2023.

Labeling:
Refer to the Clinical Labeling review dated 14 September 2021 and the Clinical Review to the second class 2 resubmission dated 18 May 2022. Since the Clinical Labeling and Clinical reviews, updates include recommendations to DDD from Division of Risk Management (DRM) by Dr. Lindsey Crist and Dr. Cynthia LaCivita on the Prescribing Information (PI) during internal labeling meetings to modify the previously recommended statement from, (b) (4)

(b) (4) to "All healthcare professionals should receive instruction and training prior to preparation and administration of YCANTH" given that no Risk Evaluation and Mitigation Strategies (REMS) will be required (see review by Dr. Lindsey Crist, DRM dated 20 July 2023). Labeling negotiations are currently ongoing at the time of this review.

Updated Safety Information:
Refer to the Clinical Review to the second class 2 resubmission dated 18 May 2022. The safety update report (SUR) submitted by the applicant with this third class 2 resubmission on 23 January 2023 was reviewed.

SUR 23 January 2023:
Reporting period: 15 October 2021 to 15 December 2022

There were no ongoing clinical trials with VP-102 for molluscum at the cut-off date, and no clinical trials for molluscum were ongoing or completed since NDA 212905 was resubmitted on 24 November 2021.

To this date, two clinical studies in indications other than molluscum contagiosum have been conducted with VP-102: a Phase 2 Study VP-102-105, for the assessment of VP-102 in the treatment of verruca vulgaris (common warts), and a Phase 2 Study VP-102-104 for assessment of VP-102 in the treatment of external genital warts (EGW). The results of these studies were included in the Safety Update Report submitted previously on 23 December 2020. Thus, no new safety data on clinical trials with VP-102 are summarized in this Safety Update Report.

Relevant safety data from published literature was also summarized by the applicant in the SUR from articles published from 16 October 2021 and 15 December 2022. The applicant reported no SAEs or deaths documented in the published literature for subjects treated with topical cantharidin prior to the safety cutoff date.

Reviewer comment: No new safety signals based on the additional safety data presented in the resubmission was identified. No changes are recommended for the proposed labeling based on the updated safety information submitted by the applicant with the resubmission.

Summary and Conclusion:
The deficiencies noted in the CR letters dated 13 July 2020, 16 September 2021, and 23 May 2022 by CMC and OPMA regarding drug manufacturing facilities inspection have been resolved. Therefore, this reviewer recommends approval of NDA 212905 for Ycanth (cantharidin topical solution), 0.7% for the treatment of molluscum contagiosum in patients 2 years and older, once agreed upon labeling is achieved.

Recommendation for Action: Approval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E KIM
07/20/2023 11:28:06 AM

AMY S WOITACH
07/20/2023 09:51:34 PM

CLINICAL REVIEW

NDA #:	212905, Class 2 resubmission
Submission Date:	24 November 2021
Study Name:	VP-102
Brand Name:	Ycanth (pending)
Generic Name:	cantharidin
Dosage Form:	Topical solution
Dosage Strength:	0.7%
Reviewer:	Mary Kim, M.D.
Team Leader:	Amy Woitach, D.O., M.S.
Division Director:	Kendall Marcus, M.D.
Regulatory Project Managers:	Qianyiren Song and Matthew White (covering)
Center:	Center for Drug Evaluation and Research
Office:	Office of New Drugs, Office of Immunology and Inflammation
Division:	Division of Dermatology and Dentistry
Sponsor:	Verrica Pharmaceuticals Inc
Submission Type:	Response to a Complete Response Action
Indication Sought:	For the treatment of Molluscum contagiosum in patients 2 years and older
Subject:	Clinical Review of NDA 212905 Second Resubmission after Second Complete Response
Date in DARRTS:	18 May 2022

Background:

NDA 212905 for VP-102 for the topical application to treat molluscum contagiosum was submitted on 13 September 2019 under the 505(b)(1) regulatory pathway. Reference is made to the NDA multidisciplinary review completed on 09 July 2020. Per the review, the submitted evidence had met the evidentiary standard for providing substantial evidence of effectiveness. However, although cantharidin solution, 0.7% itself appeared safe in clinical trials per the review, the applicator at the time of the NDA submission had inherent flaws with the potential for medical errors once marketed. A Complete Response (CR) Letter was provided by the FDA on 13 July 2020 due to deficiencies of the device design, drug product, and manufacturing aspects adversely impacting the final combination product generating an unfavorable overall benefit/risk assessment. Refer to the CR letter dated 13 July 2020 and the Clinical Labeling Review dated 14 September 2021 for details regarding the contents of the original CR letter.

Regarding the CMC issues, the CR letter dated 13 July 2020 states:

"PRODUCT QUALITY

1) The proposed drug product specification does not include test to assure the drug product can be safety and accurately expelled onto the lesion area and avoid the adjacent healthy skin. The specification for the final assembled drug product should be revised to include the following:

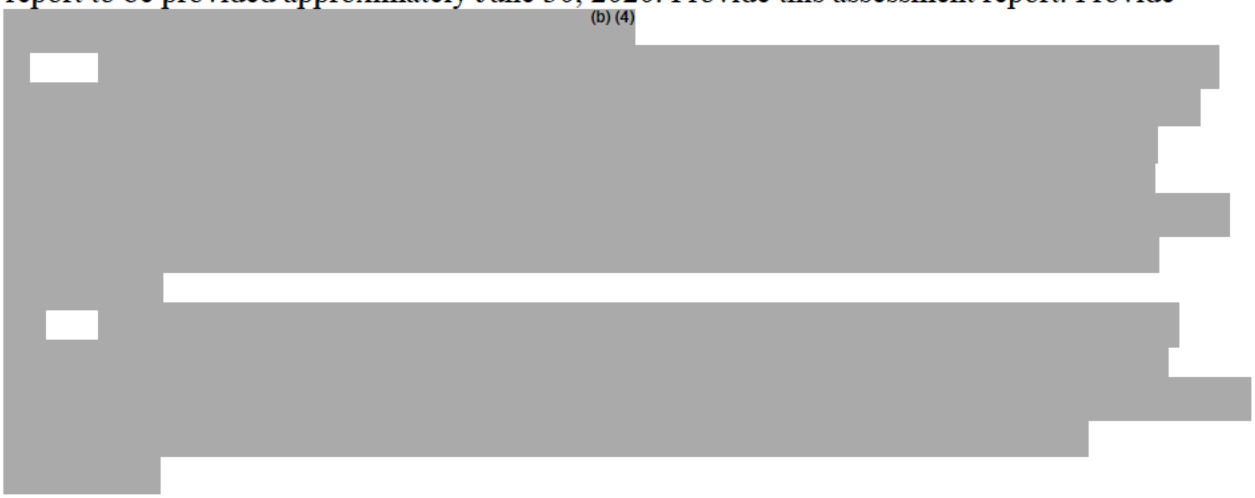
a. A test for the crushing force of the glass ampule.

b. A leakage test after ampule crushing to assure there is no drug leakage at release and during shelf-life.
c. A droplet test to demonstrate that the users are capable of dispensing various amount of drug product as needed to the affected skin area while avoiding the adjacent healthy skin.
2) The extraction solutions, [redacted] used in the extractable/leachable study are considered inadequate because:
a. [redacted]
b. Leachable compounds were detected during drug product testing for related substances that were not detected in the extractable studies. Extractable/leachable studies you have committed to in the amendment dated January 23, 2020 should be conducted and the results of these studies should be submitted to the application.
3) The drug product quality is not assured and the expiration dating period cannot be established because the registration drug product batches provided in the application were not fully assembled [redacted] In order to assure the drug product quality and established expiration dating period for the drug product, at least 3 months of long-term and accelerated stability data from three batches of fully assembled [redacted] drug product with at least 3 times-points post manufacture (at initial, 1 months, 2 months, and 3 months) should be submitted to the application.

FACILITIES
4) Our field investigator could not complete inspection of the manufacturing facility [redacted] because the facility was not ready for inspection. Satisfactory inspection is required before this NDA can be approved. Please notify us in writing when this facility is ready for inspection.
5) We have not completed our inspection of your [redacted] manufacturing facility due to travel restrictions associated with COVID-19 pandemic. An inspection of [redacted] facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

PROCESS
[redacted]

report to be provided approximately June 30, 2020. Provide



The applicant submitted a response to the complete response action on 23 December 2020.

Chemistry, Manufacturing, and Control (CMC) concluded that the applicant had provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance, cantharidin and the drug product, YCanth (trade name pending) (cantharidin) Solution, 0.7% (w/v) for topical use with the resubmission dated 23 December 2020.

However, a recommendation for a CR for the resubmission dated 23 December 2020 was made from a CMC perspective due to a determination by the Office of Pharmaceutical Manufacturing Assessment (OPMA) facility inspection as inadequate-major (withhold). A CR letter dated 16 September 2021 was issued for:

"FACILITY INSPECTIONS
During a recent inspection of the (b) (4) for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

Regarding the issues identified by the Division of Medication Error and Prevention and Analysis (DMEPA), a separate general advice letter was sent on 22 September 2021 to address the results of the human factors (HF) validation study which had identified use errors with critical tasks. In the general advice letter, the Agency provided recommendations from DMEPA (refer to the DMEPA review dated 15 September 2021) to improve the proposed user interface to further mitigate the residual risk in order to ensure safe and effective use of the product.

The applicant submitted a response to the second complete response action on 24 November 2021. On 14 December 2021, the applicant submitted a response to the Agency's general advice letter dated 22 September 2021. The submission included the implemented label and labeling changes and a supplemental HF validation study.

CMC/OPMA findings:
A recommendation for a CR for the resubmission dated 24 November 2021 was made from a CMC/OPMA perspective due to a determination by the OPMA facility inspection as inadequate-major (withhold).

DMEPA findings:
DMEPA reviewed the supplemental human factors (HF) validation study report submitted by the applicant on 14 December 2021 under NDA 212905 for Ycanth (cantharidin) as a response to the Agency's general advice letter dated 22 September 2021 (refer to the DMEPA memorandum dated 4 March 2022 and DMEPA review by Oluwamurewa Oguntimein, PhD, MHS, CPH, MCHES, dated 11 April 2022). DMEPA noted that the HF validation study showed no use errors, (e.g. failures, difficulties, or close call) with non-critical tasks. DMEPA concluded that the results of the HF validation study demonstrate that representative users can use the product, as designed, safely and effectively. DMEPA evaluation of the proposed packaging, label and labeling did not identify areas of vulnerability that may lead to medication errors. DMEPA found the proposed packaging, proposed labels and labeling (pending final agreed upon labeling), and the results of the human factors (HF) validation study acceptable. DMEPA has no additional recommendations at this time.

Labeling:
Refer to the Clinical Labeling review dated 14 September 2021. Since the Clinical Labeling review, updates include recommendations to DDD from DMEPA on the Prescribing Information (PI) (refer to the DMEPA review dated 15 September 2021) to add a statement under the Highlights of PI, Dosage and Administration section to alert the health care provider that additional important information is in the FPI (e.g., see Full Prescribing Information for instructions on the preparation and administration.). The statement, "For additional instructions on preparation and administration of YCANTH, see Full Prescribing Information. (2.1, 2.2, 2.3)" was added to the Highlights of PI, Dosage and Administration section. Additional updates since the Clinical Labeling review, include an edit to the applicant's proposed statement, (b) (4) to "Avoid contact with the treatment area, including oral contact, after YCANTH treatment" in section 17 Patient Counseling Information. A statement to avoid contact with the treatment area, including oral contact, was also added to sections 2 Dosage and Administration and 5 Warnings and Precautions (including the Highlights of PI for Warnings and Precautions).

The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI (Refer to the OPDP review by Nazia Fatima, PharmD, MBA, RAC, dated 12 April 2022). The Division of Medical Policy Programs (DMPP) Patient Labeling reviewed and provided comments regarding the applicant's proposed Medication Guide (MG) and PI (Refer to the OPDP and DMPP review by Sharon Mills, BSN, RN, CCRP, and Nazia Fatima, PharmD, MBA, RAC dated 07 April 2022). These comments are reflected in final labeling. Labeling negotiations are currently ongoing.

Updated Safety Information:
Safety update reports (SURs) submitted by the applicant on 23 December 2020 and 24 November 2021 were reviewed.

SUR 23 December 2020:
Reporting period: 13 September 2019 (date of NDA 212905 submission) to 29 October 2020

There were no ongoing clinical trials with VP-102 for molluscum at the cut-off date, and no clinical trials for molluscum were ongoing or completed since NDA 212905 was submitted on 13 September 2019.

During this SUR reporting period, two clinical studies in indications other than molluscum contagiosum had been conducted with VP-102.

1) A phase 2, open-label, study VP-102-105, for the assessment of VP-102 in the treatment of verruca vulgaris (common warts). Study VP-102-105 was initiated on 27 March 2018 and was completed (last patient last visit) on 15 July 2019 and included 21 subjects in the safety population (subjects who met screening eligibility criteria for the study and received at least one application of study drug) in cohort 1 (treatment interval of at least 14 days between treatments with longer treatment intervals allowed depending on the clinical response. No paring allowed) and 34 subjects in the safety population in cohort 2 (treatment interval of 21 days between treatments. Paring of lesions was allowed). VP-102 was to remain in contact with treated lesions for 24 hours, under occlusive tape, after which it was to be removed by washing with soap and water. Most subjects in both cohorts had 4 treatment visits.

The most common treatment emergent adverse events (TEAEs) were application site reactions under the SOC of general disorders and administration site conditions (20/21 subjects in cohort 1 and 32/34 subjects in cohort 2) including application site vesicles, application site pain, application site erythema, application site scab, application site pruritus, application site dryness, application site edema, application site discoloration, application site exfoliation, and application site erosion, with 6 subjects across both cohorts graded with severe TEAE of application site reactions. Three subjects had enlargement of the treated wart known as ‘ring wart’ (PT papilloma viral infection).

In addition to general disorders and administration site conditions, the system organ classes reported by more than one subject were infections and infestations (4 subjects), respiratory, thoracic and mediastinal disorders (4 subjects), skin and subcutaneous tissue disorders (4 subjects), and metabolism and nutritional disorders (2 subjects). The system organ classes reported by only one subject were eye disorders, gastrointestinal disorders, immune system disorders, neoplasms benign, malignant and unspecified (including cysts and polyps), and renal and urinary disorders.

There were no deaths or treatment-emergent serious adverse events (SAEs) reported in study VP-102-105.

and

2) A phase 2, double-blind, placebo-controlled study VP-102-104 for assessment of VP-102 for the treatment of external genital warts (EGW). Study VP-102-104 was initiated on 25 June 2019 and completed on 08 July 2020 and included 99 subjects in the safety population (all randomized subjects who received at least one application of study drug (VP-102 or placebo was administered once every 21 ±4 days) in the 6-hour or 24-hour groups.

The most common TEAEs were application site reactions under the SOC of general disorders and administration site conditions (29/29 VP-102 6-hour group, 8/22 placebo 6-hour group, 28/28 VP-102 24-hour group, and 6/20 placebo 24-hour group), including application site vesicles, application site pain, application site erythema, application site pruritus, application site scab, application site discoloration, application site dryness, application site erosion, application site edema, application site exfoliation, and injection site pain. Severe TEAEs were reported in two subjects who were randomized to the VP-102 24-hour treatment group (application site vesicles and application site pruritus).

There were no deaths reported in study VP-102-104.

There were 3 SAEs reported in study VP-102-104 (pneumonia in the placebo 24-hour group, musculoskeletal chest pain in the VP-102 6-hour group, and bipolar disorder in the placebo 6-hour group).

Relevant safety data from published literature was also summarized by the applicant in the SUR from articles published from 01 August 2019 to 29 October 2020. The applicant reported no SAEs or deaths documented in the published literature for subjects treated with topical cantharidin prior to the safety cutoff date. There was one case study of a severe cantharidin poisoning in a 51-year old male after ingesting a tea formulation/preparation containing cantharidin that reported burning sensation in the oral cavity, diarrhea and hematuria, acute kidney injury, and atypical neurological symptoms. The potential for systemic toxicity following inappropriate oral injection of cantharidin is described in the draft PI.

SUR 24 November 2021:
Reporting period: 23 December 2020 to 15 October 2021

There were no ongoing clinical trials with VP-102 for molluscum at the cut-off date, and no clinical trials for molluscum were ongoing or completed since NDA 212905 was submitted on 13 September 2019.

To this date, two clinical studies in indications other than molluscum contagiosum have been conducted with VP-102: a Phase 2 Study VP-102-105, for the assessment of VP-102 in the treatment of verruca vulgaris (common warts), and a Phase 2 Study VP-102-104 for assessment of VP-102 in the treatment of external genital warts (EGW). The results of these studies were included in the Safety Update Report submitted previously on 23 December 2020 (see above). Thus, no new safety data on clinical trials with VP-102 are summarized in this Safety Update Report.

Relevant safety data from published literature was also summarized by the applicant in the SUR from articles published from 29 October 2020 to 15 October 2021. The applicant reported no SAEs or deaths documented in the published literature for subjects treated with topical cantharidin prior to the safety cutoff date. There was one case study of a 7-year-old female who presented to the emergency department with 3 days of lip and tongue pain who developed ulcers on the lip and tongue after receiving treatment for finger warts with cryotherapy, followed by trichloroacetic acid 20% and cantharidin 0.7% solution. The warts were left uncovered and while the patient denied finger-sucking, the caretakers revealed the patient habitually sucked her thumb. Instructions for topical use only, to avoid contact with the treatment area, including oral contact, after treatment, and to seek medical attention immediately if inappropriately or accidentally administered orally are included in the draft PI. In addition, Ycanth formulation contains an oral deterrent (denatonium benzoate), unlike cantharidin formulations currently used in the healthcare setting in the United States.

Reviewer comment: No new safety signals based on the additional safety data presented in the resubmissions were identified. No changes are recommended for the proposed labeling based on the updated safety information submitted by the applicant with the resubmissions.

Summary and Conclusion:
The deficiencies noted in the CR letters dated 13 July 2020 and 16 September 2021 by CMC and OPMA regarding drug manufacturing facilities inspection have not been resolved. Therefore, I recommend a complete response of NDA 212905 for Ycanth (cantharidin topical solution), 0.7% for the treatment of molluscum contagiosum in patients 2 years and older.

Recommendation for Action: Complete Response

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E KIM
05/18/2022 02:05:28 PM

AMY S WOITACH
05/18/2022 02:13:21 PM

Office of Clinical Pharmacology Review

NDA Number	212905
Submission Date	09/13/2019
Priority or Standard	Standard
Brand Name	YCANTH®
Generic Name	Cantharidin
Dosage Form and Strength	Solution, 0.7%
Route of Administration	Topical
Proposed Indication	Treatment of Molluscum contagiosum in patients 2 years of age and older
Applicant	Verrica Pharmaceuticals, Inc.
OCP Primary Reviewer	Luke Oh, Ph.D.
OCP Secondary Reviewer	Chinmay Shukla, Ph.D.

Table of Contents

Clinical Pharmacology

1.1. Executive Summary

Cantharidin is an inhibitor for protein phosphatases types 1 and 2A. The Applicant believes that the topical application of cantharidin weakens desmosomes in the epidermis through the release of neutral serine proteases and thus having activity in the treatment of molluscum contagiosum.

The Applicant has developed a film-forming VP-102 topical solution containing cantharidin, 0.7% to treat molluscum contagiosum, an infection caused by a poxvirus. Clinical Pharmacology review focuses on Phase 2 maximal use pharmacokinetic (PK) study (VP-102-103) in subjects with molluscum contagiosum. Of the16 subjects that completed the study aged 2 years to 15 years, there was only one subject 2 years of age that had quantifiable plasma cantharidin concentration (3.39 ng/mL) at the 2-hour timepoint. In all other subjects, the systemic concentrations of cantharidin were below the lower level of quantitation (LLOQ = 2.5 ng/mL). Overall, the PK results indicate that there is a minimal systemic exposure of cantharidin following topical application of VP-102 0.7% solution to subjects with molluscum lesions.

1.1.1. Recommendations

From Clinical Pharmacology perspective, the overall data provided in this NDA supports the approval of the drug product to treat subjects with molluscum contagiosum.

1.1.2. Post-marketing requirement/post-marketing commitment

None.

1.2. Summary of Clinical Pharmacology Assessment

1.2.1. Pharmacology and Clinical Pharmacokinetics

The maximal use PK study (VP-102-103) results demonstrated that there was only 1 subject out 16 subjects that showed quantifiable plasma cantharidin concentration of 3.39 ng/mL at 2 hours post-dose and no quantifiable levels were observed at later 2 time points (i.e. at 6 and 24 hours post-dose). The rest of 15 subjects in the study exhibited plasma cantharidin below of LLOQ of 2.5 ng/mL at all time points post-dose.

Summary of safety: Overall, 88 treatment-emergent adverse events (TEAEs) were reported in 29/33 (87.9%) subjects. Most TEAEs were reported as mild; only 3 subjects reported moderate TEAEs, and no severe TEAEs were reported. 21 (63.6%) subjects experienced TEAEs that were considered related to VP-102; most of these (20 subjects) were local skin reaction TEAEs, which were expected as part of the study treatment regimen. Most frequent local skin reaction TEAE

was pain, which was reported in 18 (54.5%) subjects. There was no death occurred during the study. No subjects experienced a severe adverse event or TEAEs leading to discontinuation from the study.

Reviewer's comments: *This reviewer notes that the bioanalytical assay is not very sensitive as per current standards. The purpose of maximal use study is to inform systemic safety. Since there are no systemic safety signals noted and furthermore, the treatment needs to be repeated once every 3 weeks for up to 4 treatment cycles; additional PK assessment by conducting another maximal use PK study using a more sensitive bioanalytical assay will not be needed.*

1.2.2. General Dosing and Therapeutic Individualization

General Dosing

Topical application of the product (i.e., a single-use applicator containing 450 µL of 0.7% (b) (4) cantharidin solution) to the affected molluscum skin lesion once every 3 weeks appears reasonable. Each applicator contains (b) (4) of cantharidin.

Therapeutic Individualization

There is no therapeutic individualization in this application.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this application from a Clinical pharmacology perspective.

1.3. Comprehensive Clinical Pharmacology Review

1.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Phase 2 study (VP-102-103) was conducted in subjects (2 – 15 years of age) with molluscum contagiosum to determine the potential for systemic exposure to cantharidin under maximal use conditions in a subset of subjects called as exposure treatment group. The standard treatment group (N = 16) was defined as subjects having less than 21 lesions. VP-102 [0.7% (w/v) cantharidin] was applied topically once every 3 weeks for up to 4 treatments by applying the drug to molluscum lesions. The exposure treatment group (N = 17) was defined as subjects having 21 or more molluscum lesions and this was considered as upper range of disease severity. Out of the 17 subjects enrolled in the maximal use subset, 16 subjects competed the study with one subject missing the 2-hour post-dose PK sampling time point.

PK assessment was conducted for the exposure treatment group, which showed that systemic exposure of cantharidin was below the LLOQ (2.5 ng/mL) in all but one subject who had quantifiable cantharidin concentration of 3.39 ng/mL at a single time point of 2 hours post-dose. Based on the results from the study VP-102-103, the Applicant did not collect additional

PK samples in other clinical studies, and PK parameters have not been calculated for cantharidin due to lack of sufficient number of quantifiable concentrations.

Reviewer comments: *The Applicant's maximal use PK study had 2 treatment groups based on the number of lesions. The mean ± SD number of treated molluscum lesions in the exposure treatment group (i.e. under maximal conditions) was 91.4 ± 94.0 ranging from 37 to 441 lesions. The mean ± SD number of treated molluscum lesions in the standard treatment group was 21.8 ± 16.0 ranging from 3 to 52 lesions. In comparison, the mean numbers of lesions treated per subjects were 45.5 and 38.7 lesions in the pivotal studies, VP-102-101 and VP-102-102, respectively. The molluscum lesions treated in the maximal use PK study were markedly greater indication the upper range of the disease severity.*

1.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall efficacy data provide evidence that cantharidin is effective for the treatment of molluscum contagiosum. See Section 7 of this multi-discipline review for details of the study design and efficacy results of the Phase 3 trials.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of topical application to the lesions once every 3 weeks (b) (4) is appropriate for the treatment of subjects with molluscum contagiosum.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Effect of intrinsic factors on the PK could not be assessed due to limited quantifiable systemic concentrations. An alternative dosing regimen or management strategy is not necessary for subpopulation.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions are not applicable as cantharidin solution is administered by topical application. The applicant has not assessed drug interaction potential. Drug interaction assessment is not needed due to limited systemic absorption and dosing regimen once every 3 weeks (b) (4)

1.4. OCP Appendices (Technical documents supporting OCP recommendations)

1.4.1. Study VP-102-103

Title: A Phase 2, open-label study to evaluate the safety, efficacy and systemic exposure of VP-102 topical film forming solution [0.7% (w/v) cantharidin] in subjects (2 years and older) with molluscum contagiosum

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

Study population: A total of 33 subjects (2 to 15 years of age) were enrolled. PK was assessed in a subset of subjects called the exposure treatment group (n= 17) and there were 3 subjects in the 2 to 5 years age range.

Dose/Dosing regimen: VP-102 solution was applied once every 21 days to the molluscum lesions until complete clearance or for a maximum of 4 treatment sessions [Day 84, End of Study (EOS)].
VP-102 was prepared in a single-use applicator delivering up to 450 µL of a 0.7% w/v cantharidin formulation in a film-forming excipient system. Each applicator contains (b) (4) of cantharidin. Topical application of VP-102 leaves a thin film on the lesion as VP-102 solvent evaporates.

Study design: This study was conducted to evaluate the safety, efficacy and systemic exposure of VP-102 topical film forming solution (0.7% cantharidin) in subjects 2 years and older with molluscum contagiosum. The study had two groups as following:

- Exposure treatment group – 16/17 subjects completed. Subjects presented with 21 or more lesions on Day 1. At least 3 subjects were between 2 to 5 years of age.
- Standard treatment group – 16/16 subjects completed. Subjects presented with 1 – 20 lesions on Day 1.

In the Exposure treatment group, blood samples for pharmacokinetic assessment were collected at pre-dose and at 2, 6, and 24 hours post-dose on Day 1. Subjects in both groups received topical application of VP-102 on Day 1 and every 21 days until Day 84 (EOS) or until complete clearance of lesion.

Results:
Of 16 completed subjects in the exposure treatment group, a single subject 2 years of age had quantifiable plasma concentration of cantharidin (3.39 ng/mL) at 2 hours post-dose, and plasma concentration of cantharidin was not quantifiable at 6 hours and 24 hours post-dose. The rest of subjects did not have any quantifiable concentrations of cantharidin in the plasma (LLOQ 2.5 ng/mL) at all time points.

1.4.2. Summary of Bioanalytical Method Validation and Performance

The Applicant submitted validation study report 14I0376R-03 and bioanalytical study report 17G0123H-A01G to quantify the plasma cantharidin concentrations using gas chromatography – mass spectrometry (GC/MS). The LLOQ was determined by GC/MS was 2.5 ng/mL of cantharidin. The assay validation results are summarized in Table 3.

Table 3. Validation results of the GC/MS bioanalytical methods used for measuring plasma concentration of cantharidin in Study VP-102-103

Analytes	**Cantharidin**
Matrix	Human plasma
Standard curve assay range	1 ng/mL – 200 ng/mL
Intra-run precision (%)	2.7 to 9.6
Intra-run accuracy (%)	2.0 to 9.6
Inter-run precision (%)	3.0 to 11.7
Inter-run accuracy (%)	2.9 to 6.9
Freeze/thaw matrix stability	3 cycles at -80 °C
Room temperature stability	24 hours
Long term stability	3 months at - 80°C
Incurred sample reanalysis (ISR)	65 of 66 plasma samples evaluated from 17 subjects showed the cantharidin levels below the LLOQ (2.5 ng/mL). Only one sample collected at 2 hour post-dose in 1 subject showed 3.39 ng/mL of plasma cantharidin. Subsequently ISR was not conducted.

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CLINICAL LABELING REVIEW

NDA #:	212905
Submission Date:	23 December 2020
Study Name:	VP-102
Brand Name:	Ycanth (pending)
Generic Name:	cantharidin
Dosage Form:	Topical solution
Dosage Strength:	0.7%
Reviewer:	Mary Kim, M.D.
Team Leader:	Amy Woitach, D.O., M.S.
Division Director:	Kendall Marcus, M.D.
Regulatory Project Manager:	Qianyiren Song
OND Division:	Division of Dermatology and Dentistry
Sponsor:	Verrica Pharmaceuticals Inc
Submission Type:	Response to a Complete Response Action
Indication Sought:	For the treatment of Molluscum contagiosum in patients 2 years and older
Review start date:	11 June 2021
Review complete date:	14 September 2021
Date in DARRTS:	14 September 2021

Background:

NDA 212905 for VP-102 for the topical application to treat molluscum contagiosum was submitted on 13 September 2019 under the 505(b)(1) regulatory pathway. Reference is made to the NDA/BLA multidisciplinary review completed on 09 July 2020. Per the review, the submitted evidence had met the evidentiary standard for providing substantial evidence of effectiveness. However, although cantharidin solution, 0.7% itself appeared safe, the applicator at the time of the NDA submission had inherent flaws. A Complete Response (CR) Letter was provided by the FDA on 13 July 2020 due to deficiencies of the device design, drug product, and manufacturing aspects adversely impacting the final combination product generating an unfavorable overall benefit/risk assessment. The CR letter dated 13 July 2020 states:

"PRODUCT QUALITY
1) The proposed drug product specification does not include test to assure the drug product can be safety and accurately expelled onto the lesion area and avoid the adjacent healthy skin. The specification for the final assembled drug product should be revised to include the following:

a. A test for the crushing force of the glass ampule.
b. A leakage test after ampule crushing to assure there is no drug leakage at release and during shelf-life.
c. A droplet test to demonstrate that the users are capable of dispensing various amount of drug product as needed to the affected skin area while avoiding the adjacent healthy skin.

2) The extraction solutions, (b) (4) used in the extractable/leachable study are considered inadequate because:
a. (b) (4) .
b. Leachable compounds were detected during drug product testing for related substances that were not detected in the extractable studies. Extractable/leachable studies you have committed to in the amendment dated January 23, 2020 should be conducted and the results of these studies should be submitted to the application.
3) The drug product quality is not assured and the expiration dating period cannot be established because the registration drug product batches provided in the application were not fully assembled (b) (4) . In order to assure the drug product quality and established expiration dating period for the drug product, at least 3 months

of long-term and accelerated stability data from three batches of fully assembled [redacted] (b) (4) drug product with at least 3 times-points post manufacture (at initial, 1 months, 2 months, and 3 months) should be submitted to the application.

FACILITIES

4) Our field investigator could not complete inspection of the manufacturing facility [redacted] (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA can be approved. Please notify us in writing when this facility is ready for inspection.

5) We have not completed our inspection of your [redacted] (b) (4) manufacturing facility due to travel restrictions associated with COVID-19 pandemic. An inspection of [redacted] (b) (4) facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

PROCESS

[redacted] (b) (4)

HUMAN FACTORS

11) As we previously communicated, our review of the human factors (HF) validation study data noted use errors and difficulties with the critical task- 'Break the Ampule'. We note one use error and three difficulties with the critical task. The use error occurred when the user removed the cap and paperboard sleeve, tipped the applicator upside down and broke the ampule with two hands. Additionally, three other users had difficulty breaking the ampule, which required two hands to break. Of these three use difficulties, one user also tilted the applicator horizontally. Based on your use-related risk analysis (URRA), this task is considered critical because premature cap removal and incorrect applicator orientation can lead to accidental exposure to the patient or healthcare provider's (HCP's) mouth or eyes leading to serious harm. Despite the use error and difficulties with critical task, you did not propose any additional mitigation strategies to address the use issues (e.g., reducing the force required to break the ampule).

We note your heuristic analysis submitted on April 10, 2020 indicates that the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with

paperboard sleeve on is 19 lbs. From this information you concluded that the force to break the ampule could increase the potential for use errors - "there is a potential that users will struggle to break the glass ampule due to the amount of force required. There is risk that some users may remove the paperboard sleeve in order to try and break the glass ampule. There is also potential for users to utilize other means to break the ampule if they are unable to generate enough force with their hands."

We also reviewed your April 10, 2020 threshold/comparative analyses with Eskata and Levulan Kerastick; products with some similarities to the proposed product in this review. We determined that the Levulan Kerastick has a different user interface than your proposed product because the Levulan Kerastick includes the Kerastick Krusher device as a means of breaking the ampule prior to administration. This difference may impact performance of the critical task of breaking the ampule. Furthermore, with respect to the comparative analyses to the Eskata product, we note postmarketing medication error cases that report accidental exposure to patient and health care professionals when using the product. Given some of the similar design attributes with your proposed product, we are concerned that accidental exposure can occur with cantharidin topical solution, which may present a different risk. As such, we have determined that a leveraging approach for your proposed product is not appropriate and the residual risk with your product is unacceptable.

In summary, we remain concerned that your proposed cantharidin combination product is not safe for use by HCPs. We are concerned that the risk of accidental exposure will outweigh the benefit of the treatment with this combination product. Inherent design issues exist with this product that may contribute to serious harm if accidental exposure occurs during use. Thus, additional mitigation strategies are needed and could include the need for device design changes to optimize applicator use along with other revisions to the product user interface taking into consideration our previously identified concerns and the data collected from your HF validation study. After you implement additional risk mitigation strategies/modifications, we recommend you conduct an additional HF validation study to ensure that these modifications address the observed use errors and use difficulties and do not introduce any new risks.

We recommend you submit your revised HF validation study protocol for feedback from the Agency before commencing the study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

As you further develop your proposed product and prepare your next human factors study protocol to address the above concerns, we have the following additional recommendations:

a. You indicated in your comparative analysis submitted on April 10, 2020 that the Levulan Kerastick product is similar to your proposed product. We note the Kerastick Krusher device has a means of breaking the ampule prior to administration that differs from your product. The design of the Levulan Kerastick product may inform how you address the break force issues identified during your human factors product development.
b. We noted use errors, difficulties, and subjective feedback indicating concerns with the readability of the Instructions for Use (IFU), but you have not proposed additional risk mitigation strategies to address the use errors and difficulties. Thus, we recommend additional mitigation strategies to address these use errors and difficulties as part of the overall changes to the user interface.
c. We disagree with your characterization of some tasks as non-critical. Tasks that could cause harm to users, as noted in your URRA, should be noted as critical tasks (e.g. Inspect Applicator; (b) (4) ; Apply Solution; and Allow Solution to Dry). Additionally, we note that the task 'Remove Cap' in your URRA does not assess the risk of incorrect timing of cap removal, which can increase the risk of accidental exposure. Because of the potential for causing harm to the user or patient, these tasks should be re-categorized as critical tasks in your updated URRA."

The review forewent labeling discussions due to the complete response recommendation.

The applicant resubmitted a response to the complete response action on 23 December 2020.

Drug Product and Manufacturing Deficiencies:
Chemistry, Manufacturing, and Control (CMC) concluded that the applicant has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substance, cantharidin and the drug product, YCanth (trade name pending) (cantharidin) Solution, 0.7% (w/v) for topical use with this resubmission.

A recommendation for a CR for the resubmission was made from a CMC perspective due to a determination by the Office of Pharmaceutical Manufacturing Assessment (OPMA) facility inspection as inadequate-major (withhold).

Device Design Deficiencies:

The Human Factor study submitted to address the CR was conducted with trained users and identified use errors with critical tasks. A discipline review (DR) letter describing the Division of Medication Error and Prevention and Analysis (DMEPA) reviewer's concern regarding the applicability of the Human Factors (HF) study for identifying risks in untrained users was conveyed on 04 May 2021. The Applicant submitted a response to the discipline review letter on 13 May 2021 which constituted a major amendment. A major amendment review extension letter was sent on 25 May 2021 with a new PDUFA date of 23 September 2021. DMEPA reviewed the data submitted in the amendment and concluded that modifications to the proposed user interface and labeling are needed to mitigate potential medical errors. Dr. Avani Bhalodia's DMEPA draft review from September 7, 2021 describes the errors that occurred with the following critical tasks: 1) putting on personal protective equipment (PPE), 2) inspecting the applicator, and 3) the knowledge task question to request additional break tools. DMEPA recommends modifications to the proposed user interface and labeling to mitigate potential medical errors. Refer to Avani Bhalodia, PharmD, BCPS, final DMEPA review (pending submission to DARRTS).

Reviewer comments:

The clinical review team concurs with DMEPA that the proposed user interface and labeling should be improved to further mitigate the residual risks. Of note, DMEPA has identified that a lack of break tool availability may lead to a critical use issue. The clinical review team agrees that the applicant should address mitigation of this potential risk. The clinical review team envisions more than one approach to achieve this goal and recommends that the applicant present options to the Agency for consideration and that the Agency not necessarily require the applicant to package one break tool with each applicator.

DMEPA is recommending that the applicant evaluate labeling modifications in an additional HF study. It is not clear to this reviewer that all theoretical risks will need to be addressed prior to marketing approval.

While the consequences of systemic toxicity with accidental ingestion of the product or ocular exposure are significant, the risk of these events occurring is likely low with proper use and mitigation strategies reflected in the recommended user interface and labeling. As noted by the Applicant, the total volume of solution contained within the ampule is 0.45 mL inside a flexible applicator tube of approximately (b) (4) *This volume ratio design feature, along with the* (b) (4) *that creates a pressure drop, limits the maximum distance any solution can be expelled from the applicator. A formal force expulsion study was conducted by applying maximum force across the entire tube length with the applicator pointed at a downward angle. The maximum distance drug solution was expelled was 38mm (NDA 212905, SN0025).*

It is expected that as clinicians gain experience with the product, it is likely that the identified use errors will decrease. Mitigation of all, including newly identified medical errors will continue to be addressed throughout the product's lifecycle with insight from real world experience.

The clinical review team recommends sending DMEPA comments (pending the final DMEPA review in DARRTS) as an advice letter or information request (IR) for future labeling discussions after the complete response letter for CMC deficiencies has been sent to the Applicant.

Labeling Review:

Summary of Additional Clinical Labeling Considerations and Recommendations at the time of this review (deferred negotiations with the Applicant with this cycle's resubmission given the planned complete response as above):

Preliminary labeling recommendations are summarized in Table 1.

Table 1. Summary of Major Labeling Changes

Requested applicant to use "YCANTH" or "cantharidin" instead of VP-102 as appropriate throughout the label.

Section	Additional Comments
2 Dosage and Administration	The reviewer agrees with the following changes and recommendations made by the labeling team. Re-organized the information previously in applicant's proposed subsection 2.1 to include important safety information related to administration in subsection 2.1 Important Administration Instructions and added subsection 2.2 dosage/administration overview. Included only text related to dosage and administration of the product in section 2. Removed (b) (4) Incorporated edits for brevity, use of command language, and removal (b) (4) Requested applicant to provide more specific discard instructions in subsection 2.3 Dosage and Administration Instructions. Recommended applicant place break tool illustration together with other illustrations at the beginning of subsection 2.3 Dosage and Administration Instructions.
4 Contraindications	See reviewer comments below
5 Warnings and Precautions	The reviewer agrees with the following changes and recommendations made by the labeling team. Recommended avoidance of (b) (4)

	[redacted] (b) (4) recommended further description of the toxicity risk in section 5. See reviewer comments below. Per the Warnings and Precautions, Contraindications and Boxed Warning Sections of Labeling guidance, section 5 should include risk mitigation strategies and recommendations for management of adverse reactions. Text to reflect the guidance was inserted. Regarding [redacted] (b) (4) removed applicant's statement, [redacted] (b) (4) See reviewer comments below.
6 Adverse Reactions	Added the number and percent of subjects who removed YCANTH prior to the 24-hour predetermined timepoint due to severe blistering, severe pain, or other severe treatment emergent adverse events. Regarding [redacted] (b) (4) removed applicant's statement, [redacted] (b) (4) See reviewer comments below. Edited applicant's proposed adverse reactions table to include incidence ≥1%. See reviewer comments below.
8 Use in Specific Populations	See Division of Pediatrics and Maternal Health (DPMH) Labeling Consult Review dated April 3, 2020. Replaced the term, [redacted] (b) (4) with "low" systemic exposure after topical administration with YCANTH in sections 8.1 and 8.2 per clinical pharmacology given PK study results (see section 12 Clinical Pharmacology in the label). Refer to clinical pharmacology labeling review (not yet submitted in DARRTS at the time of this review). Added, "Avoid application of YCANTH solution to areas with increased risk for potential ingestion by or ocular exposure to the breastfeeding child" in section 8.2 Lactation and received DPMH concurrence by email correspondence.
10 Overdosage	Strengthened section to include information on toxicity associated with unapproved, inappropriate intentional or unintentional/accidental oral use/ingestion. Added Poison Control center contact information. See reviewer comments below.

12 Clinical Pharmacology	Refer to clinical pharmacology labeling review for all changes (not yet submitted in DARRTS at the time of this review). In section 12.2 Pharmacodynamics, the review team added: "The pharmacodynamics of cantharidin in the treatment of molluscum contagiosum are unknown."
14 Clinical Studies	Moved details of (b) (4) Removed (b) (4)
17 Patient Counseling Information	Edited section to match recommended edits made in section 5. Regarding (b) (4), removed (b) (4) See reviewer comments below.

Additional explanations pertaining to the clinical rationale for labeling recommendations are discussed below.

Section 4 Contraindications

Reviewer comments:

There were no reported cases of anaphylaxis to topical application of cantharidin in the pivotal studies Trial 1 (NCT03377790) and Trial 2 (NCT03377803) (n = 266, and n = 262, respectively) or in the literature.

However, there are reported cases of systemic hypersensitivity to Milian's solution which contains methylene blue and gentian violet in the literature (Bruneau et al.)

Consequently, the reviewer removed (b) (4)

Section 5 Warnings and Precautions

Reviewer comments:

The following description of the toxicity risk was added by the review team:

"YCANTH is for topical use only. YCANTH is not for oral, mucosal, or ophthalmic use.

Life threatening or fatal toxicities can occur if YCANTH is administered orally [see Overdosage (10)]. Adverse reactions to oral ingestion of cantharidin have included renal failure, blistering and severe damage to the gastrointestinal tract, coagulopathy, seizures, and flaccid paralysis (b) (4) (b) (4) to seek medical attention immediately if YCANTH is accidently ingested.

Ocular toxicity can occur if YCANTH comes in contact with the eyes. Adverse reactions from contact of YCANTH with the eyes can include corneal necrosis, ocular perforation, and deep ocular injuries (b) (4) Do not apply YCANTH near or to the eyes. If YCANTH comes in contact with the eyes, flush eyes with water for at least 15 minutes and seek medical attention immediately."

Section 6 Adverse Reactions

Reviewer comments:

YCANTH was primarily studied in Trial 1(NCT03377790) and Trial 2 (NCT03377803) (n = 266, and n = 262, respectively), which were two randomized, double-blind, placebo-controlled Phase 3 studies. *In Section 6.1 Clinical Trials Experience, the reviewer added,* "YCANTH Solution or vehicle could be removed prior to the 24-hour timepoint if severe blistering, severe pain, or other treatment-emergent adverse events were experienced and was removed prior to the 24-hour timepoint in 109/311 (35%) subjects treated with YCANTH Solution and 46/216 (21%) subjects treated with vehicle."

The reviewer recommends avoiding promotional terms such as (b) (4) *per the labeling tool. Therefore, after the sentence,* "Location skin reactions at the application site were observed in 97% of subjects treated with YCANTH during both trials," *the reviewer removed,* (b) (4)

As an alternative, the applicant may provide and present data observed in clinical trials to support terms (b) (4)

E.g. XX percent of local skin reactions (LSRs) resolved by XX weeks. Also, the reviewer recommends separating LSRs out by type when presenting data from clinical trials regarding time to complete resolution.

In Section 6.1, the applicant proposed a table of percentage of subjects with adverse reactions (b) (4) by severity in Trial 1 and Trial 2 which reflected exposure to YCANTH or vehicle in 527 pooled subjects with molluscum contagiosum (Table 1).

(b) (4)

Source: Applicant's proposed Table 1 in section 6.1 of the label.

The applicant also proposed the statement, (b) (4) *The reviewer recommends removing the terms,* (b) (4) *in labeling (see below).*

Given the limited number of subjects and number of adverse reactions reported for certain adverse reactions to achieve statistical significance, previous request for the applicant to provide raw [adverse events] incidence

rates at ≥1% for the placebo-controlled period through Day 84 in their safety analysis (see pre-NDA meeting minutes dated 03/25/2019), and multidisciplinary review, the reviewer evaluated the adverse reactions for the percentage of subjects with adverse events with an incidence of ≥1% and selected adverse reactions as shown in Table 2.

Table 2. Percentage of Subjects with Selected Adverse Reactions (Incidence ≥1%) by Severity in Trial 1 and Trial 2 (Safety Population)

	YCANTH N=311			Vehicle N=216		
Preferred Term Name	*Mild*	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*
Application site vesicles	*60%*	*32%*	*4%*	*27%*	*2%*	*0%*
Application site pain and pain	*41%*	***20%***	*2%*	*16%*	*1%*	*0%*
Application site pruritus and pruritus	*47%*	***8%***	***1%***	***30%***	***7%***	*0%*
Application site scab and scab	*39%*	*9%*	*0%*	*20%*	*1%*	*0%*
Application site erythema and erythema	*24%*	*21%*	*<1%*	*20%*	*7%*	*0%*
Application site discoloration	*28%*	*4%*	*<1%*	*12%*	*1%*	*0%*
Application site dryness	*19%*	*2%*	*0%*	*14%*	*1%*	*0%*
Application site edema	*7%*	*3%*	*0%*	*3%*	*1%*	*0%*
Application site erosion	*6%*	*1%*	*0%*	*1%*	*0%*	*0%*
Contact dermatitis	***0%***	***1%***	***0%***	***0%***	***0%***	***0%***

Source: Reviewer modified version of applicant's Table 1 in Section 6.1 of the proposed label.

Per the labeling review tool, an adverse reaction is an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

The reviewer does not consider (b) (4) *as* (b) (4)

Additionally, (b) (4)

Summary rationale for selected adverse reactions in Table 2:

The reviewer combined similar terms such as application site pain and pain, application site pruritus and pruritus, application site erythema and erythema, and application site scab and scab.

For adverse events with an incidence of ≥1%, the reviewer excluded adverse reactions that had a placebo incidence greater than the YCANTH incidence. The following selected preferred term names, each individually with an adverse event incidence of ≤1% for subjects treated with YCANTH, but ≥1% when pooled, were noted to have a placebo incidence greater than the YCANTH incidence when pooled: impetigo, bullous impetigo, cellulitis, infection, pyoderma, skin infection, staphylococcal abscess, staphylococcal abscess, staphylococcal infection, subcutaneous abscess, abscess limb, staphylococcal skin infection, and infected bites, and therefore, excluded. The reviewer also excluded the following adverse reactions with an incidence of >1% given that these adverse reactions (b) (4)

The following selected adverse reactions with ≥1% were considered for inclusion but ultimately excluded (Table 3):

(b) (4)

Source: Review team based on applicant's data.

Section 10 Overdosage

Reviewer comments:

The review team added the following to strengthen section 10 Overdosage:

"YCANTH is not for oral use [see Warnings and Precautions (5.1)]. The oral medial lethal dose (LD50) of cantharidin is 0.5 mg/kg. If YCANTH is ingested, a dose of 10 mg could be fatal. One applicator contains 3.15 mg of cantharidin. Oral ingestion of cantharidin has resulted in renal failure, blistering and severe damage to the gastrointestinal tract, coagulopathy, seizures, and flaccid paralysis.

If YCANTH is ingested, monitor patients closely and administer appropriate supportive measures. Contact a Poison Center (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations."

References

Bruneau. A propos de l'article Choc anaphylactique consécutif à l'application de solution de Milian [Apropos of the article: anaphylactic shock following the application of Milian's solution]. Phlebologie. 1972;25(1):11..

Moed L, Shwayder TA, Chang MW. Cantharidin revisited: a blistering defense of an ancient medicine. Arch Dermatol. 2001;137(10):1357-1360. doi:10.1001/archderm.137.10.1357.

Rivaud C, Gerault A, Frau E, Faye M. Lésions oculaires par insectes vésicants [Eye injuries caused by vesicatory insects]. *J Fr Ophtalmol*. 1990;13(1-2):47-50.

National Center for Biotechnology Information. PubChem Compound Summary for CID 5944, Cantharidin. https://pubchem.ncbi.nlm.nih.gov/compound/Cantharidin. Accessed May. 17, 2021.

Ghura HS, Camp RD. Scarring molluscum contagiosum in patients with severe atopic dermatitis: report of two cases. *Br J Dermatol*. 2001;144(5):1094-1095. doi:10.1046/j.1365-2133.2001.04211.x

Piérard-Franchimont C, Piérard GE. Cantharidin-induced acantholysis. *Am J Dermatopathol*. 1988;10(5):419-423.

Singh M, Acharya M, Gandhi A, Prakash U. Molluscum-related keratoconjunctivitis. Indian J Ophthalmol. 2019;67(7):1176. doi:10.4103/ijo.IJO_1808_18.

Paller, AS and Macini, AJ. Hurwtiz Clinical Pediatric Dermatology: A Texbook of Skin Disorders of Childhood and Adolescence. 4th edition. Philadelphia: Elsevier Saunders; 2011.

Bolgonia, JL, Jorizzo JL, and Schaffer JV. Dermatology. 3rd edition. Elsevier Saunders; 2012.

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: July 13, 2020
To: NDA 212905
Regulatory Pathway: 505(b)(1)
From: Snezana Trajkovic, M.D., CDTL, DDD

SUBJECT
Submission type: NDA 212905
Submission date: September 13, 2019
Drug: cantharidin solution, 0.7%
Indication: treatment of molluscum contagiosum in patients 2 years of age and older
Route of administration: topical
Applicant: Verrica Pharmaceuticals, Inc.

Background
The Applicant submitted a New Drug Application (NDA) 212905 for cantharidin solution, 0.7% for the treatment of Molluscum Contagiosum (MC) in patients 2 years and older under the 505(b)(1) regulatory pathway.
Cantharidin is a naturally occurring compound from the body fluids of the blister beetle. Currently, cantharidin is commercially available in a 0.7% concentration in a base of flexible collodion and is on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act for the treatment of molluscum contagiosum, however, it is not approved by the Agency for any indication.

The applicant submitted data from two adequate and well-controlled trials which provided evidence of the effectiveness of cantharidin solution, 0.7% for the treatment of molluscum contagiosum in patients 2 years of age and older.

The applicant conducted a comprehensive assessment of the safety of cantharidin in the target population. The size of the safety database and the safety evaluations were sufficient to characterize the local and systemic adverse reactions.

However, significant drug applicator design and Chemistry, Manufacturing, and Control (CMC) drug product and manufacturing deficiencies are outstanding at the time of completion of NDA review. Therefore, the complete response is recommended for this application.

Recommendation:
This reviewer recommends complete response for the NDA 212905.

The cross-discipline team leader (CDTL) review is complete. Refer to the Multi-Disciplinary Review and Evaluation for the details.

Snezana Trajkovic, M.D.,
Clinical Team Leader,
Division of Dermatology and Dentistry

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SNEZANA TRAJKOVIC
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NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212905
Priority or Standard	Standard
Submit Date(s)	September 13, 2019
Received Date(s)	September 13, 2019
PDUFA Goal Date	July 13, 2020
Division	Kendall Marcus, MD Director Division of Dermatology and Dentistry
Review Completion Date	July 09, 2020
Established/Proper Name	cantharidin
(Proposed) Trade Name	YCANTH *pending
Pharmacologic Class	505(b)(1)
Code Name	N/A
Applicant	Verrica Pharmaceuticals, Inc.
Dosage form	Topical solution
Applicant Proposed Dosing Regimen	Expel a small droplet onto the molluscum lesion and spread it evenly (a single-use applicator directly to the affected molluscum skin lesion), to be administered by health care professional only
Applicant Proposed Indication(s)/Population(s)	For the treatment of Molluscum contagiosum in patients 2 years and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Molluscum contagiosum infection (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	TBD
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	TBD
Recommended Dosing Regimen	TBD

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Additional Reviewers of Application

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OPDP	Matthew Falter/ Laurie Buonaccorsi
OSI	Jenn Sellers/Phillip Kronstein
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DEPI = Division of Epidemiology
DHOT = Division of Hematology Oncology Toxicology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
DRISK = Division of Risk Management
OB = Office of Biostatistics
OC = Office of Compliance
OOD = Office of Oncologic Diseases
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Jianyong Wang, PhD	OII/DPT-II	Sections: 5 and 19.3	Select one: ✓ Authored ___ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Maryjoy Mejia, MD	OII/DDD	Sections: 1-4, 7, 8.2, 8.4, 9-13, 19.2	Select one: _✓_ Authored ___ Approved
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Statistical Reviewer	Rebecca Hager, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 8.4, 19.5	Select one: _✓_ Authored ___ Approved
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Statistical Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 8.4, 19.5	Select one: ___ Authored _✓_ Approved
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Glossary

AD	atopic dermatitis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AIDS	acquired immunodeficiency syndrome
BLA	biologics license application
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CI	confidence interval
DHOT	Division of Hematology Oncology Toxicology
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
EOS	end of study
ERT	evaluation to response to treatment
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GCP	good clinical practice
GC/MS	gas chromatography–mass spectrometry
GEE	generalized estimating equation
GLP	good laboratory practice
hERG	human ether-a-go-go related gene
HCP	health care provider
HF	human factors
IC_{50}	half maximal inhibitory concentration
IFU	instructions for use
IND	Investigational New Drug
IP	intraperitoneal
ITT	intent-to-treat
IV	intravenous
LD_{50}	median lethal dose
LLOQ	lower level of quantitation
LSR	local skin reaction
MBR	Master Batch Records
MC	molluscum contagiosum
MCV	molluscum contagiosum virus
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OPMA	Office of Manufacturing Process Assessment
OSI	Office of Scientific Investigation
PeRC	Pediatric Review Committee
PK	pharmacokinetic

PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPSR	proposed pediatric study request
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
URRA	use-related risk analysis
WR	written request

1 Executive Summary

1.1. Product Introduction

Cantharidin, 0.7% is a topical solution for which Verrica Pharmaceuticals, Inc. (Applicant) seeks approval under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act, for the indication of treatment for molluscum contagiosum (MC) in patients 2 years and older. The active ingredient is cantharidin, a naturally occurring compound from the body fluids of the blister beetle. Currently, cantharidin is commercially available in a 0.7% concentration in a base of flexible collodion, and is on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act for the treatment of MC. However, it is not approved by the Agency for any indication. The proposed dosage and administration for cantharidin, 0.7% (VP-102) are as follows: apply VP-102 one time to each skin lesion at each office visit. VP-102 should be removed by washing with soap and water approximately 24 hours after treatment. VP-102 treatment sessions can be repeated every 3 weeks.

The Agency concluded that the proposed proprietary name, YCANTH, was acceptable from both a promotional and safety perspective (Proprietary Name Review by Madhuri Patel, PharmD, Division of Medication Error Prevention and Analysis dated December 3, 2019).

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the effectiveness of cantharidin in the treatment of MC in patients 2 years and older, the Applicant submitted results from two randomized, multicenter, placebo-controlled, Phase 3 studies that evaluated topical application of cantharidin solution, 0.7% to MC lesions for 24 hours, repeated every 3 weeks for up to 4 applications. The studies enrolled 528 subjects 2 years and older with MC. The primary endpoint was the proportion of subjects achieving complete clearance of all MC lesions (baseline and new) at Day 84.

Cantharidin demonstrated statistically significant (p=<0.001) superiority over vehicle for complete clearance of all MC lesions.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Cantharidin is a naturally occurring compound from the body fluids of the blister beetle. Currently, cantharidin is commercially available in a 0.7% concentration in a base of flexible collodion and is on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act for the treatment of molluscum contagiosum (MC), however, it is not approved by the Agency for any indication.

The Applicant submitted a New Drug Application (NDA) 212905 for YCANTH (cantharidin, 0.7%) topical solution for the treatment of MC in patients 2 years and older under the 505(b)(1) regulatory pathway.

To establish the effectiveness of cantharidin in the treatment of MC in patients 2 years and older, the Applicant presented results from two randomized, multicenter, placebo-controlled, Phase 3 studies (VP-102-101 and VP-102-102) that evaluated topical application of cantharidin solution, 0.7% to MC lesions for 24 hours, repeated every 3 weeks for up to 4 applications. The studies enrolled 528 subjects 2 years and older with MC. The primary endpoint was the proportion of subjects achieving complete clearance of all lesions (baseline and new) at Day 84. Results for the primary endpoint were statistically significant (p=<0.001).

The Applicant comprehensively assessed the safety of cantharidin in patients 2 years and older with MC. The safety evaluations were adequate in type and frequency to identify local and systemic treatment-emergent adverse events (TEAEs). In addition to routine safety assessments, the safety evaluations reflected what is historically known about cantharidin (e.g., mechanism of action) and its route of administration (topical). The Phase 3 studies, VP-102-101 and VP-102-102, provided the primary safety data (n=527) and adequately reflected the expected use in patients 2 years and older with MC.

Treatment with cantharidin solution was not associated with an increased risk of mortality or serious adverse events. Based on the mechanism of action as a vesicant, as well as the topical route of administration, the most common TEAEs occurred at the application site and were local skin reactions (LSRs). The majority of LSRs were either mild or moderate in severity.

Although cantharidin solution, 0.7% itself appears safe, the currently proposed applicator has inherent flaws. The design deficiencies that can lead to accidental exposure to the patient or health care provider's mouth or eyes causing serious harm, cannot be managed by prescription labeling, routine pharmacovigilance, and/or postmarketing requirements.

The Division of Medication Error Prevention and Analysis (DMEPA) identified that the proposed cantharidin combination product, particularly the break force of the ampule and paperboard sleeve, lead to significant difficulties upon attempted use of the product. The Division deemed that mitigation strategies are needed and could include the need for device design changes to optimize the applicator, specifically matching the design specification with the intended users' ability to generate the force to break the ampule. Other revisions to the product user interface (e.g., readability of the instructions for use (IFU) to ensure proper timing of cap removal and correct applicator orientation) should also be optimized. After these additional risk mitigation strategies/modifications are implemented, DMEPA recommends that the Applicant conduct an additional human factors (HF) validation study to ensure that these modifications do, in fact, address the observed use errors and use difficulties and do not introduce any new risks.

In addition to the device design flaws, the Office of Pharmaceutical Quality (OPQ) deemed that sufficient information regarding both drug product quality and the manufacturing process is lacking. The Applicant did not perform testing to assure the drug product can be safely and accurately expelled onto an MC lesion with avoidance of adjacent healthy skin. Revisions of the specification for the final assembled drug product should include: a test for the crushing force of the glass ampule, a leakage test after ampule crushing to affirm there is no drug leakage at release and during shelf-life, and a droplet test to demonstrate that the users are capable of dispensing various amounts of drug product as needed to the affected skin area, while avoiding the adjacent healthy skin. Additionally, revised extractable/leachable studies will need to be performed and at least 3 months of long-term and accelerated stability data from three batches of fully assembled (b) (4) drug product (with at least three timepoints postmanufacture, at initial, 1 month, 2 months, and 3 months) should be submitted.

The Office of Manufacturing Process Assessment (OPMA) considered the process and facilities aspects of manufacturing inadequate to support the approval of this application. Satisfactory inspections were not completed and must be conducted to assess the ability of the facilities to carry out manufacturing operations in compliance with Current Good Manufacturing Practice (CGMP). OPMA also identified that a formal risk assessment to assess the potential impact of extractables must be performed, as well as that the finalized per lot performance of the applicators (including a test for leakage after breaking the glass ampule, mimicking the actual in-use condition), along with a sampling plan, must be submitted and added to the Master Batch Records (MBR). Additionally, (b) (4) to demonstrate the Applicant's manufacturing ability at their proposed commercial scale, must be updated.

The deficiencies of the device design, drug product, and manufacturing aspects adversely impact the final combination product generating an unfavorable overall benefit/risk assessment. Hence, the review team recommends complete response for this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	MC is a self-limiting, highly transmissible cutaneous viral infection that typically presents as many, flesh-colored, firm, dome shaped papules with a central umbilication. MC is most often spread by direct skin contact but	While MC is not a life-threatening condition, it can have a significant adverse impact on the quality of life of a patient, as well as family

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	transmission via fomites on bath towels and sponges is possible. MC may affect all age groups but is most common in children. Despite being frequently seen in clinical practice, there is little epidemiologic data on MC infection in children. The prevalence of MC in the United States has been reported to be 5% to 12% in patients ages 0 to 16 years. MC has also been reported to be more common and more extensive in patients with atopic dermatitis (AD). MC is clinically diagnosed, but it can be confirmed via biopsy or microscopic examination of a crush preparation of a lesion. Lesions may occur anywhere on the body except the palms and soles and are commonly seen on the trunk, axillae, antecubital and popliteal fossae, and crural folds. The infection usually resolves spontaneously, but clearance can take anywhere from 6 months to 4 years.	members. MC is a chronic skin infection of childhood that can be associated with a number of inflammatory conditions, including molluscum dermatitis, which is characterized by eczematous patches surrounding MC lesions; papular acrodermatitis, a diffusely pruritic skin condition; and focal inflammation of individual lesions. These inflammatory reactions to MC are common and can predispose patients to secondary infection, as well as further spread via autoinoculation from scratching. The ease of spread and transmission, scarring, social stigma, and psychological stress for patients and parents often accompany the disease.
Current Treatment Options	Currently, there are no approved drug products for the treatment of MC. Various modalities have been used to treat MC, including mechanical/chemical destruction, topical or intralesional injections of immune-modulators, and antiviral drugs. Depending on the chosen therapy, treatment can be time consuming or can result in pain, irritation, dyspigmentation, or scarring. Robust evidence for the efficacy and safety of these treatments is lacking. Although MC is a self-limiting disease health care providers (HCPs) recommend treatment of lesions to prevent disease transmission and spread by autoinoculation.	There are currently no FDA approved or monographed treatments for MC. MC's self-limited course and paucity of strong evidence that definitively supports therapeutic intervention has resulted in controversy regarding the need to treat. However, patients and families often seek clinical evaluation of MC lesions. Cantharidin would add a treatment option for patients with MC.
Benefit	To establish the effectiveness of cantharidin in the treatment of MC in patients 2 years and older, the Applicant submitted results from two randomized, multicenter, placebo-controlled, Phase 3 studies that evaluated topical application of cantharidin solution, 0.7% to MC lesions for 24 hours, repeated every 3 weeks for up to 4 applications. The studies enrolled 528 subjects 2 years and older with MC.	The medical officer concludes that the submitted evidence has met the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that cantharidin is effective for treatment of MC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The primary endpoint was the proportion of subjects achieving complete clearance of all lesions (baseline and new) at Day 84. Studies VP-102-101 and VP-102-102 demonstrated the efficacy of cantharidin relative to vehicle in complete clearance of all MC lesions at Day 84.	
Risk and Risk Management	The Applicant comprehensively assessed the safety of cantharidin in patients 2 years and older with MC. The safety evaluations were adequate in type and frequency to identify local and potential systemic TEAEs. In addition to routine safety assessments, the safety evaluations reflected what is historically known about cantharidin (e.g., mechanism of action) and its route of administration (topical). The Phase 3 studies, VP-102-101 and VP-102-102, provided the primary safety data (n=527) and adequately reflected the expected use in patients 2 years and older with MC. Treatment with cantharidin solution was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the development program for cantharidin. Based on the mechanism of action as a vesicant, as well as the topical route of administration, the most common TEAEs occurred at the application site and were LSRs. The majority of LSRs were either mild or moderate in severity. No significant adverse reactions have been identified during the review of this application that would warrant a risk evaluation and mitigation strategy (REMS). During the review of this application, significant drug applicator design and product quality deficiencies were identified that adversely impacted the final decision on product approvability. The following device and product quality deficiencies were identified: Device Deficiencies	The size of the safety database and the scope of the safety analyses were sufficient to characterize the safety profile of cantharidin. Topical cantharidin solution, 0.7% was generally well tolerated in subjects 2 years and older with MC. The safety evaluation reflected what has long been known about cantharidin, given its historical use and mechanism of action as a vesicant. As has been endorsed for several years and underscored by this application's safety analyses, topical use by or under direct supervision of an HCP ensures appropriate use and confers rare complications. Although cantharidin solution, 0.7% itself appears safe, the current applicator has inherent flaws. The design deficiencies that can lead to accidental exposure to the patient or HCP's mouth or eyes causing serious harm cannot be managed by prescription labeling, routine pharmacovigilance, and/or postmarketing requirements. Mitigation strategies are needed and could include the need for device design changes to optimize the applicator, specifically matching

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The inherent design of the applicator may contribute to accidental exposure during use and serious harm to patients and health care providers. In particular, the break force of the ampule and paperboard sleeve have been points of concern as identified through use-related risk analysis, HF study design, and observed errors/close calls/use difficulties with critical and noncritical tasks. Additionally, Chemistry, Manufacturing, and Control reviewers listed numerous drug product and manufacturing deficiencies: <u>Drug Product Deficiencies</u>: 1. The proposed drug product specification does not include a test to assure the drug product can be safely and accurately expelled onto the lesion area and avoid the adjacent healthy skin. The specifications for the final assembled drug product should be revised to include the following: a. A test for the crushing force of the glass ampule. b. A leakage test after ampule crushing to assure there is no drug leakage at release and during shelf-life. c. A droplet test to demonstrate that the users are capable of dispensing various amounts of drug product as needed to the affected skin area while avoiding the adjacent healthy skin. 2. The extraction solutions (b) (4) used in the extractable/leachable study are considered inadequate since (b) (4) 2) leachable compounds were detected during drug product testing for related substances that were not detected in the extractable studies. Extractable/leachable studies the Applicant committed to in the amendment dated January 23, 2020 should be conducted and the results of the studies should be submitted to the application.	the design specification with the intended users' ability to generate the force to break the ampule as well as other revisions to the product user interface (e.g., readability of the IFU to ensure proper timing of cap removal and correct applicator orientation). Resolution of all drug product and manufacturing deficiencies are necessary to ensure the final assembled drug product is safe.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	3. The drug product quality is not assured and the expiration dating period cannot be established because the registration drug product batches provided in the application were not fully assembled (b) (4) In order to assure the drug product quality and establish an expiration dating period for the drug product, at least 3 months of long-term and accelerated stability data from three batches of fully assembled (b) (4) drug product (with at least 3 timepoints post manufacture at initial, 1 month, 2 months, and 3 months) should be submitted to the application. <u>Manufacturing Deficiencies</u>: 1. Facilities: a. Our field investigator could not complete inspection of the manufacturing facility (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. b. We have not yet completed our inspection of (b) (4) manufacturing facility due to travel restrictions associated with the COVID-19 pandemic. An inspection of (b) (4) facility is required before this application can be approved, as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. 2. Process: (b) (4)	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4) Due to above listed product quality deficiencies, this reviewer recommends complete response for this application.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
✓	Patient experience data were not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

MC is a self-limited cutaneous infection caused by the poxvirus of the Molluscipox genus, or the molluscum contagiosum virus (MCV). MCV genotype 1 is the most prevalent and the cause of 98% of cases in the United States. MCV genotype 2 occurs more commonly in the anogenital area of sexually active adolescents and adults.

MC is a highly transmissible condition and predisposes affected patients to autoinoculation by scratching or rubbing. Close contacts (e.g., family members) are at high risk of infection by direct skin or mucous membrane transmission, or via fomites. Typically, molluscum contagiosum presents as asymptomatic, discrete, pearly, smooth, flesh-colored, dome shaped papules with a central umbilication anywhere on the body except the palms and soles. The most common areas of involvement include the trunk, axillae, antecubital and popliteal fossae, and crural folds. Lesions located in the anogenital region are acquired by sexual transmission, and most of patients are adults and teenagers.

Molluscum lesions usually appear 2 to 6 weeks after viral exposure. The condition lasts for several months to a few years, with an average of about 1 year. Because MCV lives only in the epidermis, once the papules are cleared, the virus is also cleared and cannot be transmitted to others.

MC is most commonly seen in children (0 to 16 years old) with a prevalence of 5.1% to 11.5% (Dohil et al. 2006). The number of cases in adults has varied over time. Certain populations are at a higher risk for the infection, including HIV-positive patients who have prolonged infections, and patients with atopic diseases who tend to have a larger number of lesions and prolonged courses of infection. One study has shown an increase in the infection over the last two decades (Becker et al. 1986), paralleling the increase in sexually transmitted diseases. In the 1980s, molluscum contagiosum prevalence increased as a result of the acquired immunodeficiency syndrome (AIDS) epidemic. However, since the enhancement of antiretroviral therapy, the number of molluscum contagiosum cases in AIDS patients has decreased substantially.

2.2. Analysis of Current Treatment Options

There are currently no U.S. Food and Drug Administration (FDA)-approved or monographed treatments for MC. Generally, health care providers (HCPs) recommend treatment of lesions for cosmetic reasons or to prevent transmission and autoinoculation. Treatments include mechanical destruction (e.g., cryotherapy, curettage, pulsed dye laser therapy), chemical/drug treatment (e.g., cantharidin, potassium hydroxide, podophyllotoxin, benzoyl peroxide, tretinoin, trichloroacetic acid, lactic acid, glycolic acid, salicylic acid), immune-modulating therapy (e.g., imiquimod, interferon-alpha, cimetidine), and antiviral drug therapy (e.g., cidofovir).

Table 1. Treatment Armamentarium Relevant in Patients With Molluscum Contagiosum

Treatment Classification	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA approved			
None			
Other treatments–unapproved			
Chemical/drug	Topical	Literature reports	Transient local skin reactions; uncommon scarring
Mechanical	Physical removal	Literature reports	Discomfort, minor bleeding, scarring
Immunomodulatory	Topical, oral	Literature reports	Local skin reactions for topical agents; CNS effects with cimetidine
Antiviral	Topical, IV	Literature reports	Local skin reactions with topical cidofovir; Renal toxicity with IV cidofovir

Source: Reviewer's own
Abbreviations: CNS, central nervous system; IV, intravenous

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cantharidin, 0.7% in a base of [redacted] (b) (4) has been marketed for decades as an unapproved product for the treatment of MC. In February 2015, cantharidin was recommended for inclusion on the list of bulk drug substances for use in compounding under section 503A of the FD&C Act for the treatment of MC.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed cantharidin under Investigational New Drug (IND) 131163.

1. A Pre-IND 131163 meeting was held on August 16, 2016 during which the following were discussed:
   - The Agency clarified the drug approval process and requirements compared to cantharidin's inclusion on the list of drugs that can be compounded under section 503A of the FD&C Act.
   - [redacted] (b) (4)
   - The Agency recommended a dose-ranging study to investigate the concentration, frequency of use, and treatment duration appropriate for VP-102.
   - The Agency recommended "complete clearance" defined as 100% reduction in baseline lesion count as a primary efficacy endpoint.
2. The Applicant opened the IND on March 21, 2017 with a Phase 3 protocol (Protocol VP-102-101) evaluating cantharidin, 0.7% (w/v) in subjects 2 years and older with MC.
3. An End of Phase 2 meeting was held on September 13, 2017 during which the following were discussed:
   - The Agency recommended specifying a minimum baseline disease severity for subject inclusion in the study(s), as well as inclusion of subjects with inflamed MC.
   - The Division recommended an in-office visit to obtain investigator observed local skin reactions 24 to 48 hours after drug application, at least after the first drug application with adequate monitoring for local skin reactions after subsequent drug applications.
   - The Applicant agreed with the recommended primary endpoint of "complete clearance of MC" at the end of study visit, Day 84, including subjects who clear earlier than Day 84.
4. After two Special Protocol No Agreements were issued on November 11, 2017 and January 26, 2018, the Applicant submitted a final Special Protocol Assessment on February 6, 2018. The Agency issued a Special Protocol Agreement on March 23, 2018.

5. On March 5, 2019, the Agency communicated an Agreed Initial Pediatric Study Plan for a partial waiver of patients under 2 years old because necessary studies would be impossible or highly impracticable.
6. On March 27, 2019 a Pre-New Drug Application (NDA) meeting was held. There was an agreement on the following:
    - Waiver of conduct of thorough QT study
    - Agreement on the proposed pooling strategy

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

For Phase 3 study, VP-102-101, two clinical investigator sites, #009 of Scott L. Katz, MD and #003 of Claude T. Ashley, Jr., MD, PhD, were selected for inspection because of large enrollment, treatment effect size, protocol deviations, and prior inspection histories. According to the review by Jenn W. Sellers, MD, based on the results of the site inspections, study VP-102-101 appears to have been adequately conducted and the data from these sites appear acceptable in support of the treatment of MC.

For Phase 3 study, VP-102-102, two clinical investigator sites were initially planned for inspection, however, because of the COVID-19 global pandemic, the ability to conduct on-site good clinical practice inspections was significantly limited. At the time of this review, OSI was unable to determine if Protocol VP-102-102 was conducted adequately and whether the study data are reliable in support of the treatment of MC.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) deemed that sufficient information regarding drug product quality and the manufacturing process is lacking, hence from the OPQ perspective, this NDA is recommended for complete response until the following deficiencies are satisfactorily resolved.

Drug Product Deficiencies

The proposed drug product specification does not include testing to assure the drug product can be safely and accurately expelled onto an MC lesion with avoidance of adjacent healthy skin. Drug Product Reviewer, Dr. Zhengfang Ge, recommended the specification for the final assembled drug product be revised to include:

1. A test for the crushing force of the glass ampule.
2. A leakage test after ampule crushing to affirm there is no drug leakage at release and during shelf-life.
3. A droplet test to demonstrate that the users are capable of dispensing various amounts of drug product, as needed, to the affected skin area while avoiding the adjacent healthy skin.

Additionally, the extractable/leachable study was considered inadequate. In an amendment from January 23, 2020, the Applicant committed to conducting revised extractable/leachable studies, which will be submitted to the application in another review cycle.

The registration drug product batches that were provided in the application were not fully assembled (b) (4) hence the expiration dating period could not be established. At least 3 months of long-term and accelerated stability data from three batches of fully assembled (b) (4) drug product (with at least three timepoints postmanufacture, at initial, 1 month, 2 months, and 3 months) should be submitted to the application.

Manufacturing Deficiencies

Office of Manufacturing Process Assessment (OPMA) Reviewer, Dr. Zhao Wang, considered the process and facilities aspects of manufacturing inadequate to support the approval of this application. The identified deficiencies and resolutions are included below.

Facilities

Inspections of multiple manufacturing facilities were not completed. Once the facilities are ready for inspection and travel restrictions because of the COVID-19 pandemic are lifted, satisfactory inspections must be conducted to assess the ability of the facilities to carry out manufacturing operations in compliance with Current Good Manufacturing Practice (CGMP).

Process

The Applicant committed to assessing the potential impact of extractables by a formal risk assessment with a report to be provided by June 30, 2020. Additionally, the Applicant will need to provide justification if a leachable study is to be waived. The finalized per lot performance of the applicators including a sampling plan must be submitted and added to the Master Batch Records (MBR) by May 2020. The applicator performance test should include a test for leakage after breaking the glass ampule, mimicking the actual in-use conditions.

Dr. Wang also established that the Applicant must provide (b) (4)

4.3. Clinical Microbiology

Microbiology reviewer, Dr. Eric Adeeku, considered the drug product, YCANTH (cantharidin) solution, 0.7%, as adequately tested for bioburden. Since crude cantharidin used in the manufacturing of the Active Pharmaceutical Ingredient for this drug product is produced from blister beetles, a viral clearance study was performed, and the material was also evaluated for adventitious agents.

4.4. Devices and Companion Diagnostic Issues

The Division of Medication Error Prevention and Analysis (DMEPA) expressed concerns that the proposed cantharidin combination product is not safe and effective for use by health care providers, stating that the risk for accidental exposure outweighs the benefit of the treatment with this combination product. Potential risks for users include straining to break the glass

ampule, removing the paperboard sleeve to try to break the glass ampule, and employing other means to break the ampule if they cannot generate enough force with their hands.

The reader is referred to the DMEPA review by James Schlick, MBA, RPh and Millie Shah, PharmD, BCPS for a detailed analysis of the proposed user interface. The inherent design of this product may contribute to serious harm if accidental exposure occurs during use. In particular, the break force of the ampule and paperboard sleeve have been points of concern identified through use-related risk analysis (URRA), human factors (HF) study design, and observed errors/close calls/use difficulties with critical and noncritical tasks.

Mitigation strategies are needed and could include the need for device design changes to optimize the applicator, specifically matching the design specification with the intended users' ability to generate the force to break the ampule. Other revisions to the product user interface (e.g., readability of the instructions for use (IFU) to ensure proper timing of cap removal and correct applicator orientation) should also be optimized. After additional risk mitigation strategies/modifications are implemented, DMEPA recommends that the Applicant conduct an additional HF validation study to ensure that these modifications do, in fact, address the observed use errors and use difficulties and do not introduce any new risks.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

When applied topically, cantharidin functions as a vesicant, weakening desmosomes in the epidermis and leading to the formation of intra-epidermal blisters. Cantharidin is extremely toxic when exposed via systemic routes. The median lethal dose (LD_{50}) value (intraperitoneal (IP) dose) in mice is very low, at only ~1 mg/kg. In a rabbit study, single intravenous (IV) doses ≥1.3 mg/kg caused 100% mortality by 24 hr postdose. In another rabbit study, following a single oral dose of 20 mg/kg cantharidin, almost all animals died within 3 hr postdose. In a rat study, a single oral dose of 6.9 mg/kg cantharidin caused a mortality rate of 3/8.

Given the highly toxic nature of cantharidin, toxicity studies in animals via oral or parenteral routes of administration would unlikely produce any useful information as systemic exposure to cantharidin would most likely not be tolerated in animals. Toxicity studies in animals to address dermal safety are also not considered necessary as cantharidin's effects on skin have been well characterized in literature. In addition, cantharidin (topical formulations) has a long history of clinical use in the treatment of MC. For these reasons, nonclinical studies in animals are waived, including in vivo safety pharmacology studies, pharmacokinetic studies, general toxicology studies, in vivo genetic toxicology studies, reproductive and developmental toxicology studies, and juvenile animal toxicology studies.

The Applicant conducted an in vitro human ether-a-go-go related gene (hERG) assay and three in vitro genotoxicity studies with cantharidin. These studies have been previously reviewed and are summarized in this review. Cantharidin did not show significant inhibition on the hERG current (IC_{50}>300μM). Cantharidin was negative for mutagenicity in a bacterial reverse mutation assay. A chromosomal aberration assay in human lymphocytes was inconclusive, as chromosome evaluation was not feasible in the study. Cantharidin was positive in an in vitro micronucleus assay and a follow-up CREST analysis indicated that the positive response in inducing micronuclei was primarily caused by an aneugenic mechanism. Overall there were no significant genotoxicity concerns for cantharidin.

There are two novel excipients (nitrocellulose and gentian violet) in the proposed topical formulation, and the proposed levels for acetone and denatonium benzoate are higher than the maximal approved levels listed in the FDA's inactive ingredient database. It is determined that there are no significant safety concerns for any of the proposed uses of these excipients in this formulation.

There are extensive pharmacology and toxicology studies of cantharidin in published literature. Relevant summary pharmacology and toxicology information from literature is described in this review. Such information is considered to be generally accepted scientific knowledge. Therefore, this NDA is considered a 505(b)(1) application, from a pharmacology/toxicology perspective.

This NDA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical PMC/PMR for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary Pharmacology

Cantharidin is a lipophilic natural compound obtained from the body fluids of the blister beetle, primarily of the family Meloidae. When applied topically, cantharidin functions as a vesicant, weakening desmosomes in the epidermis. Application of cantharidin to the skin causes the release of neutral serine proteases, locally resulting in the destruction of intercellular desmosomes responsible for holding the layers of the skin together (Bertaux et al. 1988). Intracellular tonofilaments are also weakened, leading to the result of acantholysis and a fluid-filled thin-walled intra-epidermal vesicle. The superficial nature of the blisters is attributed to a lesser effect of cantharidin on hemidesmosomes in the basal layer of skin, compared to the more superficial desmosomes.

The precise mechanism of action related to the effectiveness of cantharidin in the treatment of molluscum contagiosum is unknown.

Reviewer's comments: Although the effectiveness of cantharidin in the treatment of molluscum contagiosum is considered related to its function as a blistering agent, the exact mechanism of action is not clear. Therefore, it is recommended that the established pharmacologic class designation for cantharidin be omitted from the highlights of the prescribing information section of the drug label.

Secondary Pharmacology

Cantharidin has shown antitumor activity in vitro against a number of human cancer cell lines, by inducing cell cycle arrest and apoptosis (Bonness et al. 2006; Kuo et al. 2010). Cantharidin is a potent inhibitor of protein phosphatases types I and IIA (Li and Casida 1992; Honkanen 1993).

Safety Pharmacology

Study 1: Effect of cantharidin on cloned hERG potassium channels expressed in human embryonic kidney cells (Study# 170922.WFU)

The in vitro effects of cantharidin on the hERG channel current (a surrogate for I_{Kr}, the rapidly activating delayed rectifier cardiac potassium current) was evaluated. Two concentrations of cantharidin were evaluated (30 and 300μM). Cantharidin inhibited hERG current by 1.9% at

30μM and 3.5% at 300μM. The hERG inhibition at 30 and 300μM was not statistically significant when compared to vehicle control values. The IC_{50} for the inhibitory effect of cantharidin on hERG current was not calculated (>300μM). The positive control terfenadine inhibited hERG current by 84.4% at 60nM.

Cantharidin did not show significant inhibition on the hERG current under the study conditions.

5.4. ADME/PK

None.

5.5. Toxicology

5.5.1. General Toxicology

Single-dose toxicity information was obtained from animal studies conducted with cantharidin in mice, rats, and rabbits by the dermal, oral, IP, and IV routes of administration that have been reported in the published literature.

Single-Dose IP Toxicity Studies

In a mouse study (Graziano et al. 1987), IP doses of cantharidin in methoxytriglycol at 0, 1, 3, and 10 mg/kg were administered. IP doses of 3 and 10 mg/kg caused moderate to severe poisoning signs at 30 min postdose.

The LD_{50} value (IP dose) for cantharidin in mice was reported as 1.0±0.4 mg/kg (Matsuzawa et al. 1987).

In a rat study (Bagatell et al. 1969), an IP dose of 10 mg cantharidin in 0.1M Tris buffer was administered to male albino rats. Histopathology examination showed severe and extensive damage to structures containing epithelial cells in many organs, including kidney, liver, esophagus, stomach, small intestine, large intestine, bladder, and ureters, beginning at 10 min post injection. The epithelial cells underwent cytolysis and an apparent disruption of structure, with separation of cells from one another.

Single-Dose IV Toxicity Studies

In a rabbit study (Rabkin et al. 1979), IV bolus doses of cantharidin were administered to four groups: vehicle control (7 mg/mL acetone), low dose (0.6 or 1.1 mg/kg), mid dose (1.3 or 1.5 mg/kg), and high dose (1.9 mg/kg). Electrocardiograms (ECG) were continuously monitored before and after dosing. A mortality rate of 100% was observed at mid dose and high dose by 24 hr. Survival time was inversely related to drug dose and had a mean of 3 hr in the high dose group. ECG examination showed that cantharidin induced fatal arrhythmias, which were usually ventricular tachycardia leading to ventricular fibrillation, occasionally asystole, and rarely idioventricular rhythm.

Single-Dose Oral Toxicity Studies

In a rabbit study (Rolf et al. 1985), cantharidin was administered orally at 20 mg/kg in a 5 mL vehicle of carbowax to tap water (3:2). With one exception, all the animals died between 2 to 3 hr postdose, because of ventricular fibrillation.

In a rat study (Qualls et al. 2013), cantharidin was administered orally at 6.9 mg/kg to 8 male Sprague Dawley rats, which were surgically implanted with telemetry transmitters for evaluating heart rate, locomotor activity, and body temperature. The mortality rate was 3/8. Study findings included: decrease in locomotor activity and body temperature, decrease in urine volume, and acantholysis of the nonglandular epithelium of the stomach and dilatation of the proximal convoluted tubule.

Single-Dose Dermal Toxicity Studies

In a mouse study (Tarayre et al. 1984), topical doses of cantharidin (2.5, 6.25, 25, 62.5, 125, 250, and 500 μg) applied to the ear of male Swiss mice, caused dose-dependent local edema, with the maximal response achieved at 62.5 μg. Inflammation (measured by ear weight) did not appear to increase further with the 125 μg dose. The application of 250 and 500 μg cantharidin induced toxic responses because of mice licking each other, therefore inflammation was not measured.

In a mouse study (Ivetic Tkalcevic et al. 2012), cantharidin induced ear edema in male CD-1 mice at topical doses of 12.5, 18.5, and 25 μg. No significant differences in edema responses were noted among the three doses. Cantharidin 25 μg applied to the ear produced edema and blisters at 6 hr, edema and neutrophils peaked at 16 hr, necrotic ulcers showed at 48 hr, re-epithelization completed by 120 hr, and granular tissue appeared by 168 hr.

In a rat study (Boris and Hurley 1977), topical doses of cantharidin at 50 μg or more induced significant ear inflammation (measured by punch weight). The inflammation response appeared to reach the maximal level at 400 μg, since doses of 800 or 1000 μg did not cause further increments in response.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study 2: Bacterial reverse mutation assay (Study# AE58BG.502ICH.BTL)

Key study findings:	The mutagenicity of cantharidin was negative in the Ames test under the study conditions.
GLP compliance:	Yes
Test system:	*S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvrA
Study validity:	Yes

In Vitro Assays in Mammalian Cells

Study 3: In vitro mammalian chromosomal aberration assay in human peripheral blood lymphocytes (HPBL) (Study# AE58BG.341ICH.BTL)

Key study findings:	The clastogenic potential of cantharidin was evaluated in a chromosomal aberration assay in human lymphocytes. Condensed and distorted metaphase chromosomes were noted at several concentrations with less than 50% cytotoxicity. Chromosome evaluation was not feasible and therefore the study was terminated without attempting to score the slides. No conclusion can be made as to the clastogenic potential of cantharidin under the study conditions.
GLP compliance:	Yes
Test system:	Human peripheral blood lymphocytes
Study validity:	This assay was terminated prior to attempting to score the slides for the evaluation of chromosomal aberrations.

Study 4: In vitro mammalian cell micronucleus assay in TK6 cells with CREST staining of micronucleus (Study# AE58BG.361CRESTICH.BTL)

Key study findings:	The genotoxic potential of cantharidin was evaluated in an in vitro mammalian cell micronucleus assay in TK6 cells. A positive response (increase in micronuclei induction) was mainly noted in the prolonged treatment (27-hr) cell cultures with no metabolic activation, at cantharidin concentrations of 1, 1.4, and 1.6 μg/mL. Subsequently, as a follow-up approach to identify the mechanism of the positive response (aneugenic or clastogenic), CREST analysis (kinetochore staining) was conducted. The results of the CREST analysis indicated that cantharidin induced micronucleus formation primarily cause by an aneugenic mechanism.
GLP compliance:	Yes
Test system:	TK6 cells
Study validity:	Yes

Genotoxicity Evaluation

Cantharidin was negative in a bacterial reverse mutation assay. Because of an inadequate in vitro chromosomal aberration assay with inconclusive results, the Applicant completed the in vitro genotoxicity test battery with an in vitro micronuclei assay per request. The test result was positive. A follow-up CREST analysis indicated that the positive response in inducing micronuclei was primarily caused by an aneugenic mechanism. Given the highly toxic nature of cantharidin, in vivo genotoxicity testing is not considered useful and therefore a waiver request for in vivo genotoxicity testing has been granted.

For the risk assessment of cantharidin as a primary aneugen, it is considered appropriate to compare exposure levels and calculate a safety margin. In the in vitro micronucleus assay, the positive response was primarily noted after prolonged treatment (27-hr). The concentrations with increased micronuclei (1, 1.4, and 1.6 μg/mL) did not produce similar positive responses after 4-hr exposure. It would be preferable if a no-genotoxic-effect-level could be identified under the 27-hr treatment conditions. However, considering that similar positive responses were not noted under the 4-hr treatment conditions, it is considered acceptable to use the lowest dose in the 27-hr treatment (1 μg/mL) for the safety margin assessment.

In the clinical pharmacokinetic (PK) study VP-102-103, systemic exposure to cantharidin in 16 subjects with severe molluscum was measured. The systemic exposure to cantharidin was very low, as indicated by plasma levels that were below the limits of quantitation (2.5 ng/mL) in 65 of 66 samples. Only one sample was above the limit of quantitation at 3.4 ng/mL at 2 hours post-treatment. Under such circumstances, it is considered very conservative to use the 3.4 ng/mL concentration for the calculation of safety margin.

The 1 μg/mL concentration is ~300-fold higher than the highest plasma concentration of 3.4 ng/mL, measured in human subjects. The safety margin is considered adequate. Overall there were no significant genotoxicity concerns for cantharidin.

5.5.3. Carcinogenicity

Carcinogenicity information is not needed to support this application.

5.5.4. Reproductive and Developmental Toxicology

None.

5.5.5. Other Toxicology Studies

None.

6 Clinical Pharmacology

6.1. Executive Summary

Cantharidin is an inhibitor for protein phosphatases types 1 and 2A. The Applicant believes that the topical application of cantharidin weakens desmosomes in the epidermis through the release of neutral serine proteases, thus having an effect in the treatment of MC.

The Applicant has developed a film-forming VP-102 topical solution containing cantharidin, 0.7% to treat molluscum contagiosum, an infection caused by a poxvirus. Clinical Pharmacology review focuses on Phase 2 maximal use PK study (VP-102-103) in subjects with molluscum contagiosum. Of the 16 subjects between 2 and 15 years old who completed the study , only one subject 2 years old had a quantifiable plasma cantharidin concentration (3.39 ng/mL) at the 2-hour timepoint. In all other subjects, the systemic concentrations of cantharidin were below the lower level of quantitation (LLOQ =2.5 ng/mL). Overall, the PK results indicate that there is a minimal systemic exposure of cantharidin following topical application of VP-102 0.7% solution to subjects with molluscum lesions.

6.1.1. Recommendations

From a Clinical Pharmacology perspective, the overall data provided in this NDA supports the approval of the drug product to treat subjects with MC.

6.1.2. Postmarketing Requirement/Postmarketing Commitment

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The maximal use PK study (VP-102-103) results demonstrated that there was only 1 out 16 subjects who showed a quantifiable plasma cantharidin concentration of 3.39 ng/mL at 2 hours postdose, but no quantifiable levels at later 2 time points (i.e., at 6 and 24 hours postdose). The rest of the 15 subjects in the study exhibited plasma cantharidin below LLOQ of 2.5 ng/mL at all time points postdose.

Summary of safety: Overall, 88 treatment-emergent adverse events (TEAEs) were reported in 29/33 (87.9%) subjects. Most TEAEs were reported as mild, as only 3 subjects reported moderate TEAEs and no subjects reported severe TEAEs. 21 (63.6%) subjects experienced TEAEs that were considered related to VP-102. Most of these (20 subjects) were local skin reaction (LSR) TEAEs, which were expected as part of the study treatment regimen. The most frequent LSR TEAE was pain, which was reported in 18 (54.5%) subjects. No deaths occurred during the study and no subjects experienced a severe adverse event or TEAE leading to discontinuation from the study.

Reviewer's comments: This reviewer notes that the bioanalytical assay is not very sensitive as per current standards. The purpose of maximal use study is to inform systemic safety. Since there are no systemic safety signals noted and furthermore, the treatment needs to be repeated once every 3 weeks for up to 4 treatment cycles, additional PK assessment by conducting another maximal use PK study using a more sensitive bioanalytical assay will not be needed.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Topical application of the product (i.e., a single-use applicator containing 450 μL of 0.7% (b) (4) cantharidin solution) to the affected molluscum skin lesion once every 3 weeks appears reasonable. Each applicator contains (b) (4) of cantharidin.

Therapeutic Individualization

There is no therapeutic individualization in this application.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this application from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Phase 2 study (VP-102-103) was conducted in subjects 2 to 15 years old with molluscum contagiosum, to determine the potential for systemic exposure to cantharidin under maximal use conditions in a subset of subjects called the exposure treatment group. The standard treatment group (N=16) was defined as subjects having less than 21 lesions. VP-102 [0.7% (w/v) cantharidin] was applied topically once every 3 weeks for up to 4 treatments by applying the drug to molluscum lesions. The exposure treatment group (N=17) was defined as subjects having 21 or more molluscum lesions, this being considered as the upper range of disease severity. Out of the 17 subjects enrolled in the maximal use subset, 16 subjects completed the study with one subject missing the 2-hour postdose PK sampling time point.

PK assessment was conducted for the exposure treatment group, showing that systemic exposure of cantharidin was below the LLOQ (2.5 ng/mL) in all but one subject, who had a quantifiable cantharidin concentration of 3.39 ng/mL at a single time point 2 hours postdose. Based on the results from the study VP-102-103, the Applicant did not collect additional PK samples in other clinical studies, and PK parameters have not been calculated for cantharidin because of lack of a sufficient number of quantifiable concentrations.

Reviewer comments: The Applicant's maximal use PK study had 2 treatment groups based on the number of lesions. The mean ± standard deviation (SD) of treated number of molluscum lesions in the exposure treatment group (i.e., under maximal conditions) was 91.4±94.0 ranging from 37 to 441 lesions. The mean ± SD number of treated molluscum lesions in the standard treatment group was 21.8±16.0 ranging from 3 to 52 lesions. In comparison, the mean numbers of lesions treated per subjects were 45.5 and 38.7 lesions in the pivotal studies, VP-102-101 and VP-102-102, respectively. The molluscum lesions treated in the maximal use PK study were markedly greater indication the upper range of the disease severity.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall efficacy data provide evidence that cantharidin is effective for the treatment of molluscum contagiosum. See Section 7 of this multidiscipline review for details of the study design and efficacy results of the Phase 3 trials.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of topical application to the lesions (once every 3 weeks (b) (4) is appropriate for the treatment of subjects with molluscum contagiosum.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Effect of intrinsic factors on the PK could not be assessed because of limited quantifiable systemic concentrations. An alternative dosing regimen or management strategy is not necessary for the subpopulation.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions are not applicable, as cantharidin solution is administered by topical application. The Applicant has not assessed drug interaction potential, since a drug interaction assessment is not needed because of limited systemic absorption and dosing regimen once every 3 weeks (b) (4)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support of their NDA, the Applicant submitted the following five studies:

- 3 Controlled Clinical Studies in Molluscum Subjects
  - VP-102-101 and VP-102-102 – identical Phase 3, multicentered, randomized, double-blind, placebo-controlled; multiple sites in U.S.
    (b) (4)
- 2 Uncontrolled Clinical Studies in Molluscum Subjects
  - VP-102-103 – Phase 2 open-label safety, efficacy, and PK study of VP-102
    (b) (4)

The table below provides a summary of the aforementioned studies submitted for cantharidin solution, 0.7% to treat MC in patients 2 years and older.

Table 2. Clinical Studies Relevant to NDA 212905

Study Identity NCT #	Study Design	Regimen/ Schedule/Route	Study Endpoints/ Objectives	Treatment Duration/ Follow-Up	No. of patients Enrolled	Study Population	Countries and Number of Sites
Controlled Studies to Support Efficacy and Safety							
VP-102-101 NCT03377790	Phase 3, randomized, DB, VC, multicentered study	VP-102 [0.7% w/v cantharidin] (VP) topically applied to each molluscum contagiosum lesion for 24 hours every 21 days for up to 4 applications	Primary: The proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) at 12 weeks (Day 84 visit)	12 weeks	266 VP: 160 Veh: 106 3:2 VP-102: Vehicle randomization	Patients ≥2 years with molluscum contagiosum	United States - 18
VP-102-102 NCT03377803	Phase 3, randomized, DB, VC, multicentered study	VP topically applied to each MC lesion for 24 hours every 21 days for up to 4 applications	Primary: The proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) at 12 weeks (Day 84 visit)	12 weeks	262 VP: 150 Veh: 112 3:2 VP-102: Vehicle randomization	Patients ≥2 years old with MC	United States - 15
[redacted]							(b) (4)

Study Identity NCT #	Study Design	Regimen/ Schedule/Route	Study Endpoints/ Objectives	Treatment Duration/ Follow-Up	No. of patients Enrolled	Study Population	Countries and Number of Sites
Other studies pertinent to the review of efficacy or safety							
VP-102-103 NCT03186378	Phase 2 Open-label study	VP topically applied to each MC lesion every 21 days for up to 4 applications	Primary: Determine potential systemic exposure from a single 24-hour dermal application applied to molluscum lesions	12 weeks	33 VP: 33	Patients ≥2 years with MC	United States - 1
[redacted]							(b) (4)

Source: Modified from Applicant's Table 5.2-1
Abbreviations: DB, double-blind; MC, molluscum contagiosum; VC, vehicle-controlled; Veh, vehicle randomization

7.2. Review Strategy

The Applicant conducted three clinical studies (VP-102-101, VP-102-102, and VP-102-103) in subjects with MC (b) (4) The three Applicant-conducted VP-102 studies will be the focus of the safety review given that the drug product, dose, duration of application, and frequency were the same.

The Applicant completed two identical Phase 3 randomized, double-blind, vehicle-controlled, multicentered studies (VP-102-101 and VP-102-102) to evaluate the efficacy, safety, and tolerability of cantharidin solution, 0.7%, relative to placebo, when applied once every 21 days (up to 4 times) to treatable molluscum lesions in subjects 2 years and older. The studies were conducted in the United States from February 2018 to November 2018. The primary endpoint was the proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) at 12 weeks (Day 84 visit). These studies will be reviewed as pivotal studies.

The Applicant also conducted a Phase 2 open-label study (VP-102-103) to evaluate the safety and systemic exposure of cantharidin solution, 0.7% in 33 subjects 2 years and older, following a single 24-hour application of cantharidin solution, 0.7% when applied to MC lesions every 21 days (up to 4 times). Because this study did not include a control arm, it will not be evaluated for efficacy.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies VP-102-101 and VP-102-102

Study Design

The Applicant conducted two identically-designed, randomized, double-blind, placebo-controlled, Phase 3 trials (VP-102-101 and VP-102-102) to evaluate the safety and efficacy of VP-102 topical film-forming solution (cantharidin, 0.7% [w/v]) in subjects 2 years and older with molluscum contagiosum. Subjects who met the following key inclusion criteria were eligible to be enrolled into the studies:

- Healthy subject, 2 years or older.
- Consent to having all molluscum lesions treated a and physician willing to treat all molluscum lesions initially present (e.g., lesions within 10 mm of the eyelid margins or the margin of any mucosal membrane should be evaluated carefully to ensure that they can be safely treated). Nonmucosal genital area lesions and inflamed lesions are considered treatable.
- Be otherwise medically healthy with no clinically significant medical history as determined by the investigator. Subjects exhibiting active atopic dermatitis may be enrolled.

The protocols specified the following key criteria that would exclude a subject from being enrolled in the study:

- Have any lesions present at baseline in anatomic locations that the subject/guardian or the physician is unwilling to treat.
- Have had any previous treatment of molluscum including the use of cantharidin, antivirals, retinoids, curettage, or freezing of lesions in the past 14 days.

Subjects with molluscum contagiosum from the same household could be enrolled in the study. The protocols state that for ethical and practical considerations, subjects in the same household were assigned to the same treatment group. The protocols specify that the first subjects from each household to enter the study were randomized in a 3:2 ratio to VP-102 and placebo. After the first subject from a household was randomized to a treatment, any other enrolled subject from that household was to be assigned the same randomization number and given the same treatment. This randomization by household was carried out at the study level.

The study drug was applied to all treatable molluscum lesions on subjects every 21 days (±4 days) at study visits on Days 1, 21, 42, and 63, until complete clearance or a maximum of 4 applications. Subjects who completely cleared all treatable lesions prior to Day 84 were to complete the remainder of the visits in order to monitor safety. The end of study (EOS) visit was at the Day 84 visit.

Molluscum lesions were treated without occlusion in all anatomic areas, including the face, trunk, back, arms, legs, hands, feet, anogenital region, and buttocks. The protocols specify that a single use applicator should treat up to approximately 50 lesions, and no more than 2 applicators were permitted per treatment on each subject. Subjects were instructed to wash all treated lesions with soap and warm water 24 hours after treatment, but they could remove the study drug prior to 24 hours in the event of significant blistering, significant pain, or TEAEs.

The protocols state that in order to reduce possible functional unblinding and bias, blinded assessors conducted lesion counts, while separate trained members of the research team conducted safety assessments and evaluations to response to treatment (ERTs). The blinded assessor was not required to be the same person for each subject's study visit. ERT in-person safety assessments were conducted during each treatment visit and within 48 hours after the initial treatment application. ERT phone assessments were planned for 24 hours, 7 days, and 14 days after each treatment.

Study Endpoints

The protocols and statistical analysis plans (SAPs) specify that the primary endpoint is the proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit (EOS).

The protocols and SAPs list the following secondary endpoints:

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

Statistical Analysis Plan

The SAPs define the intent-to-treat (ITT) population as all subjects who were randomized, and the per protocol (PP) population as the subjects who received all 4 planned treatments of study drug and had no major protocol violations. The protocols and SAPs list the following predetermined reasons that exclude subjects from being included in the PP population:

- Subjects treated with the incorrect study drug.
- Subjects who did not come in for scheduled required treatment visits.
- Subjects who refused to have all treatable lesions treated, or investigators who refused to treat all treatable lesions.
- Early removal of the study drug not associated with pain, blistering, or other medically appropriate reason for early removal.
- Subjects with missing lesion counts or clearance assessments.
- Subjects who began alternative treatments for their molluscum after starting the study.
- Subjects enrolled who did not meet the inclusion/exclusion criteria.

- Subjects whom had their blind broken as to their treatment group without following study procedures.

The protocols and SAPs state that the ITT population is used for the primary efficacy analyses, and analyses conducted on the PP population are considered secondary in nature. Efficacy analyses based on the ITT and PP populations are based on the treatment the subject was randomized to.

The safety population includes subjects who meet the screening eligibility criteria and receive at least one application of study drug.

The SAPs state that the variables used for efficacy analyses are based on assessing treatable lesions, so lesions that are untreatable will not be included in the analysis. A lesion is defined as untreatable if the lesion is within 10 mm of the eyelid margin, or the margin of any mucosal surface.

The protocols and SAPs specify that the primary endpoint is analyzed using a Pearson Chi-Square test. The SAPs specify that for the analysis of the primary endpoint, only EOS visits that occur between Days 68 and 100, and at least 17 days after the last treatment, are considered for determining complete clearance. Subjects with an assessment outside this EOS visit window are counted as not cleared. The SAPs specify that the secondary endpoints evaluating complete clearance at Days 63, 42, and 21 are analyzed using a similar method to those of the primary endpoint. The following visit windows are defined for a report of clearance to be considered:

- Day 21: Days 17 to 25 (±4 days from planned visit day)
- Day 42: Days 34 to 52 (±8 days from planned visit day)
- Day 63: Days 51 to 75 (±12 days from planned visit day)

Sequential testing was the prespecified method to control the overall study-wise significance level at 0.05. If the primary endpoint was significant, then the secondary endpoints were tested in the order listed above in the Study Endpoints section. If any hypothesis test failed to reach statistical significance, the testing ceased for confirmatory purposes. Any significant differences detected for endpoints listed below an endpoint that does not meet significance at the α=0.05 level were considered exploratory only.

Subjects who did not have an assessment of complete clearance of all treatable lesions at Day 84 were considered to have missing data for the primary endpoint. The primary method to handle this missing data was to consider all subjects with missing complete clearance data as not having achieved complete clearance. The protocols and SAPs state that it was assumed that the proportion of subjects with missing data would be greater for subjects treated with VP-102 than for subjects treated with the placebo, because subjects treated with VP-102 were assumed to be more likely to clear prior to Day 84, meaning they would be less likely to return for their Day 84 (EOS) visit. Therefore, the applicant stated that this method for handling missing data would be a conservative approach. The SAPs state that missing data for the secondary endpoints are handled using the same methods as those for the primary endpoint.

The SAPs list the following sensitivity analyses for the primary endpoint:

- Analysis using only nonimputed data (complete case analysis).
- Analysis in which all subjects with missing data are considered as having achieved complete clearance.
- Analysis in which subjects treated with the placebo with missing data are considered to have complete clearance, and subjects treated with VP-102 with missing data are considered to not have complete clearance (i.e., worst-case analysis).
- Analysis using the PP population.

A Breslow-Day test is specified in the SAPs in order to consider any potential site-to-site variability of the study results. The SAPs state that, "A site with a strong deviation in treatment effect from other sites will be further investigated to try to gain a better understanding of why differences at the site may exist."

Protocol Amendments

All protocol amendments were finalized prior to the initiation of the studies.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the submitted clinical studies were conducted in accordance with the ethical principles that are consistent with the International Council for Harmonisation guidelines for Good Clinical Practice.

Financial Disclosure

Refer to Appendix 14.2.

Patient Disposition

Study VP-102-101 randomized a total of 266 subjects, 160 to VP-102 and 106 to placebo, from 17 centers, while study VP-102-102 randomized 262 subjects, 150 to VP-102 and 112 to placebo, from 15 centers. All centers were in the United States.

Table 3 presents the percentage of subjects who discontinued the studies and the reasons, as classified by the Applicant. In study VP-102-101, there were similar percentages of discontinuation between the treatment groups, while there was a higher percentage of subjects who discontinued in the VP-102 arm in study VP-102-102. The most common reason for discontinuation was withdrawal by parent/guardian. Based on the details of the reasons for discontinuation in study VP-102-101, it appears that 1 subject in the VP-102 arm and 3 subjects in the placebo arm withdrew because of lack of efficacy, and 1 subject in the VP-102 arm withdrew because of an adverse event (AE). Similarly, in study VP-102-102, it appears 2 subjects

in the VP-102 arm withdrew because of an AE and 2 subjects in the placebo arm withdrew because of lack of efficacy.

Table 3. Disposition of Subjects Enrolled in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Disposition	**VP-102 N=160 n (%)**	**Placebo N=106 n (%)**	**VP-102 N=150 n (%)**	**Placebo N=112 n (%)**
Discontinued	10 (6.3)	6 (5.7)	11 (7.3)	4 (3.6)
Withdrawal by subject	1 (0.6)	0	0	0
Withdrawal by parent/guardian	7 (4.4)	4 (3.8)	7 (4.7)	2 (1.8)
Lost to follow-up	0	2 (1.9)	3 (2)	1 (0.9)
Adverse event	1 (0.6)	0	0	1 (0.9)
Other	1 (0.6)	0	1 (0.7)	0

Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: ITT, intent-to-treat

Protocol Violations/Deviations

Subjects included in the Per Protocol population were those who received all four planned treatments of cantharidin/placebo (or attained early clearance of all lesions), had no major protocol violations, and did not have one of the exclusion deviations listed in Section 6 of the SAP. The table below details major protocol deviations for both Phase 3 studies, VP-102-101 and VP-102-102.

Table 4. Reported Major Protocol Deviations

Study Treatment Group	Subject ID	Reported Deviation	Detail
VP-102-101			
Cantharidin	(b) (6)	Informed consent	ICF Signature pages contained the printed name of the subject instead of the printed name of the Parent/Guardian.
		Broken blind	Staff who previously treated subject became blinded assessor during subsequent visit
		Procedure not done	Pregnancy test not done, and patient had reached menarche.
		Informed consent	Child Assent ICF was not signed
Placebo			Staff who previously treated subject became blinded assessor during subsequent visit
		Informed consent	HIPAA authorization signature incorrectly dated
		Informed consent	ICF Signature pages contained the printed name of the subject instead of the printed name of the Parent/Guardian.
		Incorrect kit	Site assigned incorrect kit to subject
		Incorrect randomization/sibling link	Subject was randomized incorrectly. Subject is siblings with (b) (6) The site created a separate randomization, but the subject was treated with the correct medication. An extra kit was requested from subject (b) (6).

Study Treatment Group	Subject ID	Reported Deviation	Detail
VP-102-102	(b) (6)		
Cantharidin		Scheduled visit not done	Treatment 4 and EOS visit were not completed because of site oversight. Subject reported all lesions cleared at Day 14 phone call after Treatment 3.
		Broken blind	The blinded assessor had assisted the Primary Investigator with the study assessments during prior visits.
		Clearance assessment	An unlicensed MD performed the physical exam at the Screening Visit.
		Incorrect number of applicators	The subject's 184 lesions were treated with 5 applicators at Treatment Visit 1. Per IP Instructions, a maximum of 2 applicators are allowed to be used per Treatment Visit.
Placebo		Incorrect applicator	Subject was treated with 2 applicators at Treatment 1: One applicator from IP Kit 20893 (subject was randomized and assigned this Kit), and one applicator from IP Kit 20538 (Assigned to Subject (b) (6) sibling of subject (b) (6)).
		Incorrect randomization/sibling link	Subject was mistakenly linked as a sibling to subject (b) (6). Correct Sibling Subject Number is (b) (6)

Source: Reviewer's own
Abbreviations: EOS, end of study; ICF, informed consent form; ID, identifier; IP, Investigational product

Table of Demographic Characteristics

Table 5 presents the demographic characteristics of subjects enrolled in Studies VP-102-101 and VP-102-102. Most subjects were between 2 and 11 years old. There were only 8 and 9 adult subjects enrolled in Studies VP-102-101 and VP-102-102, respectively. The majority of subjects were classified as white and not Hispanic or Latino. Study VP-102-102 enrolled more Hispanic/Latino subjects than study VP-102-101. Otherwise, demographic characteristics were generally balanced between treatment arms and across studies.

Table 5. Demographic Characteristics of Subjects Enrolled in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Demographic Characteristic	VP-102 N=160	Placebo N=106	VP-102 N=150	Placebo N=112
Age				
Mean (SD)	7.5 (5.3)	6.3 (4.7)	7.4 (8.0)	7.3 (6.7)
Median	6	5	6	6
Range (min, max)	2, 41	2, 40	2, 60	2, 54
2-5 Years	65 (40.6)	54 (50.9)	72 (48)	52 (46.4)
6-11 Years	74 (46.3)	41 (38.7)	66 (44)	48 (42.9)
12-17 Years	14 (8.8)	10 (9.4)	7 (4.7)	8 (7.1)
≥18 Years	7 (4.4)	1 (0.9)	5 (3.3)	4 (3.6)

	VP-102-101		VP-102-102	
Sex				
Male	75 (46.9)	45 (42.5)	81 (54)	66 (58.9)
Female	85 (53.1)	61 (57.5)	69 (46)	46 (41.1)
Race				
White	135 (84.4)	98 (92.5)	142 (94.7)	104 (92.9)
Black or African American	10 (6.3)	5 (4.7)	3 (2)	3 (2.7)
Asian	4 (2.5)	1 (0.9)	2 (1.3)	0
American Indian or Alaska Native	0	0	0	1 (0.9)
Other	11 (6.9)	2 (1.9)	3 (2)	4 (3.6)
Ethnicity[a]				
Hispanic or Latino	20 (12.5)	8 (7.5)	38 (25.3)	23 (20.5)
Not Hispanic or Latino	140 (87.5)	98 (92.5)	112 (74.7)	87 (77.7)

Source: Reviewer's analysis (similar to Applicant's analysis).
All values are expressed as n (%), unless otherwise specified.
[a] 2 (1.8%) subjects did not report ethnicity in the placebo arm in study VP-102-102
Abbreviations: ITT, intent-to-treat; SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Table 6 presents baseline disease characteristics. Subjects had a median of 14 to 17 lesions in study VP-102-101 and a median of 10 to 14 lesions in study VP-102-102. In both studies, subjects in the placebo arm had a slightly higher mean and median number of lesions at baseline than subjects in the VP-102 arm. There was a greater percentage of subjects in study VP-102-102 who had previous treatment for molluscum than in study VP-102-101.

Table 6. Baseline Disease Characteristics of Subjects Enrolled in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Disease Characteristic	**VP-102 N=160**	**Placebo N=106**	**VP-102 N=150**	**Placebo N=112**
Baseline lesion count[a]				
Mean (SD)	22 (23)	25 (25)	19 (23)	20 (19)
Median	14	17	10	14
Range (min, max)	1, 107	1, 110	1, 184	1, 86
Time since clinical diagnosis (days)				
Mean (SD)	127 (222)	129 (205)	118 (176)	124 (193)
Median	25	32	28	30.5
Range (min, max)	1, 1247	1, 1302	1, 977	1, 957
Previous treatment for molluscum				
Yes	41 (25.6)	30 (28.3)	48 (32)	42 (37.5)
No	119 (74.4)	76 (71.7)	102 (68)	70 (62.5)
Active atopic dermatitis				
Yes	12 (7.5)	13 (12.3)	11 (7.3)	7 (6.3)
No	148 (92.5)	93 (87.7)	139 (92.7)	105 (93.8)

Source: Reviewer's analysis (similar to Applicant's analysis).
All values are expressed as n (%), unless otherwise specified.
[a] One subject did not have a baseline lesion count. This subject was randomized to active treatment but was not treated.
Abbreviations: SD, standard deviation; ITT, intent-to-treat

Table 7 presents the different numbers of subjects randomized per household. There were 86% and 76% of households with only 1 randomized subject, and 12% and 19% of households with 2

randomized subjects in Studies VP-102-101 and VP-102-102, respectively. Few households had 3 or 4 randomized subjects.

Table 7. Household Enrollment in Studies VP-102-101 and VP-102-102

	VP-102-101			VP-102-102		
Sample Size Per Household	**VP-102 N_H=137 n (%)**	**Placebo N_H=91 n (%)**	**Overall N_H=228 n (%)**	**VP-102 N_H=123 n (%)**	**Placebo N_H=81 n (%)**	**Overall N_H=204 n (%)**
1 subject	116 (85)	80 (87)	196 (86)	99 (80)	57 (70)	156 (76)
2 subjects	18 (13)	9 (10)	27 (12)	20 (16)	19 (23)	39 (19)
3 subjects	3 (2)	1 (1)	4 (2)	4 (3)	4 (5)	8 (4)
4 subjects	0	1 (1)	1 (0.4)	0	1 (1)	1 (0.5)

Source: Reviewer's analysis
Abbreviations: N_H, number of households

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The safety population is defined as all randomized subjects who received at least one treatment. In study VP-102-101, 1 subject (b) (6) was randomized to VP-102 but was never treated, and two subjects (b) (6) were randomized to placebo but received VP-102. Therefore, the safety population of study VP-102-101 consisted of 161 subjects in the VP-102 arm and 104 subjects in the placebo arm in study VP-102-101. For one of the two subjects who were randomized to placebo and received VP-102 (b) (6), the study report states that the site assigned the incorrect kit to the subject. For the other subject (b) (6) the study report states that the subject was siblings with a previous subject (b) (6) but was mistakenly randomized separately. The Data Management team was able to assign the correct treatment kit to this subject so that the subject received the same treatment as their sibling. For by household efficacy analyses subsequently discussed in this review, this household was analyzed in the VP-102 group.

Table 8 presents the number of treatments received for the safety population. The majority of subjects received all 4 treatments, though subjects in the VP-102 arms tended to receive less treatments.

Table 8. Number of Treatments Administered in Studies VP-102-101 and VP-102-102, Safety Population

	VP-102-101		VP-102-102	
Number of Treatments	**VP-102 N=161 n (%)**	**Placebo N=104 n (%)**	**VP-102 N=150 n (%)**	**Placebo N=112 n (%)**
1 treatment	18 (11.2)	7 (6.7)	11 (7.3)	2 (1.8)
2 treatments	18 (11.2)	7 (6.7)	17 (11.3)	4 (3.6)
3 treatments	38 (23.6)	12 (11.5)	32 (21.3)	6 (5.4)
4 treatments	87 (54)	78 (75)	90 (60)	100 (89.3)

Source: Reviewer's analysis (same as Applicant's analysis).

Table 9 provides further results for the safety population on the number of subjects who were treated at each visit and the reasons why subjects were not treated (i.e., did not attend the visit, did not receive treatment because of a lesion count of 0, or did not receive treatment for

other reasons). There was a higher proportion of subjects in the VP-102 arm who were not treated because of a lesion count of 0 than in the placebo arm.

Table 9. Number of Subjects Treated at Each Visit in Studies VP-102-101 and VP-102-102, Safety Population

	VP-102-101		VP-102-102	
Treatment Visits Disposition	**VP-102 N=161 n (%)**	**Placebo N=104 n (%)**	**VP-102 N=150 n (%)**	**Placebo N=112 n (%)**
Treatment 1				
Received treatment	161 (100)	104 (100)	150 (100)	112 (100)
Treatment 2				
Received treatment	134 (83.2)	97 (93.3)	136 (90.7)	109 (97.3)
Did not attend visit	4 (2.5)	3 (2.9)	6 (4.0)	1 (0.9)
Not treated - lesion count of 0	19 (11.8)	4 (3.8)	8 (5.3)	2 (1.8)
Not treated - other reason	4 (2.5)	0	0	0
Treatment 3				
Received treatment	116 (72.0)	89 (85.6)	119 (79.3)	104 (92.9)
Did not attend visit	9 (5.6)	5 (4.8)	10 (6.7)	4 (3.6)
Not treated - lesion count of 0	32 (19.9)	10 (9.6)	19 (12.7)	4 (3.6)
Not treated - other reason	5 (3.1)	0	2 (1.3)	0
Treatment 4				
Received treatment	93 (57.8)	78 (75.0)	94 (62.7)	103 (92.0)
Did not attend visit	9 (5.6)	7 (6.7)	11 (7.3)	4 (3.6)
Not treated - lesion count of 0	55 (34.2)	18 (17.3)	43 (28.7)	5 (4.5)
Not treated - other reason	5 (3.1)	1 (1.0)	2 (1.3)	0

Source: Applicant's response to IR
Abbreviations: IR, information request

Regarding prior and concomitant medications, in study VP-102-101, subject (b) (6), who was randomized to cantharidin, applied a single dose of topical imiquimod for an unspecified indication. Subject (b) (6) received cantharidin and reported use of a topical "molluscum stick" for an unspecified indication. Subjects (b) (6) and (b) (6) who were randomized to the placebo, used ZymaDerm topically twice daily for undefined indications.

In study VP-102-102, subject (b) (6), who was randomized to cantharidin, reported use of ZymaDerm for an unspecified indication.

Efficacy Results – Primary and Secondary Endpoints

The number and percentage of subjects who had missing lesion count data at each visit are presented in Table 10. There was generally a low percentage of missing data in both studies. There tended to be a higher amount of missing data on the VP-102 arm compared to the placebo arm in study VP-102-102, though this trend was not observed in study VP-102-101.

Table 10. Missing Lesion Count Data by Visit in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Study Visit	VP-102 N=160 n (%)	Placebo N=106 n (%)	VP-102 N=150 n (%)	Placebo N=112 n (%)
Day 1/baseline visit	1 (0.6)	0	0	0
Day 21 visit	5 (3.1)	3 (2.8)	6 (4)	1 (0.9)
Day 42 visit	10 (6.3)	5 (4.7)	10 (6.7)	4 (3.6)
Day 63 visit	10 (6.3)	7 (6.6)	12 (8)	4 (3.6)
Day 84/EOS visit	6 (3.8)	5 (4.7)	10 (6.7)	3 (2.7)

Source: Reviewer's analysis
Abbreviations: EOS, end of study; ITT, intent-to-treat

Table 11 presents the results for the primary and secondary endpoints using the Applicant's prespecified analysis, the chi-square test. This analysis method assumes all subjects are independent and does not account for the randomization by household, or the possibility that the disease and/or drug product can spread across subjects in the same household. Therefore, this reviewer conducted a supplemental analysis using a generalized estimating equation (GEE) model for logistic regression with an exchangeable working correlation structure, a factor for treatment, and repeated measurements allowed for a household (i.e., one measurement for each subject within the household). The results from this analysis are in Table 12. Accounting for the correlation between subjects within the same household only has a small impact on the estimated treatment difference and corresponding confidence intervals (CIs). This may be attributable to the majority of households (86% and 76% in the study VP-102-101 and VP-102-102, respectively) having only 1 subject enrolled in the studies. The conclusions from both analyses are the same, as the primary endpoint and all secondary endpoints, except for complete clearance at Day 21 in study VP-102-102, were statistically significant.

Table 11. Complete Clearance Results by Visit (Primary and Secondary Endpoints) Analyzed by Chi-Square Test in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Study Visit Parameter	VP-102 N=160	Placebo N=106	VP-102 N=150	Placebo N=112
Day 84 (EOS), n (%)	74 (46.3)	19 (17.9)	81 (54.0)	15 (13.4)
Trt Diff (95% CI)	28.3 (17.7, 39.0)		40.6 (30.4, 50.8)	
P-value	<0.001		<0.001	
Day 63, n (%)	51 (31.9)	18 (17.0)	42 (28.0)	5 (4.5)
Trt Diff (95% CI)	14.9 (4.7, 25.1)		23.5 (15.4, 31.7)	
P-value	0.007		<0.001	
Day 42, n (%)	33 (20.6)	10 (9.4)	19 (12.7)	4 (3.6)
Trt Diff (95% CI)	11.2 (2.8, 19.6)		9.1 (2.8, 15.4)	
P-value	0.015		0.010	
Day 21, n (%)	18 (11.3)	4 (3.8)	8 (5.3)	2 (1.8)
Trt Diff (95% CI)[a]	7.5 (1.4, 13.6)		3.5 (-1.7, 8.7)	
P-value	0.030		0.196	

Source: Reviewer's analysis based on the prespecified chi-squared test (same as Applicant's analysis).
Subjects with missing data are imputed as nonresponders.
[a] For study VP-102-102, the 95% confidence interval and p-value are based on Fisher's exact test as the expected cell count was less than 5, so the chi-square test may not be valid.
Abbreviations: CI, confidence interval; EOS, end of study; ITT, intent-to-treat; Trt Diff, treatment difference

Table 12. Complete Clearance Results by Visit (Primary and Secondary Endpoints) Analyzed by GEE in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Study Visit Parameter	**VP-102 N=160**	**Placebo N=106**	**VP-102 N=150**	**Placebo N=112**
Day 84 (EOS), %	46.3	17.7	53.7	13.3
Trt Diff (95% CI)	28.7 (18.9, 38.4)		40.4 (30.1, 50.7)	
P-value	<0.001		<0.001	
Day 63, %	32.1	17.4	27.5	4.2
Trt Diff (95% CI)	14.7 (4.3, 25.1)		23.3 (14.9, 31.6)	
P-value	0.010		<0.001	
Day 42, %	20.4	10.1	12.7	3.5
Trt Diff (95% CI)	10.3 (1.5, 19.1)		9.2 (2.7, 15.6)	
P-value	0.035		0.013	
Day 21, %	11.3	3.6	5.3	1.9
Trt Diff (95% CI)	7.7 (1.7, 13.6)		3.3 (-1.0, 7.7)	
P-value	0.033		0.184	

Source: Reviewer's analysis based on GEE model for logistic regression with an exchangeable working correlation structure, a factor for treatment, and repeated measurements allowed for a household.
Subjects with missing data are imputed as nonresponders.
Abbreviations: CI, confidence interval; EOS, end of study; GEE, generalized estimating equation; ITT, intent-to-treat; Trt Diff, treatment difference

To further investigate efficacy by household, this reviewer conducted a post hoc sensitivity analysis by household evaluated using a chi-square test. If there was at least 1 failure in a household, then that household was treated as a failure. Note that including only 1 observation per household decreases the sample size, and therefore, these tests may be underpowered. Additionally, this is a conservative way to evaluate households, as some subjects who were successful may be disregarded in this analysis. While this analysis evaluates a conservative scenario that may not be realistic, the results for the primary endpoint at Day 84 are still statistically significant. This provides additional support for the results of the primary endpoint.

Table 13. Complete Clearance Results by Visit Analyzed by Household (Household Treated as Failure if at Least 1 Nonresponder) in Studies VP-102-101 and VP-102-102

	VP-102-101		VP-102-102	
Study Visit Parameter	**VP-102 N=137**	**Placebo N=91**	**VP-102 N=123**	**Placebo N=81**
Day 84 (EOS), n (%)	56 (40.9)	16 (17.6)	61 (49.6)	7 (8.6)
Trt Diff (95% CI)	23.3 (11.9, 34.6)		41.0 (30.2, 51.7)	
P-value	<0.001		<0.001	
Day 63, n (%)	41 (29.9)	18 (19.8)	27 (22)	1 (1.2)
Trt Diff (95% CI)	10.1 (-1.1, 21.4)		20.7 (13.0, 28.4)	
P-value	0.087		<0.001	
Day 42, n (%)	25 (18.2)	10 (11.0)	13 (10.6)	1 (1.2)
Trt Diff (95% CI)	7.3 (-1.9, 16.4)		9.3 (3.4, 15.3)	
P-value	0.137		0.010	
Day 21, n (%)	12 (8.8)	4 (4.4)	6 (4.9)	0
Trt Diff (95% CI)[a]	4.4 (-2, 10.7)		4.9 (-0.2, 10.4)	
P-value	0.207		0.083	

Source: Reviewer's analysis based on a post hoc sensitivity analysis by household using a chi-squared test.
If there was at least 1 failure in a household, then that household was treated as a failure.
Subjects with missing data are imputed as nonresponders.
[a] For study VP-102-102, the 95% confidence interval and p-value are based on Fisher's exact test as the expected cell count was less than 5, so the chi-square test may not be valid
Abbreviations: CI, confidence interval; EOS, end of study; Trt Diff, treatment difference

Table 14 summarizes the treatment differences, CIs, and p-values for the 3 methods, presented in Table 11, Table 12, and Table 13, using the chi-square test, GEE model, and an analysis by household where a household was treated as a failure if it contained at least 1 subject who was a nonresponder. This last conservative analysis generally resulted in smaller treatment differences, especially in study VP-102-101. Otherwise, the conclusions for the analyses were generally consistent.

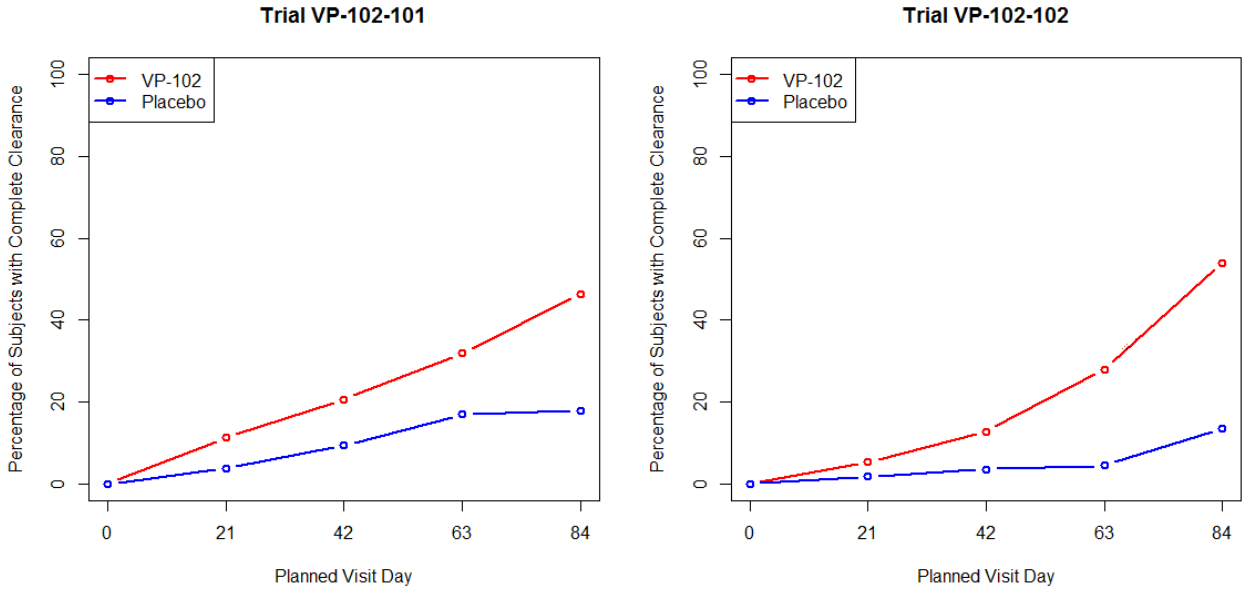
Table 14. Treatment Difference for Complete Clearance and 95% Confidence Interval by Visit and Analysis Method in Studies VP-102-101 and VP-102-102

Study Visit	VP-102-101		VP-102-102	
Analysis Method	**Trt Diff (95% CI)**	**P-value**	**Trt Diff (95% CI)**	**P-value**
Day 84				
Chi-Square	28.3 (17.7, 39.0)	<0.001	40.6 (30.4, 50.8)	<0.001
GEE	28.7 (18.9, 38.4)	<0.001	40.4 (30.1, 50.7)	<0.001
By household	23.3 (11.9, 34.6)	<0.001	41.0 (30.2, 51.7)	<0.001
Day 63				
Chi-Square	14.9 (4.7, 25.1)	0.007	23.5 (15.4, 31.7)	<0.001
GEE	14.7 (4.3, 25.1)	0.010	23.3 (14.9, 31.6)	<0.001
By household	10.1 (-1.1, 21.4)	0.087	20.7 (13.0, 28.4)	<0.001
Day 42				
Chi-Square	11.2 (2.8, 19.6)	0.015	9.1 (2.8, 15.4)	0.010
GEE	10.3 (1.5, 19.1)	0.035	9.2 (2.7, 15.6)	0.013
By household	7.3 (-1.9, 16.4)	0.137	9.3 (3.4, 15.3)	0.010
Day 21				
Chi-Square	7.5 (1.4, 13.6)	0.030	3.5 (-1.7, 8.7)	0.196
GEE	7.7 (1.7, 13.6)	0.033	3.3 (-1.0, 7.7)	0.184
By household	4.4 (-2, 10.7)	0.207	4.9 (-0.2, 10.4)	0.083

Source: Reviewer's analysis.
Subjects with missing data are imputed as nonresponders.
Abbreviations: CI, confidence interval; GEE, generalized estimating equation; Trt Diff, treatment difference

Figure 1 presents the proportion of subjects with complete clearance by visit. Note that this does not account for the correlation between patients in the same household.

Figure 1. Proportion of Subjects With Complete Clearance by Visit in Studies VP-102-101 and VP-102-102



Source: Reviewer's figure.
Subjects with missing data are imputed as nonresponders.
Percentages do not account for correlation between subjects in the same household.

The results for the primary endpoint of complete clearance at Day 84 was further investigated by household size as presented in Table 15. The results by household size at Days 63, 42, and 21 are in Table 25, Table 26, and Table 27 respectively, in Appendix 14.5. There are relatively few households that enrolled more than 1 subject, though there is still a trend in efficacy for VP-102 compared to placebo for these households.

Table 15. Complete Clearance at Day 84 by Household Size in Studies VP-102-101 and VP-102-102

	VP-102-101		VP-102-102	
Household Size Successes vs. Failures	**VP-102 N_H =137 n (%)**	**Vehicle N_H =91 n (%)**	**VP-102 N_H =123 n (%)**	**Placebo N_H =81 n (%)**
1 subject	N_H =116	N_H =80	N_H =99	N_H =57
Success	53 (45.7)	16 (20)	51 (51.5)	7 (12.3)
Failure	63 (54.3)	64 (80)	48 (48.5)	50 (87.7)
2 subjects	N_H =18	N_H =9	N_H =20	N_H =19
2 successes	4 (22.2)	0	9 (45)	0
1 success, 1 failure	11 (61.1)	2 (22.2)	4 (20)	4 (21)
2 failures	3 (16.7)	7 (77.8)	7 (35)	15 (79)
3 subjects	N_H =3	N_H =1	N_H =4	N_H =4
3 successes	0	0	1 (25)	0
2 successes, 1 failure	1 (33.3)	0	3 (75)	0
1 success, 2 failures	2 (66.7)	0	0	2 (50)
3 failures	0	1 (100)	0	2 (50)
4 subjects	N_H =0	N_H =1	N_H =0	N_H =1
1 success, 3 failures	0	1 (100)	0	1 (100)

Source: Reviewer's analysis.
Subjects with missing data are imputed as nonresponders.
Abbreviations: N_H, number of households

Efficacy Results – Sensitivity Analyses

Table 16 presents the results of the prespecified sensitivity analyses to evaluate alternative methods for handling missing data. "Responder imputation" refers to an analysis in which all subjects with missing data are classified as having achieved complete clearance. The "worst-case" analysis refers to an analysis in which subjects treated with the placebo with missing data are considered to have complete clearance, and subjects treated with VP-102 with missing data are considered to not have complete clearance. Lastly, the results are evaluated for the PP population and observed data only. The conclusions of all the sensitivity analyses are consistent with that of the primary analysis. While worst-case imputation may not be based on a reasonable or scientifically-justified assumption, the results from this imputation provide confidence that the superiority of VP-102 compared to placebo was not driven by the method chosen to handle missing data.

Table 16. Sensitivity Analyses for the Primary Endpoint (GEE Analysis) in Studies VP-102-101 and VP-102-102

Analysis Population Missing Data Method, Parameter	VP-102-101			VP-102-102		
	VP-102	Placebo	Trt Diff (95% CI)	VP-102	Placebo	Trt Diff (95% CI)
ITT Population	**N=160**	**N=106**		**N=150**	**N=112**	
Nonresponder imputation, %	46.3	17.7	28.7 (18.9, 38.4)	53.7	13.3	40.4 (30.1, 50.7)
Responder imputation, %	49.9	22.4	27.4 (16.7, 38.2)	60.5	16.1	44.4 (33.9, 54.8)
Worst-case analysis, %	46.3	22.4	23.9 (13.1, 34.6)	53.7	16.1	37.6 (26.9, 48.2)
PP population	**N=122**	**N=83**		**N=120**	**N=98**	
No imputation necessary, %	48.0	20.1	28 (15.8, 40.1)	59.0	13.3	45.7 (34.6, 56.8)
Observed Data	**N=154**	**N=101**		**N=140**	**N=109**	
Complete case analysis, %	48.0	18.5	29.4 (19.4, 39.4)	57.7	13.7	44 (33.5, 54.5)

Source: Reviewer's analysis based on GEE model for logistic regression with an exchangeable working correlation structure, a factor for treatment, and repeated measurements allowed for a household.
Subjects with missing data are imputed as nonresponders.
Abbreviations: CI, confidence interval; GEE, generalized estimating equation; ITT, intent-to-treat; Trt Diff, treatment difference; PP, per protocol

Untreatable Lesions

The primary endpoint only considered complete clearance of all treatable lesions. A lesion was considered to be untreatable if it was located in an area that could not be safely treated. Nonmucosal genital area lesions and inflamed lesions were considered treatable, per protocol, whereas lesions within 10mm of the eyelid margins or the margin of any mucosal membrane were evaluated carefully to ensure that they could be safely treated. Table 17 presents the number of subjects with untreatable lesions at each visit. One subject had 6 untreatable lesions at Day 84, while all other subjects with untreatable lesions had 3 or fewer at all visits.

There was one subject (b) (6) in the VP-102 arm in study VP-102-101 who had 2 untreatable lesions at Day 84 but had complete clearance of all treatable lesions. All other

subjects with untreatable lesions at Day 84 in both studies did not have complete clearance of treatable lesions at Day 84. Therefore, this does not affect the overall conclusions of efficacy.

Table 17. Number of Subjects With Untreatable Lesions in Studies VP-102-101 and VP-102-102, ITT Population

	VP-102-101		VP-102-102	
Study Visit	VP-102 N=160 n (%)	Placebo N=106 n (%)	VP-102 N=150 n (%)	Placebo N=112 n (%)
Day 84 (EOS)	4 (2.5)	3 (2.8)	1 (0.7)	3 (2.7)
Day 63	5 (3.1)	1 (0.9)	0	0
Day 42	6 (3.9)	1 (0.9)	1 (0.7)	3 (2.7)
Day 21	2 (1.3)	1 (0.9)	4 (2.7)	2 (1.8)

Source: Reviewer's analysis based on Applicant's response to IR
Abbreviations: EOS, end of study; IR, information request; ITT, intent-to-treat

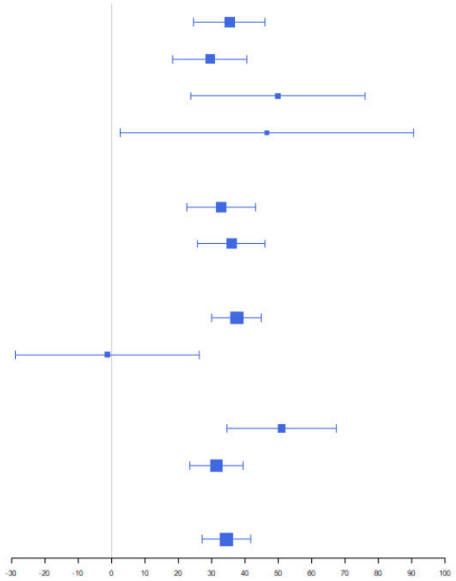
8.1.3. Findings in Special/Subgroup Populations

Sex, Race, and Age

Figure 2 presents results for the primary endpoint by age group, sex, race, and ethnicity for the pooled data from Studies VP-102-101 and VP-102-102. The results for the response rates, the treatment differences, and the corresponding 95% CIs are based on the GEE analysis, discussed in Section 8.1.2, to account for correlation between subjects in the same household. The majority of subjects in the studies were white, and therefore, the results for this subgroup were consistent with the overall results. There were few subjects in the studies who identified with racial groups other than white, so while there was no observed trend in efficacy, it is difficult to make conclusions regarding efficacy in this subgroup. It appears that Hispanic or Latino subjects had higher efficacy than those who were not. There was not a clear difference in efficacy based on age or sex subgroups.

Figure 2. Complete Clearance at Day 84 by Age, Sex, Race, and Ethnicity - Pooled Results From Studies VP-102-101 and VP-102-102, ITT Population

Subgroups	(n[V],n[P])	VP-102	Placebo	Difference
Age				
2-5 Years	(137, 106)	49.6%	14.2%	35.5%
6-11 Years	(140, 89)	46.5%	16.8%	29.6%
12-17 Years	(21, 18)	66.6%	16.7%	50%
>= 18 Years	(12, 5)	66.7%	20%	46.7%
Sex				
Male	(156, 111)	50.1%	17.1%	33%
Female	(154, 107)	50%	14%	36%
Race				
White	(277, 202)	51%	13.4%	37.6%
Other	(33, 16)	42.6%	43.7%	-1.1%
Ethnic				
Hispanic or Latino	(58, 31)	60.7%	9.5%	51.2%
Not Hispanic or Latino	(252, 185)	47.7%	16.2%	31.4%
Overall	(310, 218)	50.1%	15.6%	34.5%



Source: Statistical analyst's figure based on statistical reviewer's GEE analysis.
The treatment difference and 95% confidence intervals are depicted.

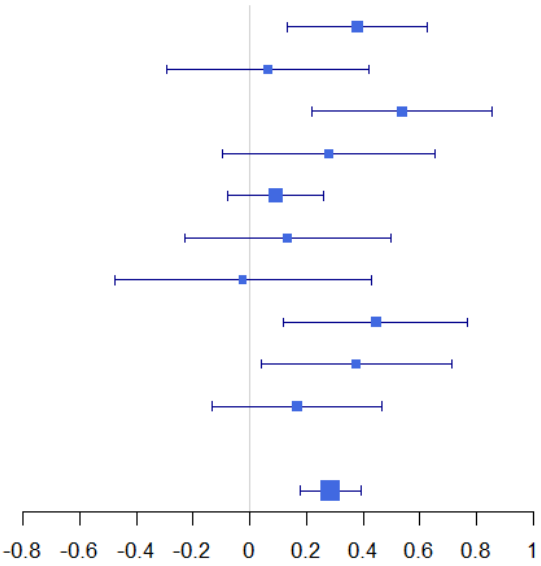
Center

Study VP-102-101 randomized a total of 266 subjects from 17 centers in the U.S., and study VP-102-102 randomized 262 subjects from 15 centers in the U.S. The protocols and SAPs specified the Breslow-Day test in order to consider any potential site-to-site variability of study results. The SAPs did not specify pooling small sites. The Breslow-Day test resulted in a p-value of 0.265 in study VP-102-101 and a p-value of 0.008 in study VP-102-102. These p-values, however, may have been affected by the small sample sizes in the majority of sites. To investigate this issue further, efficacy was investigated by site.

Figure 3 and Figure 4 present the results of the primary endpoint (i.e., the proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit) by site for Studies VP-102-101 and VP-102-102, respectively. Only sites with more than 10 subjects total are depicted. In each figure, the number of subjects per treatment arm, the proportion of responders in the VP-102 arm, the proportion of responders in the placebo arm, and the treatment difference are summarized. The treatment difference and its 95% CI are depicted. The figures depict the sites, ordered by the total number of subjects enrolled and randomized at each site, with the largest sites appearing at the top. It does not appear that any one, or few, sites drove the efficacy results.

Figure 3. Complete Clearance Rates and Treatment Difference at Day 84 by Site for Study VP-102-101, ITT Population

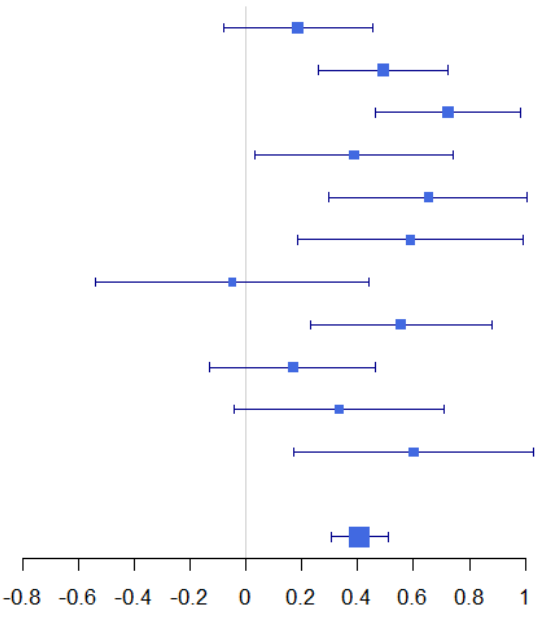
Site ID	(n[V], n[P])	VP-102	Placebo	Difference
3	(25, 21)	0.52	0.14	0.38
37	(16, 14)	0.56	0.5	0.06
9	(19, 10)	0.74	0.2	0.54
7	(18, 6)	0.44	0.17	0.28
12	(11, 13)	0.09	0	0.09
6	(12, 10)	0.33	0.2	0.13
2	(13, 6)	0.31	0.33	-0.03
36	(9, 6)	0.44	0	0.44
11	(8, 4)	0.38	0	0.38
33	(6, 4)	0.17	0	0.17
Overall	(160, 106)	0.46	0.18	0.28



Source: Reviewer's analysis.
Only includes sites with at least 10 subjects.
Nonresponder imputation was used to handle missing data. Depicts the treatment difference and 95% confidence interval.
Abbreviations: ID, identifier

Figure 4. Complete Clearance Rates and Treatment Difference at Day 84 by Site for Study VP-102-102, ITT Population

Site ID	(n[V], n[P])	VP-102	Placebo	Difference
22	(27, 18)	0.41	0.22	0.19
27	(22, 18)	0.55	0.06	0.49
31	(17, 10)	0.82	0.1	0.72
32	(16, 11)	0.75	0.36	0.39
18	(8, 9)	0.88	0.22	0.65
21	(7, 8)	0.71	0.12	0.59
26	(10, 4)	0.2	0.25	-0.05
28	(9, 5)	0.56	0	0.56
20	(6, 6)	0.17	0	0.17
23	(6, 6)	0.33	0	0.33
17	(5, 6)	0.6	0	0.6
Overall	(150, 112)	0.54	0.13	0.41



Source: Reviewer's analysis.
Only includes sites with at least 10 subjects.
Nonresponder imputation was used to handle missing data. Depicts the treatment difference and 95% confidence interval.
Abbreviations: ID, identifier

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety of cantharidin solution, 0.7% focused on pooled data from Phase 3 studies, VP-102-101 and VP-101-102, and data from the Phase 2 study, VP-102-103. Data from these three studies were pulled together to compare incidences of AEs. These studies were chosen as the focus of the safety review because of the similarity of design, the homogeneous population, as well as the cantharidin dose, dosing regimen, schedule, and duration of treatment that reflects anticipated use. The obtained data allowed the direct comparison of AE rates in cantharidin-treated subjects to placebo-treated subjects.

The Applicant provided pooled data analyses using the following strategy:

- Pool A: Study VP-102-103
- Pool B: Studies VP-102-101 and VP-101-102
- Pool C: Studies VP-102-101, VP-102-102, and VP-102-103
- (b) (4)

For our safety review, the safety population included subjects in Pools B and C who were randomized and received at least 1 application.

(b) (4)

To determine the safety profile of cantharidin solution, 0.7% the review team analyzed the following types of pooled data: Exposure, demographics, baseline characteristics, TEAEs, LSRs, serious adverse events (SAEs), AEs leading to discontinuation, vital signs, and findings from physical examinations.

8.2.2. Review of the Safety Database

Overall Exposure

<u>Pools B and C Data</u>

The safety analysis set (safety population) included all randomized subjects who received at least one study drug application.

In Pool B (Phase 3 studies: VP-102-101 and VP-102-102), a total of 311 subjects received at least one cantharidin application. Of these subjects, 177 (57%) received 4 applications, being one application every 21 days during 84 days of treatment. The extent of exposure to cantharidin was dependent on the number of molluscum lesions treated and on the number of treatment visits needed to reach clearance. The mean and median number of lesions treated in the Pool B population were comparable to those in the individual studies and were 42 lesions and 27 lesions, respectively. The total number of treatment visits for subjects receiving cantharidin

were 516 and 501 for study VP-102-101 and study VP-102-102, respectively, and 1017 overall for Pool B subjects.

In study VP-102-103, 33 subjects received at least one cantharidin application resulting in an overall exposure of 344 subjects in Pool C (VP-102-101, VP-102-102, and VP-102-103). Similar to Pool B, a greater number of subjects receiving placebo (82%) warranted all 4 treatment visits compared to those receiving cantharidin (57%).

The overall exposure of the safety population is summarized in the following tables:

Table 18. Extent of Exposure in Pool B:Safety Population

	VP-102-101		VP-102-102		Pool B VP-102-101 and VP-102-102	
Parameter	**VP-102 N=161**	**Placebo N=104**	**VP-102 N=150**	**Placebo N=112**	**VP-102 N=311**	**Placebo N=216**
Number of treatments administered, n (%)						
1	18 (11)	7 (7)	11 (7)	2 (2)	29 (9)	9 (4)
2	18 (11)	7 (7)	17 (11)	4 (4)	35 (11)	11 (5)
3	38 (24)	12 (12)	32 (21)	6 (5)	70 (23)	18 (8)
4	87 (54)	78 (75)	90 (60)	100 (89)	177 (57)	178 (82)
Total treatments	516	369	501	428	1017	797
Number of lesions treated						
Mean	46	85	39	60	42	72
SD	50.93	99.46	41.51	54.71	46.68	80.24
Median	29	53	27	46	27	49
Range (min-max)	1-295	1-543	1-271	3-314	1-295	1-543
Total lesions treated	7,333	8,857	5,803	6,759	13,136	15,616
Subject removed product in less than 24 hours, n (%)						
Yes	57 (35)	20 (19)	52 (35)	26 (23)	NA	NA
No	104 (65)	84 (81)	98 (65)	86 (77)	NA	NA

Source: Modified Applicant's Table, ISS Table 4.2, study VP-102-101 Table 14.3, and study VP 102-102 Table 14.3
Abbreviations: ISS, integrated summary of safety; NA, not available; SD, standard deviation

Table 19. Extent of Exposure in Study VP-102-103 and Pool C: Safety Population

	Pool A VP-102-103	Pool C VP-102-101, VP-102-102, and VP-102-103	
Parameter	**VP-102-103 N=33**	**VP-102 N=344**	**Placebo N=216**
Number of treatments administered, n (%)			
1	4 (12)	33 (10)	9 (4)
2	5 (15)	40 (12)	11 (5)
3	5 (15)	75 (22)	18 (8)
4	19 (58)	196 (57)	178 (82)
Total number of treatment visits	105	1122	797
Number of lesions treated			
N	33	344	216
Mean (SD)	58 (76.05)	44 (50.29)	72 (80.24)
Median	41	29	49
Range (min-max)	3-441	1-441	1-543
Total number of lesions treated	1,902	15,038	15,616

Source: Modified Applicant's Table, ISS Table 4.1 and ISS Table 4.3
Abbreviations: ISS, integrated summary of safety; SD, standard deviation

Adequacy of the safety database:

The safety database provided by the Applicant is sufficient to characterize the safety of cantharidin solution, 0.7% in the treatment of MC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of cantharidin for the treatment of MC.

Categorization of Adverse Events

For the safety analysis set, the Applicant defined an AE as "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."

AEs were categorized by system-organ class and preferred term using the Medical Dictionary for Regulatory Activities version 19.1 (or higher) for VP-102-103, and version 20.0 for Phase 3 studies and all pooled studies. The coding of adverse events in the NDA submission appeared adequate and allowed for accurate estimation of AE risk.

The investigator was responsible for performing periodic and special assessments for AEs. AE collection began once the subject signed informed consent and continued until the EOS visit was complete. All unresolved AEs were followed for 30 days after study completion.

Investigators categorized AEs by seriousness, severity, causality, duration, and action taken with the study drug. Serious adverse events occurring during the studies were to be reported by telephone or email within 24 hours after the investigator became aware of the SAE, then electronically recorded into the safety module under a Serious Adverse Event report form. If additional information to complete the SAE report form was needed, the investigator would not wait before notifying the medical monitor via the SAE Hotline. The SAE report form was to be updated by the investigator when additional information was received.

In this study, a serious adverse event was defined as an AE that met any of the following criteria:

- Resulted in death.
- Was life-threatening.
- Required hospitalization or a prolongation of an existing hospitalization.
- Persistently or significantly incapacitated or substantially disrupted the ability to conduct normal life functions.
- Was considered as any other important medical event that may not result in death, be life-threatening, or require hospitalization, but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition.

The investigator assessed severity for each AE and SAE reported during the study. The severity of each AE and SAE was assigned a classification of mild, moderate, or severe and recorded in the electronic case report form. Local Skin Reactions were rated based on the severity ratings in the Site Local Skin Reaction Guide.

The investigator assessed the relationship between study product and the occurrence of each AE or SAE and categorized the potential relationship as follows:

- Definitely related: The AE has a temporal relationship to the administration of the study product or research intervention and follows a known pattern of response, and no alternative cause is present.
- Possibly related: The AE has a temporal relationship to the administration of the study product or research intervention and follows a suspected pattern of response, but an alternative cause is present.
- Probably related: The AE has a temporal relationship to the administration of the study product or research intervention and follows a known or suspected pattern of response, but an alternative cause may be present.
- Unrelated: The AE has no temporal relationship to the administration of the study product or research intervention and follows no known or suspected pattern of response, and an alternative cause is present.

The Applicant presented standard AE analyses. The definition of AE and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable.

Routine Clinical Tests

Routine safety monitoring included: vital signs (body temperature and heart rate) taken at each treatment visit before study drug application, abbreviated physical examinations at screening and at the EOS visit, concomitant medications, and adverse events. Clinical laboratory evaluations and ECGs were not conducted during the development program for cantharidin because of the negligible systemic exposure.

Overall, safety monitoring performed during the conduct of studies supporting this NDA was appropriate and adequate for evaluation of the safety of cantharidin.

8.2.4. Safety Results

Deaths

There were no deaths during the development program for cantharidin solution, 0.7%.

Serious Adverse Events

In the safety population (Studies VP-102-101, VP-102-102, and VP-102-103), no subject who received cantharidin solution, 0.7% experienced an SAE. One subject who received vehicle experienced a SAE (acute appendicitis requiring appendectomy).

Dropouts and/or Discontinuations Due to Adverse Effects

In Pool B (Studies VP-102-101 and VP-102-102), seven subjects treated with cantharidin discontinued treatment because of five AEs: application site pain (3 subjects), application site pruritus (1 subject), application site vesicles (5 subjects), contact dermatitis (1 subject), and staphylococcal abscess (1 subject). All of these AEs were considered related to study drug administration.

> Narrative: Subject (b) (6), staphylococcal abscess
>
> (b) (6) developed a severe staphylococcal abscess several days following Treatment Visit 2 in a location where molluscum lesions were present. The abscess resolved following oral antibiotic treatment. The subject's guardian decided to discontinue the study before Treatment Visit 3.

No subjects in study VP-102-103 (open-label) discontinued or were withdrawn from the study because of adverse events.

One subject in study VP-102-102 on vehicle discontinued the study because of Gianotti-Crosti syndrome.

Significant Adverse Events

No other significant adverse events were reported during the conduct of studies that support this application.

Treatment-Emergent Adverse Events and Adverse Reactions

Common Adverse Events

There were 5166 TEAEs reported in 560 subjects. TEAEs were reported in nearly all subjects receiving cantharidin (96% in Pool C) and in more than half of subjects receiving placebo (69% in Pool C).

The table below summarizes TEAEs by preferred term that occurred frequently in the safety population and highlights that the most common TEAEs occurred at the application site and were LSRs.

Table 20. TEAEs by Preferred Term in ≥1% of Subjects Across All Pools

	Pool A VP-102-103 N=33	Pool B VP-102-101, VP-102-102 N=527		Pool C VP-102-101, VP-102-102, VP-102-103 N=560	
Preferred Term	VP-102 N=33 n (%)	VP-102 N=311 n (%)	Placebo N=216 n (%)	VP-102 N=344 n (%)	Placebo N=216 n (%)
Application site vesicles	1 (3)	298 (96)	63 (29)	299 (87)	63 (29)
Application site pain	0	193 (62)	36 (17)	193 (56)	36 (17)
Application site pruritus	0	169 (54)	75 (35)	169 (49)	75 (35)
Application site scab	0	147 (47)	47 (22)	147 (43)	47 (22)
Application site erythema	0	139 (45)	58 (27)	139 (40)	58 (27)
Application site discoloration	0	100 (32)	27 (13)	100 (29)	27 (13)
Application site dryness	0	63 (20)	31 (14)	63 (18)	31 (14)
Application site edema	0	29 (9)	10 (5)	29 (8)	10 (5)
Application site erosion	0	22 (7)	2 (1)	22 (6)	2 (1)
Application site scar	0	8 (3)	5 (2)	8 (2)	5 (2)
Pain[a]	19 (58)	2 (1)	1 (1)	21 (6)	1 (1)
Otitis media[b]	0	8 (3)	4 (2)	8 (2)	4 (2)
Pharyngitis streptococcal[b]	0	8 (3)	7 (3)	8 (3)	7 (3)
Sinusitis[b]	0	6 (2)	2 (1)	6 (2)	2 (1)
Nasopharyngitis[b]	0	5 (2)	2 (1)	5 (2)	2 (1)
Pyrexia[b]	1 (3)	5 (2)	4 (2)	6 (2)	4 (2)
Upper respiratory tract infection[b]	1 (3)	5 (2)	4 (2)	6 (2)	4 (2)
Conjunctivitis[b]	0	4 (1)	2 (1)	4 (1)	2 (1)
Headache[b]	5 (15)	4 (1)	0 (0)	9 (3)	0
Pruritus[b]	0	4 (1)	5 (2)	4 (1)	5 (2)
Cough[b]	6 (18)	3 (1)	2 (1)	9 (3)	2 (1)
Vomiting[b]	4 (12)	2 (1)	2 (1)	6 (2)	2 (1)
Oropharyngeal pain[b]	3 (9)	2 (1)	1 (1)	5 (2)	1 (1)
Rhinorrhea[b]	4 (12)	0	0	4 (1)	0
Scar[c]	4 (12)	0	0	4 (1)	0

Source: Modified Applicant's Table ISS Table 5.5.2, ISS Table 5.2.2, ISS Table 5.5.1, ISS Table 5.5.3, ISS Table 5.3.1, and ISS Table 5.3.3.
[a] Pain, reported as "painful blisters" or "pain to molluscum blisters" were coded with a PT of "pain."
[b] All TEAEs with these preferred terms were considered Unrelated to treatment. Other listed preferred terms had a combination of Related and Unrelated TEAEs.
[c] The PT of 'Scar', reported in 4 subjects in VP-102-103, was considered by the Investigator of this single center, open-label study as part of the normal healing process of molluscum lesions and is unrelated to VP-102 administration.
Abbreviations: ISS, integrated summary of safety; TEAE, treatment-emergent adverse event

Reviewer Comment: The safety analysis identified that all TEAEs related to study drug administration occurring in at least 1% of subjects were LSRs.

Based on the mechanism of action as a vesicant, as well as the topical route of administration of cantharidin, LSRs were considered adverse events of special interest. LSRs were observed in 93% of subjects treated with cantharidin across all pooled studies, compared to 59% of subjects treated with placebo(Pool C). Similarly, in Pool B, 97% of subjects treated with cantharidin and 59% treated with placebo experienced at least one LSR.

Of note, there was a difference in safety data collection methodology between Pool A (VP-102-103) and Pool B (VP-102-101, VP-102-102). In the single open-label PK study, VP-102-103, investigators were instructed to consider "anticipated" application site reactions, such as blisters, as a normal response to cantharidin application and not adverse events. Hence, although blisters were apparent, they were not documented as LSRs or AEs in study VP-102-103.

As a result, specific LSR categories were generated by the Applicant based on Agency recommendations during Guidance meetings. These categories included: blistering, pain, pruritis, erythema, edema, erosion/ulceration, flaking/scaling/dryness, scabbing/crusting, and pigmentation changes. In Pool B (VP-102-101, VP-102-102), incidences of LSRs by these categories matched the incidences of LSRs by preferred term occurring in ≥1% of Pool B subjects. This alignment underscores that LSRs were expected because of the molluscum condition and the anticipated pharmacodynamic response to cantharidin.

Table 21. Local Skin Reactions by Frequency (≥1%) and by Preferred Term, Pool B

	VP-102-101, VP-102-102 N=527	
Preferred Term	**VP-102 N=311 n (%)**	**Placebo N=216 n (%)**
Application site vesicles	298 (96)	63 (29)
Application site pain	193 (62)	36 (17)
Application site pruritus	169 (54)	75 (35)
Application site scab	147 (47)	47 (22)
Application site erythema	139 (45)	58 (27)
Application site discoloration	100 (32)	27 (13)
Application site dryness	63 (20)	31 (14)
Application site edema	29 (9)	10 (5)
Application site erosion	22 (7)	2 (1)
Application site scar	8 (3)	5 (2)

Source: Modified Sponsor's Table ISS 6.3.2
Abbreviations: ISS, integrated summary of safety

The majority of LSRs were either mild or moderate in severity for both the cantharidin and placebo groups. Subjects treated with cantharidin experienced mild (55%) or moderate (29%) application site vesicles compared to that reported for the placebo group (27% mild; 2% moderate). Other frequent mild or moderate LSRs seen in cantharidin-treated subjects were application site pruritus (54%), application site scab (47%), application site erythema (45%),

application site dryness (20%), application site discoloration (32%), and application site pain (62%).

Laboratory Findings

No clinical laboratory evaluations were conducted during the development program for cantharidin because of the negligible systemic exposure.

Vital Signs

No clinically significant vital sign abnormalities were reported in the cantharidin group.

Electrocardiograms

No ECGs were performed during the development program for cantharidin because of the negligible systemic exposure.

QT

The Applicant did not conduct a thorough QT study during the studies in the development program. The Applicant submitted a tQT study waiver to the NDA. The QT-IRT review team agreed that a waiver from requirement to conduct a thorough QT study for cantharidin solution, 0.7% was reasonable and provided the following conclusion:

> *"Based on the review of the hERG patch clamp data, we agree with the sponsor's request for a waiver for a thorough QT study. At the highest expected systemic exposure level of 3.4 ng/mL, the safety margin against hERG channel block far exceeds 17311X; therefore, we conclude that cantharidin does not acutely interact with hERG channels at the highest expected systemic exposure level."*

Immunogenicity

This section of the review is not applicable to this product.

8.2.5. Analysis of Submission-Specific Safety Issues

Refer to Section 8.2.4 for discussion of LSRs.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

No clinical outcome assessment analyses informing safety or tolerability was performed as part of the safety review.

8.2.7. Safety Analyses by Demographic Subgroups

The safety of cantharidin was assessed for each study, as well as for pooled data (Pool A, Pool B, and Pool C) by subgroups of: gender, race, age, history of atopic dermatitis (AD), active AD, treatable lesions at baseline, and Fitzpatrick Skin Type.

In the safety population, subjects had a mean age of 7 years in both the cantharidin group and placebo group. Subjects in Pool C were male (51% in cantharidin group and 51% in the placebo group) and were mostly Caucasian (89% cantharidin, 93% placebo).

Subjects who were included in cantharidin efficacy and safety data appear generally representative of the population of patients with molluscum contagiosum. expected to receive cantharidin in the United States.

Gender

The overall incidence of TEAEs were comparable between females and males in all three studies. Specifically, LSRs occurred in similar rates across gender. No safety signals emerged from individual studies or from the integrated data from Pools A, B, and C when analysis of AEs by gender was conducted.

Race

LSRs by preferred term were dissimilar across the race subgroups for: application site pruritis (47% Caucasian, 68% non-Caucasian), application site discoloration (28% Caucasian, 38% non-Caucasian), application site edema (9% Caucasian, 3% non-Caucasian), and application site erosion (7% Caucasian, 3% non-Caucasian). However, because of the small number of non-Caucasian subjects, no meaningful conclusion could be drawn with regard to LSR and race. Even with these differences, race-dependent safety signals were not evident during the safety analysis of cantharidin.

Table 22. TEAEs by Race and by Preferred Term in at Least 5% Subjects in Pool C, Safety Population

	VP-102-101, VP-102-102 and VP-102-103	
	Caucasian N=307	Non-Caucasian N=37
Preferred Term	n (%)	n (%)
TEAEs reported	3788	474
Subjects with at least one TEAE	296 (96)	35 (95)
Subjects with at least one LSR TEAE	287 (94)	34 (92)
Application site vesicles	268 (87)	31 (84)
Application site pain	170 (55)	23 (62)
Application site pruritus	144 (47)	25 (68)
Application site scab	131 (43)	16 (43)
Application site erythema	125 (41)	14 (38)
Application site discoloration	86 (28)	14 (38)
Application site dryness	56 (18)	7 (19)
Application site edema	28 (9)	1 (3)
Application site erosion	21 (7)	1 (3)

Source: Modified Sponsor's ISS Table 5.1.2.2, ISS Table 5.1.3.2, ISS Table 5.5.2.2, ISS Table 5.5.3.2, and ISS Table 5.2.2.2
Abbreviations: ISS, integrated summary of safety; LSR, local skin reaction; TEAE, treatment-emergent adverse event

Fitzpatrick Skin Type

Local skin reactions were assessed by the following three Fitzpatrick skin type subgroupings: I or II, III or IV, and V or VI. In Pool C, except for pain associated with blisters (V/VI: 5%; III/IV: 4%; I/II: 9%) and application site erosion (V/VI: 7%; III/IV: 8%; I/II: 5%), cantharidin-treated subjects with skin type V or VI were observed to have overall higher incidences of all other LSRs.

Because the number of subjects was disproportionately lower in the Fitzpatrick skin type V/VI (n=44), I/II (n=119), and III/IV (n=181) subgroups, a relevant conclusion regarding the impact of Fitzpatrick skin type on the occurrence of TEAEs/LSRs could not be made.

Table 23. TEAEs by Fitzpatrick Skin Type and by Preferred Term in at Least 5% of Subjects Treated With Cantharidin in Pool C: Safety Population

	VP-102-101, VP-102-102, and VP-102-103		
Parameter	**Fitzpatrick Type I or II N=119 n (%)**	**Fitzpatrick Type III or IV N=181 n (%)**	**Fitzpatrick Type V or VI N=44 n (%)**
TEAEs Reported	1503	2191	568
Subjects with at least 1 local skin reaction TEAE	107 (90)	171 (95)	43 (98)
Preferred term			
Application site vesicles	96 (81)	162 (90)	41 (93)
Application site pain	66 (56)	97 (54)	30 (68)
Application site pruritus	55 (46)	88 (49)	26 (59)
Application site scab	51 (43)	74 (41)	22 (50)
Application site erythema	51 (43)	66 (37)	22 (50)
Application site discoloration	27 (23)	57 (32)	16 (36)
Application site dryness	23 (19)	31 (17)	9 (21)
Application site edema	9 (8)	15 (8)	5 (11)
Application site erosion	5 (4)	14 (8)	3 (7)
Pain (experienced as pain associated with blisters)	11 (9)	8 (4)	2 (5)

Source: Modified Applicant's Summary of Clinical Safety Table 2.7.4-58
Abbreviations: TEAE, treatment-emergent adverse event

Age

Reported TEAEs were assessed by the following age groups: 2 to 5 years, 6 to 11 years, 12 to 18 years, and 19 years and older. The majority of subjects were between 2 and 11 years old (500; 89%). Because of the large difference in the number of subjects in the older age groups (12 to 18 years and 19 years and older), compared with the groups representing those 11 years and older, meaningful conclusions could not be made regarding the differences in AEs between younger and older subjects. There were no safety signals related to the age of subjects in any of the individual studies or in any of the pooled analyses.

History of Atopic Dermatitis and Active Atopic Dermatitis

Cantharidin treated subjects with a past history of AD or active AD at baseline generally had higher incidences of LSRs. Exceptions included application site edema (without AD 10%, with AD 4%) and application site erosion (without AD 8%, with AD 3%). However, because of the large disparity in the total number of subjects with AD (73) and without AD (549), no meaningful conclusions could be drawn in regards to AEs and subjects with AD.

Treatable Lesions at Baseline by Lesion Count

Most subjects had ≤20 treatable lesions at baseline. Subjects with higher baseline lesion counts were more likely to have moderate TEAEs (64% with 41+ lesions, 45% with 1 to 20 lesions) or severe TEAEs (14% with 41+ lesions, 4% with 1 to 20 lesions).

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant did not conduct additional specific studies or clinical trials to evaluate a potential safety concern as part of the development program.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No specific carcinogenic studies were conducted.

Human Reproduction and Pregnancy

No specific studies of pregnancy or lactation were conducted. There were no pregnancies reported during the development of cantharidin.

Subjects were not eligible to enroll in the cantharidin development program if they were pregnant, breastfeeding, sexually active, or may become sexually active and were unwilling to practice responsible birth control methods (e.g., combination of condoms and foam, birth control pills, intrauterine device, patch, shot or vaginal ring, etc.).

Female subjects who had reached menarche were required to have a negative urine pregnancy test at each visit prior to treatment with study drug.

Pediatrics and Assessment of Effects on Growth

The effects of cantharidin on growth was not evaluated. Given the lack of systemic absorption of topically applied cantharidin solution, 0.7%, it is reasonable to conclude that it is unlikely there would be an effect of cantharidin on growth. Also, because of the short duration of treatment period (84 days), the evaluation of the effects on growth could not be performed.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Given the mechanism of action as a vesicant, there is no risk for abuse potential, withdrawal, or rebound effects for cantharidin.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There has been no postmarket experience for this product at the time of this review.

Expectations on Safety in the Postmarket Setting

Cantharidin has been widely used to treat molluscum contagiosum and warts since the 1950s. Since February 2015, cantharidin has been accepted under the bulk drug substances list and can be used to compound drug products, for topical use only, in accordance with section 503A of

the FD&C Act. Compounded cantharidin has been used for decades in the U.S. for the treatment of molluscum contagiosum and common warts.

Among dermatologists and pediatricians who are the primary HCPs using cantharidin, the product's flammability and toxicity issues are common practice knowledge. The LD_{50} is around 0.5 mg/kg. If ingested, a dose of as little as 10 mg could potentially be fatal. Ingesting cantharidin can initially cause severe damage to the lining of the gastrointestinal and urinary tracts, and may also cause permanent renal damage. According to Moet L, et al. no cases of systemic toxicity or scarring have been reported with the proper use of cantharidin by a physician (Moed et al. 2001).

Most cantharidin preparations are 0.7% w/v solutions in a highly volatile solvent with a flexible-collodion base enclosed in a screw-top glass bottle intended for repeated use across multiple patients by HCPs. VP-102 is manufactured (b) (4) The Applicant added gentian violet to aid HCPs in visually recognizing already treated lesions. In addition, an oral deterrent, denatonium benzoate was included in the product.

Given its historical use spanning several decades, its well-known potential for flammability and toxicity, the modifications to the drug product (i.e., addition of acetone, dye, and oral deterrent), and application of the product by an HCP using an applicator, new safety issues in the postmarket setting are anticipated to be low.

8.2.11. Integrated Assessment of Safety

The safety profile for cantharidin solution, 0.7% was adequately characterized during the drug development program. The primary safety database consisted of 527 subjects from Studies VP-102-101 and VP-102-102 (the pooled safety analysis set). All randomized subjects who received at least one application were included in the safety analysis set.

Treatment with cantharidin solution was not associated with an increased risk of mortality or serious adverse events. There were no deaths in the development program for cantharidin. No subject who received cantharidin solution, 0.7% experienced a serious adverse event, while one subject who received vehicle experienced a serious adverse event (acute appendicitis requiring appendectomy). No cantharidin-exposed pregnancies occurred during the development program.

The currently available safety data from Studies VP-102-101 and VP-102-102 demonstrate that cantharidin solution, 0.7% appears safe to achieve complete clearance of all treatable molluscum lesions in patients 2 years and older.

8.3. Statistical Issues

The Applicant's prespecified statistical analysis, a chi-square test, assumes that all subjects are independent and does not account for the randomization of subjects by household or the possible correlation of outcomes between subjects in the same household. A GEE analysis, which accounts for this correlation, resulted in the same conclusions of those from the chi-

square analysis (Table 11 and Table 12). Efficacy was further evaluated for the different household sizes and in various sensitivity analyses. All analyses were supportive of the conclusion that there was a statistically significant difference in favor of VP-102 compared to placebo on the primary endpoint.

8.4. Conclusions and Recommendations

To establish the effectiveness of cantharidin in treating patients with MC 2 years and older, the Applicant submitted results from two randomized, multicenter, placebo-controlled, Phase 3 studies that evaluated topical application of cantharidin solution, 0.7% to MC lesions for 24 hours, repeated every 3 weeks for up to 4 applications. The studies enrolled 528 subjects 2 years and older with MC. The primary endpoint was the proportion of subjects achieving complete clearance of all lesions (baseline and new) at Day 84. Cantharidin demonstrated statistically significant (p=<0.001) superiority over vehicle for complete clearance of lesions.

The Applicant provided substantial evidence of effectiveness in treatment of MC.

The Applicant conducted a comprehensive assessment of the safety of cantharidin solution, 0.7% in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

In this reviewer's opinion, the Applicant provided adequate evidence of the safety of cantharidin solution, 0.7% and no safety signals that would preclude an approval were identified. However, significant device design and product quality deficiencies remain unresolved at the time of this review.

The DMEPA analyzed the proposed user interface and determined that it did not support the safe and effective use of the proposed product.

After reviewing the URRA, DMEPA noted that the Applicant did not evaluate the risk of incorrect timing of cap removal. Due to the potential risk for accidental exposure if the cap is removed at an inappropriate time, DMEPA recommended that the URRA be updated to include the assessment of this risk.

During the HF validation study, the Applicant did not test two important warning statements (flammable liquid and highly toxic). Additionally, specific tasks (i.e., removal of the paperboard sleeve to inspect the applicator, (b) (4) from the applicator, applying the appropriate amount of drug to target lesions, and allowing ample time for drug solution to dry) were incorrectly categorized as noncritical tasks instead of critical. Given that these critical tasks could cause harm to others, DMEPA recommended improved readability of the IFU to emphasize when to remove (b) (4) the paperboard sleeve, (b) (4) how to apply solution to a target lesion, and how to allow adequate time for the drug solution to dry.

Use errors and difficulties with breaking the glass ampule during the HF study indicated that the applicator design itself had not been fully optimized. DMEPA recommended that mitigation

strategies could include matching the product design specification with the intended users' capability to generate the force to break the ampules.

After these additional risk mitigation strategies/modifications are implemented, DMEPA recommends that the Applicant conduct an additional HF validation study to ensure that these modifications do, in fact, address the observed use errors and use difficulties and do not introduce any new risks. Refer to the DMEPA review for a detailed Human Factors analysis.

The OPQ deemed that sufficient information regarding both drug product quality and manufacturing process is lacking.

The proposed drug product specification does not include testing to assure the drug product can be safely and accurately expelled onto an MC lesion with avoidance of adjacent healthy skin. Revisions to the specification for the final assembled drug product should include: a test for the crushing force of the glass ampule, a leakage test after ampule crushing to affirm there is no drug leakage at release and during shelf-life, and a droplet test to demonstrate that the users are capable of dispensing various amounts of drug product as needed to the affected skin area while avoiding the adjacent healthy skin. Additionally, revised extractable/leachable studies will need to be performed. At least 3 months of long-term and accelerated stability data from three batches of fully assembled (b) (4) (with at least three timepoints postmanufacture, at initial, 1 month, 2 months, and 3 months) should be submitted.

The Office of Manufacturing Process Assessment (OPMA) considered the process and facilities aspects of manufacturing inadequate to support the approval of this application. Satisfactory inspections were not completed and must be conducted to assess the ability of the facilities to carry out manufacturing operations in compliance with CGMP. OPMA also identified that a formal risk assessment to assess the potential impact of extractables must be performed. The finalized per lot performance of the applicators (including a test for leakage after breaking the glass ampule, mimicking the actual in-use condition) along with a sampling plan must be submitted and added to the MBR. Additionally, the specification for (b) (4) , to demonstrate the Applicant's manufacturing ability at their proposed commercial scale, must be updated. Refer to the Integrated Quality Review for full quality assessments.

The deficiencies of the device design, drug product, and manufacturing aspects adversely impact the final combination product generating an unfavorable overall benefit/risk assessment. Hence, the review team recommends complete response for this application.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was held for this drug development program.

10 Pediatrics

The Applicant requested a partial waiver of required studies for patients under 2 years old because necessary studies would be highly impracticable to conduct in this age group. On December 6, 2017, the Pediatric Review Committee (PeRC) concurred with the Applicant's plan to request a partial waiver of studies in children under 2 years old and an assessment in patients between 2 and 17 years old. An Agreed Initial Pediatric Study Plan was issued on March 5, 2019.

(b) (4)

On September 13, 2019, the Applicant submitted this NDA (212905) with reports from studies conducted in the pediatric population (2 years and older) for the indication of treatment of MC. The reports contain all the information needed to label the product in children (PK, efficacy and safety).

(b) (4)

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The review team forewent labeling discussions because of the complete response recommendation.

12 Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk evaluation and mitigation strategies are recommended.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended.

14 Appendices

14.1. References

Bagatell, FK, K Dugan, and GF Wilgram, 1969, Structural and biochemical changes in tissues isolated from the cantharidin-poisoned rat with special emphasis upon hepatic subcellular particles, Toxicol Appl Pharmacol, 15(2):249-261.
Becker, TM, JH Blount, J Douglas, and FN Judson, 1986, Trends in molluscum contagiosum in the United States, 1966-1983, Sex Transm Dis, 13(2):88-92.
Bertaux, B, C Prost, M Heslan, and L Dubertret, 1988, Cantharide acantholysis: endogenous protease activation leading to desmosomal plaque dissolution, Br J Dermatol, 118(2):157-165.
Bonness, K, IV Aragon, B Rutland, S Ofori-Acquah, NM Dean, and RE Honkanen, 2006, Cantharidin-induced mitotic arrest is associated with the formation of aberrant mitotic spindles and lagging chromosomes resulting, in part, from the suppression of PP2Aalpha, Mol Cancer Ther, 5(11):2727-2736.
Boris, A and JF Hurley, 1977, Assessment of topical anti-inflammatory activity in rats with cantharidin-induced inflammation, J Invest Dermatol, 68(3):161-164.
Dohil, MA, P Lin, J Lee, AW Lucky, AS Paller, and LF Eichenfield, 2006, The epidemiology of molluscum contagiosum in children, J Am Acad Dermatol, 54(1):47-54.
Graziano, MJ, AL Waterhouse, and JE Casida, 1987, Cantharidin poisoning associated with specific binding site in liver, Biochem Biophys Res Commun, 149(1):79-85.
Honkanen, RE, 1993, Cantharidin, another natural toxin that inhibits the activity of serine/threonine protein phosphatases types 1 and 2A, FEBS Lett, 330(3):283-286.
Ivetic Tkalcevic, V, B Hrvacic, M Bosnar, S Cuzic, B Bosnjak, V Erakovic Haber, and I Glojnaric, 2012, Cantharidin-induced inflammation in mouse ear model for translational research of novel anti-inflammatories, Transl Res, 160(2):137-145.
Kuo, JH, YL Chu, JS Yang, JP Lin, KC Lai, HM Kuo, TC Hsia, and JG Chung, 2010, Cantharidin induces apoptosis in human bladder cancer TSGH 8301 cells through mitochondria-dependent signal pathways, Int J Oncol, 37(5):1243-1250.
Li, YM and JE Casida, 1992, Cantharidin-binding protein: identification as protein phosphatase 2A, Proc Natl Acad Sci U S A, 89(24):11867-11870.
Matsuzawa, M, MJ Graziano, and JE Casida, 1987, Endothal and cantharidin analogs: relation of structure to herbicidal activity and mammalian toxicity, J Agric Food Chem, 35(5):823-829.
Moed, L, TA Shwayder, and MW Chang, 2001, Cantharidin revisited: a blistering defense of an ancient medicine, Arch Dermatol, 137(10):1357-1360.
Qualls, HJ, TC Holbrook, LL Gilliam, BL Njaa, RJ Panciera, CN Pope, and ME Payton, 2013, Evaluation of efficacy of mineral oil, charcoal, and smectite in a rat model of equine cantharidin toxicosis, J Vet Intern Med, 27(5):1179-1184.
Rabkin, SW, JM Friesen, JA Ferris, and HY Fung, 1979, A model of cardiac arrhythmias and sudden death: cantharidin-induced toxic cardiomyopathy, J Pharmacol Exp Ther, 210(1):43-50.

Rolf, LL, ES Buchanan, and F Alavi, 1985, Acute toxicity of cantharidin in laboratory rabbits: a possible model for equine blister beetle disease, Toxicon, 23(1):36-37.
Tarayre, JP, M Aliaga, M Barbara, G Villanova, V Caillol, and H Lauressergues, 1984, Pharmacological study of cantharidin-induced ear inflammation in mice, J Pharmacol Methods, 11(4):271-277.

14.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and subinvestigators who participated in covered clinical studies for cantharidin. Prior to study initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were studies VP-102-101 and VP-102-102, which provided the primary data to establish effectiveness and safety of this product.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study (Name and/or Number): VP-102-101

Was a list of clinical investigators provided:	Yes ✓	No ☐ (Request list from Applicant)
Total number of investigators identified: 19		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): VP-102-102

Was a list of clinical investigators provided:	Yes ✓	No ☐ (Request list from Applicant)
Total number of investigators identified: 15		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ✓	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ✓	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Recommended revisions to the nonclinical portions of labelling

Revisions to the Applicant's proposed wording for the nonclinical portions of labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the label proposed by the Applicant. A clean copy of the recommended nonclinical portions of labeling is also provided below.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

(b) (4) YCANTH is indicated for the treatment of molluscum contagiosum.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

14.4.1. Study VP-102-103

Title: A Phase 2, open-label study to evaluate the safety, efficacy and systemic exposure of VP-102 topical film forming solution [0.7% (w/v) cantharidin] in subjects (2 years and older) with molluscum contagiosum

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

Study population: A total of 33 subjects (2 to 15 years old) were enrolled. PK was assessed in a subset of subjects called the exposure treatment group (n=17) and there were 3 subjects between 2 and 5 years old.

Dose/Dosing regimen: VP-102 solution was applied once every 21 days to the molluscum lesions until complete clearance or for a maximum of 4 treatment sessions [Day 84, EOS].

VP-102 was prepared in a single-use applicator delivering up to 450 μL of a 0.7% w/v cantharidin formulation in a film-forming excipient system. Each applicator contains (b) (4) of cantharidin. Topical application of VP-102 leaves a thin film on the lesion as VP-102 solvent evaporates.

Study design: This study was conducted to evaluate the safety, efficacy and systemic exposure of VP-102 topical film forming solution (cantharidin, 0.7%) in subjects 2 years and older with molluscum contagiosum. The study had two groups as following:

- Exposure treatment group – 16/17 subjects completed. Subjects presented with 21 or more lesions on Day 1. At least 3 subjects were between 2 and 5 years old.
- Standard treatment group – 16/16 subjects completed. Subjects presented with 1 to 20 lesions on Day 1.

In the Exposure treatment group, blood samples for pharmacokinetic assessment were collected at predose and at 2, 6, and 24 hours postdose on Day 1. Subjects in both groups received topical application of VP-102 on Day 1 and every 21 days until Day 84 (EOS) or until complete clearance of lesion.

Results: Of 16 completed subjects in the exposure treatment group, a single subject 2 years old had quantifiable plasma concentration of cantharidin (3.39 ng/mL) at 2 hours postdose, and plasma concentration of cantharidin was not quantifiable at 6 hours and 24 hours postdose. The rest of the subjects did not have any quantifiable concentrations of cantharidin in the plasma (LLOQ 2.5 ng/mL) at all time points.

14.4.2. Summary of Bioanalytical Method Validation and Performance

The Applicant submitted validation study report 14I0376R-A03 and bioanalytical study report 17G0123H-A01G to quantify the plasma cantharidin concentrations using gas chromatography – mass spectrometry (GC/MS). The LLOQ was determined by GC/MS was 2.5 ng/mL of cantharidin. The assay validation results are summarized in Table 24.

Table 24. Validation Results of the GC/MS Bioanalytical Methods Used for Measuring Plasma Concentration of Cantharidin in Study VP-102-103

Analytes	Cantharidin
Matrix	Human plasma
Standard curve assay range	1 ng/mL – 200 ng/mL
Intra-run precision (%)	2.7 to 9.6
Intra-run accuracy (%)	2.0 to 9.6
Inter-run precision (%)	3.0 to 11.7
Inter-run accuracy (%)	2.9 to 6.9
Freeze/thaw matrix stability	3 cycles at -80°C
Room temperature stability	24 hours
Long term stability	3 months at - 80℃
Incurred sample reanalysis	65 of 66 plasma samples evaluated from 17 subjects showed the cantharidin levels below the LLOQ (2.5 ng/mL). Only one sample collected at 2 hour postdose in 1 subject showed 3.39 ng/mL of plasma cantharidin. Subsequently ISR was not conducted.

Source: Validation study report 14I0376R-A03
Abbreviations: GC/MS, gas chromatography–mass spectrometry; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation

14.5. Additional Study Results

Table 25. Complete Clearance at Day 63 by Household Size in Studies VP-102-101 and VP-102-102

	VP-102-101		VP-102-102	
Household Size Successes vs. Failures	VP-102 N_H=137 n (%)	Placebo N_H=91 n (%)	VP-102 N_H=123 n (%)	Placebo N_H=81 n (%)
1 subject	N_H=116	N_H=80	N_H=99	N_H=57
Success	40 (34.5)	18 (22.5)	23 (23.2)	1 (1.8)
Failure	76 (65.5)	62 (77.5)	76 (76.8)	56 (98.3)
2 subjects	N_H=18	N_H=9	N_H=20	N_H=19
2 successes	1 (5.6)	0	3 (15)	0
1 success, 1 failure	8 (44.4)	0	8 (40)	3 (15.8)
2 failures	9 (50)	9 (100)	9 (45)	16 (84.2)
3 subjects	N_H=3	N_H=1	N_H=4	N_H=4
3 successes	0	0	1 (25)	0
2 successes, 1 failure	0	0	1 (25)	0
1 success, 2 failures	1 (33.3)	0	0	0
3 failures	2 (66.7)	1 (100)	2 (50)	4 (100)
4 subjects	N_H=0	N_H=1	N_H=0	N_H=1
1 success, 3 failures	0	0	0	1 (100)
4 failures	0	1 (100)	0	0

Source: Reviewer's analysis.
Subjects with missing data are imputed as nonresponders.
Abbreviations: N_H, number of households

Table 26. Complete Clearance at Day 42 by Household Size in Studies VP-102-101 and VP-102-102

	VP-102-101		VP-102-102	
Household Size Successes vs. Failures	**VP-102 N_H=137 n (%)**	**Placebo N_H=91 n (%)**	**VP-102 N_H=123 n (%)**	**Placebo N_H=81 n (%)**
1 subject	N_H=116	N_H=80	N_H=99	N_H=57
Success	23 (19.8)	10 (12.5)	12 (12.1)	1 (1.8)
Failure	93 (80.2)	70 (87.5)	87 (87.9)	56 (98.3)
2 subjects	N_H=18	N_H=9	N_H=20	N_H=19
2 successes	2 (11.1)	0	1 (5)	0
1 success, 1 failure	3 (16.7)	0	5 (25)	2 (10.5)
2 failures	13 (72.2)	9 (100)	14 (70)	17 (89.5)
3 subjects	N_H=3	N_H=1	N_H=4	N_H=4
3 successes	0	0	0	0
2 successes, 1 failure	1 (33.3)	0	0	0
1 success, 2 failures	1 (33.3)	0	0	0
3 failures	1 (33.3)	1 (100)	4 (100)	4 (100)
4 subjects	N_H=0	N_H=1	N_H=0	N_H=1
1 success, 3 failures	0	0	0	1 (100)
4 failures	0	1 (100)	0	0

Source: Reviewer's analysis.
Subjects with missing data are imputed as nonresponders.
Abbreviations: N_H, number of households

Table 27. Complete Clearance at Day 21 by Household Size in Studies VP-102-101 and VP-102-102

	VP-102-101		VP-102-102	
Household Size Successes vs. Failures	**VP-102 N_H=137 n (%)**	**Placebo N_H=91 n (%)**	**VP-102 N_H=123 n (%)**	**Placebo N_H=81 n (%)**
1 subject	N_H=116	N_H=80	N_H=99	N_H=57
Success	12 (10.3)	4 (5)	6 (6.1)	0
Failure	104 (89.7)	76 (95)	93 (93.9)	57 (100)
2 subjects	N_H=18	N_H=9	N_H=20	N_H=19
2 successes	0	0	0	0
1 success, 1 failure	5 (27.8)	0	2 (10)	1 (5.3)
2 failures	13 (72.2)	9 (100)	18 (90)	18 (94.7)
3 subjects	N_H=3	N_H=1	N_H=4	N_H=4
3 successes	0	0	0	0
2 successes, 1 failure	0	0	0	0
1 success, 2 failures	1 (33.3)	0	0	0
3 failures	2 (66.7)	1 (100)	4 (100)	4 (100)
4 subjects	N_H=0	N_H=1	N_H=0	N_H=1
1 success, 3 failures	0	0	0	1 (100)
4 failures	0	1 (100)	0	0

Source: Reviewer's analysis.
Subjects with missing data are imputed as nonresponders.
Abbreviations: N_H, number of households

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/s/

QIANYIREN SONG
07/09/2020 04:23:05 PM

HAMID R SHAFIEI
07/09/2020 04:27:02 PM

JIANYONG WANG
07/10/2020 08:36:48 AM

BARBARA A HILL
07/10/2020 08:52:57 AM

LUKE Y OH
07/10/2020 09:45:00 AM

CHINMAY SHUKLA
07/10/2020 09:55:58 AM

MARYJOY G MEJIA
07/10/2020 09:57:34 AM

SNEZANA TRAJKOVIC
07/10/2020 09:58:58 AM

REBECCA S HAGER
07/10/2020 10:05:26 AM

MOHAMED A ALOSH
07/10/2020 11:15:08 AM

KENDALL A MARCUS
07/10/2020 11:19:51 AM