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# Pharmacokinetic Profile, Safety, and Tolerability of Topical Berdazimer Gel, 10.3% in Patients With Molluscum Contagiosum

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## ABSTRACT

**Background:** Berdazimer (SB206) gel, 10.3% is a novel, topical, nitric oxide–releasing agent intended for molluscum contagiosum (MC) treatment.

**Methods:** A 12-week, open-label, multicenter trial evaluated the safety, tolerability, and pharmacokinetic (PK) parameters of berdazimer gel, 10.3% applied topically once daily for the treatment of MC. Patients were aged ≥6 months with >20 molluscum lesions. The primary endpoint was the PK profile of the hydrolyzed N-methylaminopropyl-trimethoxysilane (hMAP3) monomer and nitrate during a 2-week period of once-daily berdazimer gel, 10.3% application (PK period) under maximal use conditions. Safety and tolerability were evaluated throughout the 12-week study period.

**Results:** Half of the 34 enrolled patients (17) were female and most (97.1% [33/34]) were white. Patients were 2 to 12 years old (mean, 5.3 years) with a mean of 50 MC lesions at baseline (mean time since MC awareness, 12.4 months). No patients had quantifiable plasma hMAP3 concentrations on day 1. On day 15, 2 patients had quantifiable plasma hMAP3 concentrations; however, the maximum concentration (33.9 ng/mL) was >10-fold lower than the no observed adverse effect level (NOAEL) in an animal toxicology study. Mean nitrate concentration–time profiles were similar on days 1 and 15 and remained flat for all patients throughout the 2-week PK period. The highest plasma methemoglobin level observed was 3.2%. Application-site pain (13/34 [38.2%]) and application-site erythema (6/34 [17.6%]) were the most frequent treatment-emergent adverse events (TEAEs), and most TEAEs were mild or moderate.

**Conclusions:** Once-daily berdazimer gel, 10.3% was well-tolerated with minimal systemic absorption.

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## INTRODUCTION

Molluscum contagiosum (MC) is a highly contagious viral skin disease characterized by raised, umbilicated, pink-to-red lesions.[1] It is estimated that 6 million Americans suffer from MC, mostly children.[2] US Food and Drug Administration(FDA)–approved prescription medication treatments for MC remain elusive,[3] and an estimated two-thirds of patients with molluscum go untreated.[4] MC infections may, therefore, persist from months to years.[1]

Nitric oxide (NO) is a small gaseous molecule with multiple physiologic and molecular functions, possessing immunomodulatory and antimicrobial properties.[5] In the body, NO has a very short half-life and is metabolized to nitrate.[5] The short half-life of NO and known endogenous functions make it a desirable therapeutic candidate for various diseases. However, NO is an unstable gas, and efforts to harness and control its release as a potential topical treatment for dermatologic diseases has been challenging.[6]

The active ingredient in berdazimer gel, 10.3% is berdazimer sodium, a new chemical entity affixed to a diazeniumdiolate silicon backbone that holds stable NO molecules.[7] When combined with a hydrogel (proton donor) on the skin, NO is released in a controlled manner at the site of application.[6] In vitro, berdazimer acts as an anti-viral and may have immunomodulatory properties, thus having the potential to influence multiple cellular and molecular aspects of MC pathogenesis.[6,7] The objective of this open-label, multicenter trial was to evaluate the safety, tolerability, and pharmacokinetic (PK) parameters of berdazimer (SB206) gel, 10.3% once daily for the topical treatment of MC under maximal use conditions.

## MATERIALS AND METHODS

### Study Design

This was a phase 1, 12-week, open-label, multicenter trial designed to evaluate the safety, tolerability, and PK parameters of berdazimer gel, 10.3% applied topically once daily for the

treatment of MC. During the initial 2-week PK period, the patients received treatment under maximal use conditions. The study was conducted in patients with the upper range of MC severity to maximize the potential for medication absorption.

**Ethics**

The study protocol and all study materials were approved by an institutional review board before study initiation. The study was conducted in accordance with the United States (US) 21 Code of Federal Regulations, the International Conference on Harmonization guidelines, current Good Clinical Practice principles, the Declaration of Helsinki, and local regulatory requirements. All patients/caregivers provided written informed consent/assent before enrollment.

**Patients**

Males and females at least 6 months of age and weighing at least 10 kg who had more than 20 raised and palpable MC lesions and a treatment area totaling a body surface area (BSA) of 484 $cm^2$ at baseline were eligible to enroll. Exclusion criteria included: i) sexually transmitted MC; ii) MC only in the periocular area; iii) significant eczema or injury on designated medication application areas; iv) a confirmed methemoglobin level of >3.0% at baseline using a pulse co-oximeter; and v) primary source of drinking water was well water (due to the potential for elevated nitrate levels). Patients receiving current treatment for MC at the time of the screening visit could enter a wash out period of up to 14 days before the baseline visit.

**Interventions**

The 12-week study was divided into a 2-week PK period and a 10-week treatment extension period. All patients who completed the PK period could choose to enroll in the treatment extension period. The PK period included a screening visit followed by 3 clinic visits at days 1 (baseline), 8, and 15. The treatment extension period included 3 clinic visits at weeks 4, 8, and 12.

From days 1 to 15 (PK period), caregivers applied berdazimer gel, 10.3% once daily to a total treatment area of 484 $cm^2$, comprised of up to 4 areas on the body that included as many MC lesions as possible. Caregivers were instructed to cut a 22 cm x 22 cm piece of cardstock in up to 4 pieces to cover as many lesions as possible. Study site staff documented all treatment areas and marked the selected treatment areas on each patient with a surgical marker so caregivers would know where to apply berdazimer gel, 10.3%. A 3-mg quantity of study medication was considered sufficient to cover the total treatment area(s) for all patients. Caregivers applied berdazimer gel, 10.3% (berdazimer sodium gel plus hydrogel) to the designated treatment areas immediately following admixture. Berdazimer gel, 10.3% was applied once daily throughout the PK period even if lesions cleared. Lesions outside the selected treatment area or within periocular areas (ie, within 2 cm from the edge of the eye) were not treated. On days 1, 8, and 15, study site staff applied berdazimer gel, 10.3%. Patients/caregivers applied all other doses at home.

In the 10-week treatment extension period, berdazimer gel, 10.3% was applied to all individual treatable lesions and approximately 1 cm surrounding each lesion, excluding periocular areas. New lesions that appeared during the extension period were treated. Treatment continued until complete clearance or week 12, whichever came first. If lesions cleared between visits, the patient/caregiver continued treating until the next study visit, at which time the investigator confirmed clearance and discontinued berdazimer gel, 10.3% treatment.

**Assessments**

*Pharmacokinetic*

For patients <6 years, blood samples for determination of plasma hydrolyzed N-methylaminopropyl-trimethoxysilane (hMAP3) and nitrate concentrations were collected pre-application and 1-hour post-application on day 1, and pre-application and 1- and 3-hours post-application on day 15. For patients ≥6 years, blood samples were collected pre-application and 1-, 3-, and 6-hours post-application on days 1 and 15. The pre-application blood draw on day 1 was used to determine baseline hMAP3 and nitrate levels. hMAP3 is a silicon-containing hydrolyzed monomer of the polymeric berdazimer drug substance. For approximately 24 hours before the day 1 and day 15 visits, and continuing until after the final blood draw on both days, all patients and mothers of breastfed patients were instructed to adhere to a low nitrate diet (guidelines provided).

*Compliance*

During the PK period (days 1-15), caregivers recorded the time of berdazimer gel, 10.3% application in a diary. During the treatment extension period, caregivers only recorded whether berdazimer gel, 10.3% was applied.

*Safety*

Safety assessments included monitoring and reporting of adverse events (AEs) throughout the study, clinical laboratory measurements, percent blood methemoglobin at every visit, vital sign measurements, and physical examination findings. On days 1 and 15, methemoglobin was measured at the same time with PK blood draw using a Masimo Rainbow® SET® Rad-57™ pulse co-oximeter. Any clinically significant changes in laboratory values, vital signs, and methemoglobin levels were recorded as AEs. Patients with persistent methemoglobin levels >5% (confirmed by a second reading within 0.5% of initial reading within 30 minutes) at any post-baseline assessment were discontinued from the study.

Assessment of 12-lead electrocardiogram (ECG) parameters was based on triplicate ECGs (3 readings as close together as

possible within a 5-minute period, pre- and post-application on days 1 and 15). An additional single set of triplicate ECGs was captured at week 12. Clinically significant ECG changes from baseline were recorded as AEs.

*Tolerability*

Tolerability assessments included local skin condition (LSC), local skin reactions (LSRs), and scarring. Before the first berdazimer gel, 10.3% application at baseline, investigators assessed LSC in the designated treatment areas, including individual features of erythema, flaking/scaling crusting, swelling, vesiculation/pustulation, and erosion/ulceration. The pre-application LSC captured the patient's skin condition as it related to MC lesions before exposure to berdazimer gel, 10.3%.

LSRs were assessed 30 minutes post-application on day 1 and before in-clinic berdazimer gel, 10.3% application on days 8 and 15 of the PK period. LSRs were evaluated at each clinic visit during the extension period. Investigators rated LSRs on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration and reported clinically significant LSRs (including any LSR suggestive of allergic contact dermatitis) as AEs. For both LSC and LSR assessments, each component was evaluated on a 0 to 4 scale, with higher numbers indicating more severe reactions. The highest possible LSC and LSR composite scores were 24.
Scar/keloid/hypertrophic scar formation were assessed at the day 15 PK visit and through week 12 of the extension. All scars, including molluscum pitted scars, developing after baseline were reported as AEs and assessed by the investigator for treatment relatedness.

*Effectiveness*

Medication effectiveness was assessed by counting the number of active (raised, palpable, treatable) molluscum lesions per treatment area at each visit.

**Statistical and Data Analyses**

*Study populations*

The intention-to-treat (ITT) population included all enrolled patients. The safety population included all patients who received at least 1 application of berdazimer gel, 10.3%. The PK population included all patients in the safety population who had at least 1 post-application blood draw for hMAP3 and/or nitrate analysis.

*Sample size*

A minimum of 24 and a maximum of 36 patients ≥6 months of age were to be enrolled. The sample size was not based on statistical considerations; rather, the number of patients planned for enrollment was considered sufficient to achieve the study objectives. At least 6 patients ≥6 years of age and at least 6 patients <6 years of age were to be enrolled. Additional recruitment efforts were made to enroll patients <2 years of age.

*Pharmacokinetic analyses*

The primary endpoint was the PK profile of hMAP3 and nitrate as markers for systemic exposure to berdazimer sodium after topical application of berdazimer gel, 10.3% to approximately 484 $cm^2$ once daily. Plasma hMAP3 and nitrate concentrations were determined using validated liquid chromatography tandem mass spectrometry (LC/MS-MS) analytic methods with a lower limit of quantitation (LLOQ) of 5 ng/mL for hMAP3 and 300 ng/mL for nitrate. All patients in the PK population with at least 1 quantifiable hMAP3 and/or nitrate concentration were included in the PK analyses. Calculation of area under the plasma concentration–time curve (AUC) required the 1-hour, 3-hour (all patients), and 6-hour (patients ≥6 years of age) samples to be quantifiable. For calculation of mean concentrations and generation of mean concentration-versus-time profiles, all below the lower limit of quantitation (BLQ) values were set to 0 except when an individual BLQ value fell between 2 quantifiable values, in which case the value was treated as missing data.

The following standard PK parameters were calculated for days 1 and 15 using noncompartmental analysis implemented within a validated installation of Phoenix® WinNonlin® V8.1.: maximum observed plasma concentration value ($C_{max}$); time to $C_{max}$ ($T_{max}$); AUC from time 0 to 3 hours post-application ($AUC_{0-3}$); and AUC from 0 to 6 hours post-application ($AUC_{0-6}$).

*Safety*

All AEs that occurred during the study were recorded and classified based on Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) were defined as AEs with an onset on or after the first application of berdazimer gel, 10.3%. TEAEs were summarized by MedDRA preferred term, severity, relationship to berdazimer gel, 10.3% (causality), and seriousness. TEAE severity and causality were determined by investigators.

*Statistical analyses*

Descriptive statistics were used to summarize PK parameters and safety, tolerability, and effectiveness data. For continuous variables, descriptive statistics included the number of patients with non-missing values, mean, standard deviation, median, minimum, and maximum values. For categorical variables, descriptive statistics included counts and percentages of patients who were in the category or each possible value. Descriptive statistical analyses and tabulations were performed using SAS® software Version 9.4 or higher (SAS Institute Inc., Cary, NC).

## RESULTS

**Demographics and Baseline Characteristics**

Thirty-four patients were enrolled at 5 clinical centers in the US between September 16, 2019 and February 4, 2020, and all were

**TABLE 1.**

| Baseline Demographic and Clinical Characteristics and Disposition of Patients | |
|---|---|
| Characteristic | No. (%)a |
| | Berdazimer Gel, 10.3% (N=34) |
| Age, y, mean (range) | 5.3 (2–12) |
| <6 years of age | 21 (61.8) |
| ≥6 years of age | 13 (38.2) |
| Sex | |
| Female | 17 (50.0) |
| Male | 17 (50.0) |
| Race | |
| White | 33 (97.1) |
| Asian | 1 (2.9) |
| Ethnicity | |
| Non-Hispanic/Latino | 29 (85.3) |
| Hispanic/Latino | 5 (14.7) |
| Baseline in-clinic lesion count, mean (range) | 50.2 (21–212) |
| Age at MC lesion awareness, y, mean (range) | 4.8 (1.0–11.3) |
| Time since MC lesion awareness, mo, mean (range) | 12.4 (0.9–45.1) |
| Previous treatment for molluscum | |
| Yes | 10 (29.4) |
| No | 24 (70.6) |
| Disposition | |
| Completed pharmacokinetic period | 31 (91.2) |
| Withdrawal by patient/caregiver | 2 (5.9) |
| Withdrawal due to adverse event | 1 (2.9) |
| Completed treatment extension period | 29 (93.5) |
| Withdrawal by patient/caregiver | 1 (3.2) |
| Withdrawal due to adverse event | 1 (3.2) |

MC, molluscum contagiosum.
[a]Data are number (%) unless otherwise noted.

included in the PK, safety, and ITT populations. The mean age of patients was 5.3 years (range, 2-12), half were females, and most were white (33/34 [97.1%]) and non-Hispanic/Latino (29/34 [85.3%]) (Table 1). The mean number of MC lesions at baseline was 50.2 (median, 35.0; range, 21-212).

### Treatment Compliance

During the PK period, patients/caregivers were highly (97.7%) compliant with treatment application.

### Pharmacokinetic Parameters

No patients had quantifiable plasma hMAP3 concentrations at any timepoint on day 1, and 2 patients had quantifiable

**FIGURE 1.** Mean nitrate plasma concentration–time plot by age group. (A) All patients. (B) Patients ≥6 years of age. (C) Patients <6 years of age.

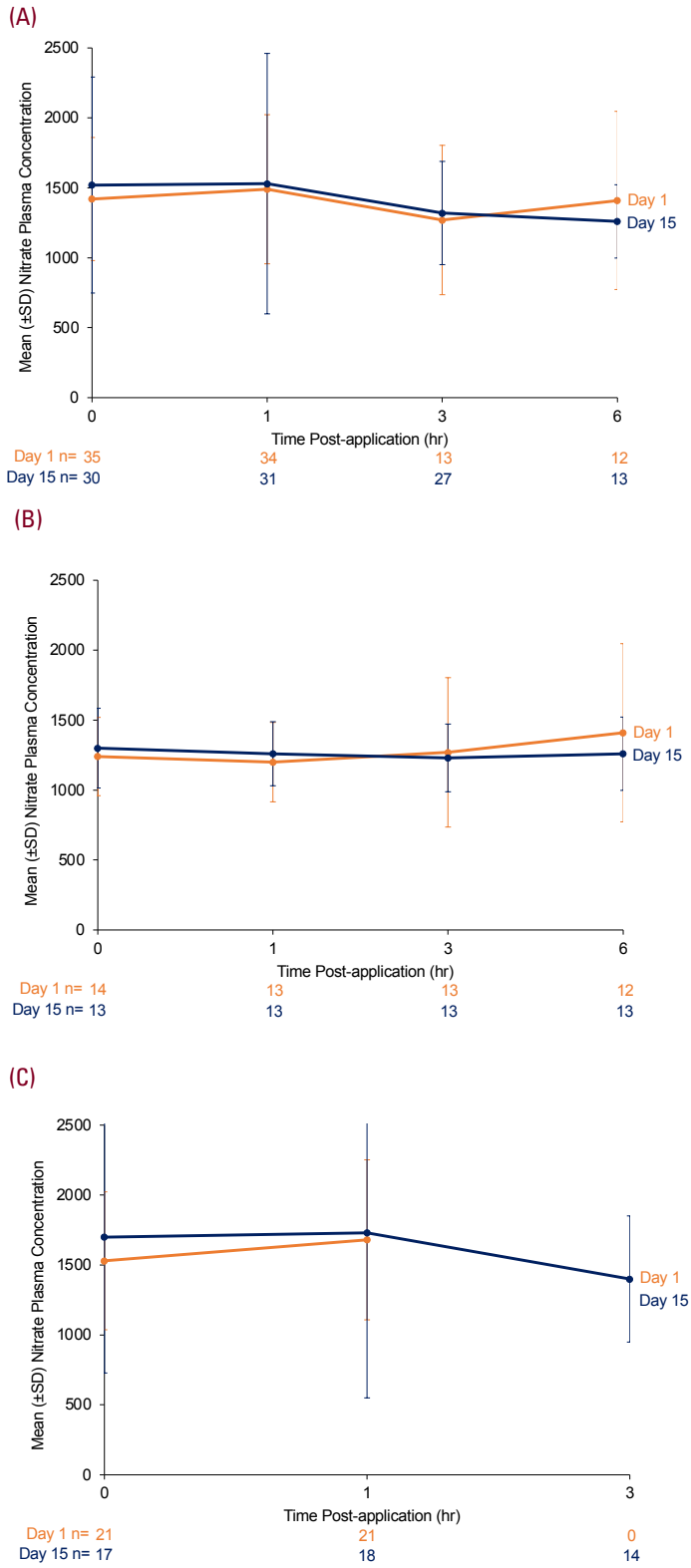


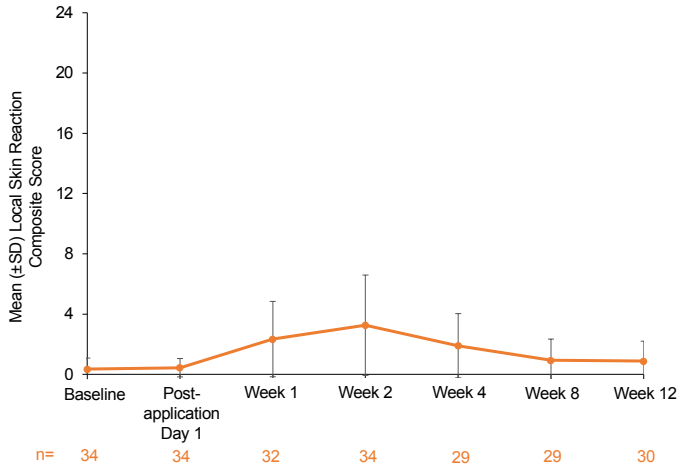
**TABLE 2.**

| Summary of Treatment-Emergent Adverse Events | |
|---|---|
| Treatment-emergent Adverse Events | No. (%) Berdazimer Gel, 10.3% (N=34) |
| Number of TEAEs reported | 37 |
| Patients with ≥1 TEAE | 16 (47.1) |
| Mild | 5 (14.7) |
| Moderate | 8 (23.5) |
| Severe | 3 (8.8) |
| Patients with ≥1 TEAEs related to berdazimer gel, 10.3% | 15 (44.1) |
| Patients with ≥1 serious TEAEs | 0 |
| Patients with ≥1 TEAEs leading to treatment discontinuation | 0 |
| Deaths | 0 |
| **TEAEs in ≥2 patients** | |
| Application-site pain | 13 (38.2) |
| Mild | 4 (11.8) |
| Moderate | 6 (17.6) |
| Severe | 3 (8.8) |
| Application-site erythema | 6 (17.6) |
| Mild | 3 (8.8) |
| Moderate | 3 (8.8) |
| Severe | 0 |
| Application-site scar | 5 (14.7) |
| Mild | 5 (14.7) |
| Moderate | 0 |
| Severe | 0 |
| Application-site exfoliation | 2 (5.9) |
| Mild | 1 (2.9) |
| Moderate | 1 (2.9) |
| Severe | 0 |
| Application-site scab | 2 (5.9) |
| Mild | 0 |
| Moderate | 2 (5.9) |
| Severe | 0 |
| Pyrexia | 2 (5.9) |
| Mild | 2 (5.9) |
| Moderate | 0 |
| Severe | 0 |

TEAE, treatment-emergent adverse events.

concentrations on day 15. A 5-year-old white male (20.0 kg, with 31 baseline molluscum lesions, 6.05% of BSA treated) had a single quantifiable concentration of 5.12 ng/mL at 2 hours post-application, close to the LLOQ of 5 ng/mL. An 11-year-old white female weighing 42.2 kg who had 48 molluscum lesions at baseline and 3.69% of BSA treated had 4 quantifiable concentrations (10.4, 20.8, 33.9, and 22.5 ng/mL on day 15 pre-application, 1-, 3-, and 6-hours post-application, respectively). Her AUC0-3 was 75.5 h*ng/mL; however, plasma hMAP3 concentrations fell below the LLOQ by week 12.

**FIGURE 2.** Local skin reaction composite score over time.




Mean nitrate plasma concentration–time data by age group are displayed in Figure 1. In general, mean nitrate concentration–time profiles (non-baseline corrected) were similar on days 1 and 15 and remained relatively flat throughout the sampling interval. Mean plasma nitrate concentrations were slightly higher in younger patients (<6 years) on day 15, with mean concentrations ranging from 1400 to 1730 ng/mL, compared with older patients (≥6 years), for whom mean concentrations ranged from 1200 to 1410 ng/mL. The 2 patients with measurable hMAP3 levels also exhibited relatively flat nitrate levels from day 1 to 15.

### Safety

Overall, 37 TEAEs were reported for 16 of 34 (47.1%) patients (Table 2). The most frequently reported TEAEs were application-site pain (13/34 [38.2%]) and application-site erythema (6/34 [17.6%]), mostly mild or moderate in severity. TEAEs of application-site scar were reported in 5 patients, and all were considered mild in severity. No patients formed keloid or hypertrophic scars. Fifteen patients had ≥1 TEAE related to berdazimer gel, 10.3%, with the most frequently reported being application-site pain (13/15 [86.7%]). Severe TEAEs were reported in only 3 patients, all application-site pain and probably medication related. There were no serious TEAEs, TEAEs leading to treatment discontinuation, or deaths.

### Tolerability

Overall, mean LSR composite scores peaked by week 2, then

declined for the remainder of the study (Figure 2). Erythema, observed in the greatest number of patients at week 2, was the most prominent parameter impacting the mean LSR composite score.

Both patients with quantifiable hMAP3 concentrations on day 15 experienced LSRs. The 5-year-old patient's LSR composite score on day 14 was 4 (highest possible score was 24), slightly above the overall safety population mean of 3.26 (SD, 3.33; range 0-11). On day 5, this patient experienced an AE of mild application-site pain (considered definitely related to berdazimer gel, 10.3%). No action was taken regarding application of berdazimer gel, 10.3%, the mild application-site pain resolved, and no other TEAEs were reported. The patient completed all study visits for both treatment periods.

The 11-year-old patient's day 14 composite LSR score was 11 compared with the overall safety population mean day composite score of 3.26 (SD, 3.33; range 0-11), indicating she had the highest LSR composite score among all patients. On day 3, the patient experienced an AE of moderate application-site pain (considered definitely related to berdazimer gel, 10.3%); on day 15, this patient experienced application-site erythema, application-site exfoliation, and application-site scab (all were moderate in severity, and all were considered definitely related to berdazimer gel, 10.3%). No action was taken regarding application of berdazimer gel, 10.3%, and all TEAEs had resolved by day 58. The composite LSR scores at Weeks 4, 8, and 12 were 3, 0, and 0, respectively. The patient completed all study visits for both treatment periods.

Other patients had composite LSR scores of ≥8 during the study; however, none of the patients had quantifiable hMAP3 concentrations. No patients had LSRs that were believed to be suggestive of allergic contact dermatitis.

**Electrocardiogram Parameters**

There were no clinically significant findings or meaningful changes in ECG parameters, including heart rate, PR interval, QRS duration, P-R-T axis, or RR interval. There were no confirmed cardiac AEs. A mild TEAE of prolonged QT interval was reported in the 11-year-old female patient with quantifiable hMAP3 levels on day 15; this AE was considered by the investigator unlikely to be related to berdazimer gel, 10.3%.

**Effectiveness**

Throughout both study periods, progressive decreases from baseline in molluscum lesion counts were observed. At week 12, the mean decrease from baseline was 68.4% (median decrease, 86.1%). Four patients achieved complete MC clearance at week 12, including the patient with 4 quantifiable hMAP3 levels on day 15.

## DISCUSSION

Once-daily topical application of berdazimer, 10.3% gel demonstrated largely minimal systemic exposure to NO as measured by the metabolite of parent compound, hMAP3, with favorable safety and tolerability in patients 2 to 12 years of age with MC. Accurate assessment of berdazimer sodium PK parameters is best achieved by measurements of the polymeric silicon-based backbone via the monomer hMAP3, which is not endogenous, rather than nitrate, which is endogenous and largely impacted by diet. There is a theoretical risk of methemoglobinemia resulting from dermal application of NO (ie, through NO binding with systemic hemoglobin); therefore, methemoglobin levels were closely monitored throughout the study.

This study supports the safety of berdazimer gel, 10.3% with respect to systemic exposure in children under maximal use conditions. The PK data herein demonstrate minimal systemic exposure under maximal use conditions in children as young as 2 years of age with MC. Only 2 patients showed quantifiable plasma hMAP3 concentrations on day 15; however, the maximum concentration (33.9 ng/mL) was >10-fold lower than the no observed adverse effect level (NOAEL) in an animal toxicology study. Plasma nitrate profiles remained relatively flat across the sampling interval for both patients, suggesting there was minimal, if any, systemic absorption of berdazimer sodium. Systemic AEs were not observed.

For the 11-year-old who experienced quantifiable hMAP3 plasma levels on day 15, the patient's LSRs may have induced disruption of the skin barrier functions and increased skin penetration of topically applied berdazimer sodium, potentially contributing to the systemic exposure measured day 15. However, other patients who had composite LSR scores of 8 or greater during the study did not have quantifiable hMAP3 concentrations. In addition, 17 of the 34 enrolled patients had 6% or higher BSA treated and, of those, only the 5-year-old patient (6.05% BSA treated) had a single quantifiable hMAP3 concentration at any timepoint during the study. The 11-year-old patient had 3.69% BSA treated, below the overall mean of 5.96% BSA treated. Thus, there does not appear to be a correlation between systemic absorption of berdazimer sodium and either high composite LSR scores or % BSA treated based on these data.

TEAEs were mostly mild or moderate, with application-site pain reported as the most frequent TEAE. TEAEs were mostly mild or moderate and considered by investigators to be related to berdazimer gel, 10.3%. No TEAEs were serious, and none required a change in berdazimer dosing. Safety and tolerability data, coupled with PK data, support a favorable safety profile for berdazimer gel, 10.3%.

Berdazimer gel, 10.3% is in late-stage clinical development[8] and, if FDA-approved, would be the first prescription medication indicated for MC. Additional formulations of berdazimer are in clinical development for other dermatologic and infectious diseases.

## DISCLOSURES

Dr Cartwright, Dr Maeda-Chubachi, and Ms. Enloe are employees of and stockholders in Novan, Inc. Dr Cartwright is a former employee of Cassiopea Inc. Funding of this manuscript and conduct of the clinical trial was funded by Novan, Inc. Dr Stripling was a study investigator and has received consulting fees from Novan, Inc.

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