NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	217424
Priority or Standard	Standard
Submit Date(s)	January 5, 2023
Received Date(s)	January 5, 2023
PDUFA Goal Date	January 5, 2024
Division/Office	DDD/OII
Review Completion Date	January 4, 2024
Established/Proper Name	Berdazimer sodium gel
(Proposed) Trade Name	ZELSUVMI
Pharmacologic Class	nitric oxide (NO) releasing agent
Code name	SB206
Applicant	LNHC (c/o Novan), Inc.
Dosage form	Topical gel
Applicant Proposed Dosing Regimen	Apply ZELSUVMI an even thin layer once daily to each MC lesion for up to 12 weeks.
Applicant Proposed Indication(s)/Population(s)	Topical treatment of Molluscum Contagiosum (MC) in adult and pediatric patients (b) (4) of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	40070004 Infection caused by molluscum contagiosum
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the topical treatment of Molluscum Contagiosum (MC) in adult and pediatric patients one year of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	40070004 Infection caused by molluscum contagiosum
Recommended Dosing Regimen	Apply ZELSUVMI an even thin layer once daily to each MC lesion for up to 12 weeks.

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Abbreviations: DHOT, Division of Hematology, Oncology, and Toxicology; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OHOP, Office of Hematology and Oncology Products

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Abbreviations: DAV, Division of Antivirals; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPV I, Division Of Pharmacovigilance I; DRM, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; PLT, Patient Labeling Team

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

ZELSUVMI (SB206 gel, 10.3%) consists of berdazimer sodium (NVN1000) gel, a new molecular entity (NME), and a proton-donating hydrogel. Mixing the two gels prior to the topical application to MC lesions releases nitric oxide (NO), a pharmacologically active agent.

ZELSUVMI was developed by the Applicant under IND 137015 for the indication of topical treatment of Molluscum Contagiosum (MC), following initial discussions with the FDA under a related (b) (4) (development of SB204 gel for the topical treatment of acne vulgaris).

The Applicant has submitted NDA 217424 under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for marketing ZELSUVMI for the indication of topical treatment of MC in adult and pediatric patients (b) (4) of age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from two adequate and well-controlled trials NI-MC302 and NI-MC304 (trials -302 and -304) provided substantial evidence of the effectiveness of berdazimer gel, 10.3% for the topical treatment of MC in the target population. Both trials assessed as their primary efficacy endpoint the proportion of subjects with complete clearance of all treatable MC lesions at Week 12, and as a key secondary efficacy endpoint the complete clearance rate of all treatable MC lesions at Week 8.

The primary efficacy endpoint results from Study NI-MC304 were statistically significant ($p<0.0001$; treatment difference of 12.8%, 95% CI (7.1%, 18.6%)), consistent across subgroups and sensitivity analyses, and supported by the findings on the key secondary endpoint at Week 8. Thus, efficacy has been demonstrated in Study NI-MC304.

In Study NI-MC302, although the results for the primary endpoint analysis at Week 12 just missed the significance threshold ($p=0.0510$), the point estimates and treatment effect estimate were similar to those observed in Study NI-MC304 (treatment difference of 9.2%, 95% CI (-0.04%, 18.4%)) and the secondary endpoint (complete clearance at Week 8) was supportive of the Week 12 result. The prespecified method of handling missing data in Study NI-MC302 was conservative, and many sensitivity analyses that used reasonable alternative methods of handling missing data had nominally significant findings. In addition, exploratory endpoints that evaluated change or percent change in lesion counts, rather than a dichotomized response endpoint, support an efficacy finding for Study NI-MC302. The complete evaluation of the efficacy results, including primary endpoint results, sensitivity and supplementary analyses, and secondary and exploratory endpoint results, were persuasive and confirm that efficacy had been demonstrated in Study NI-MC302.

Thus, Studies NI-MC304 and NI-MC302 are adequate and well-controlled trials that demonstrate substantial evidence of effectiveness. The Applicant has demonstrated that

berdazimer gel, 10.3% is effective for its intended use in the target population and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 (a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Molluscum Contagiosum (MC) is a highly transmissible, self-limited cutaneous infection caused by the Molluscum Contagiosum Virus (MCV). Affected patients are prone to autoinoculation by scratching or rubbing, and their close contacts (e.g., family members) are at high risk of infection by direct skin or mucous membrane transmission, or via fomites. MC typically 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 incubation period is typically between 2 to 6 weeks after viral exposure, and the disease lasts for several months to a few years, with an average of about one year. The main goal of therapy is to alleviate discomfort including itching, reduce autoinoculation, limit transmission of the virus to close contacts, reduce cosmetic concerns, and prevent secondary infections (Hebert et al. 2023). None of the available treatments provides a complete clearance of all MC lesions or universal response, and all are associated with one or more risks. Because treatment may be complicated by inadequate response, recurrence of new lesions, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is still a need for additional therapeutic options for this group of patients with MC.

The Applicant proposed ZELSUVMI (berdazimer) gel, 10.3% applied once daily for the topical treatment of MC in subjects (b) (4) and is seeking approval of this product via a 505(b)(1) regulatory pathway. The Applicant submitted efficacy and safety data from three phase 3, randomized, double-blind, vehicle-controlled trials (NI-MC301/-302/-304).

FDA concluded that substantial evidence of effectiveness was demonstrated through two adequate and well-controlled trials (Studies NI-MC302 and -304). The primary efficacy endpoint results from Study NI-MC304 were statistically significant ($p<0.0001$; treatment difference of 12.8%, 95% CI [7.1%, 18.6%]), consistent across subgroups and sensitivity analyses, and supported by the findings on the key secondary endpoint at Week 8. Thus, efficacy has been demonstrated in Study NI-MC304. In Study NI-MC302, although the results for the primary endpoint analysis at Week 12 just missed the significance threshold ($p=0.0510$), the point estimates and treatment effect estimate were similar to those observed in Study NI-MC304 (treatment difference of 9.2%, 95% CI [-0.04%, 18.4%]) and the secondary endpoint (complete clearance at Week 8) was supportive of the Week 12 result. The prespecified method of handling missing data in Study NI-MC302 was conservative, and many sensitivity analyses that used reasonable alternative methods of handling missing data had nominally significant findings. In addition, exploratory endpoints that evaluated change or percent change in lesion counts, rather than a dichotomized response endpoint, support an efficacy finding for Study NI-MC302. The complete evaluation of the efficacy results, including primary endpoint results, sensitivity and supplementary analyses, and secondary and exploratory endpoint results, were persuasive and confirm that efficacy had been demonstrated in

Study NI-MC302. While the third trial (Study NI-MC301) did not demonstrate efficacy on the primary endpoint, an imbalance in the amount of missing data on the two treatment arms along with a conservative method of handling missing data may have contributed to the attenuated treatment effect. Although the observed treatment effect in Study NI-MC301 was smaller than in the other two trials, the study did have a small trend in favor of the active treatment, and the results do not detract from an overall demonstration of efficacy in the development program.

Efficacy

- Trial NI-MC-304 (berdazimer v. vehicle); N=891
  - Berdazimer gel, 10.3% was statistically superior to the vehicle for the primary efficacy endpoint (EEP) at Week 12 (p<0.0001) and the key secondary EEP at Week 8 (p=0.0012) for the ITT population.
  - Primary EEP: 32.4% v. 19.7% (treatment difference of 12.8%, 95% CI [7.1%, 18.6%]).
  - Secondary EEP: 19.6% v. 11.6% (treatment difference of 7.5%, 95% CI [3.0%, 12.0%]).
- Trial NI-MC-302 (berdazimer v. vehicle); N=355
  - Berdazimer gel, 10.3% just missed the statistical significance threshold of 0.05 compared to the vehicle for the primary EEP at Week 12 (p=0.0510) for the ITT population.
  - Primary EEP: 30.0% v. 20.3% (treatment difference of 9.2%, 95% CI [-0.04%, 18.4%]).
  - Secondary EEP: 13.9% v. 5.9% (treatment difference of 7.8%, 95% CI [1.8%, 13.8%]).
- Trial NI-MC-301 (berdazimer v. vehicle); N=352
  - Berdazimer gel, 10.3% was not statistically significant compared to the vehicle for the primary EEP at Week 12 (p=0.3637) for the ITT population.
  - Primary EEP: 25.8% v. 21.6% (treatment difference of 4.3%, 95% CI [- 5.0%, 13.6%]).
  - Secondary EEP: 15.3% v. 10.3% (treatment difference of 4.7%, 95% CI [- 2.2%, 11.5%]).

Safety

Analysis of the Integrated Summary of Safety (ISS, including the combined Phase 3 trials NI-MC301/-302/-304) did not identify any significant safety signals and was adequate to characterize the safety profile of berdazimer gel, 10.3% for the treatment of MC. Adverse events reported in the ISS through Week 12 in ≥1% of subjects treated with berdazimer (and more frequently than subjects receiving vehicle), compared to

subjects treated with vehicle, included the following application site reactions: pain (18.7% v. 4.9%), erythema (11.7% v. 1.3%), pruritus (5.7% v. 1.0%), exfoliation (5.0% v. 0), dermatitis (4.9% v. 0.7%), swelling (3.5% v. 0.6%), erosion (1.6% v. 0.1%), discoloration (1.5% v. 0.1%), vesicles (1.5% v. 0.1%), irritation (1.2% v. 0), and infection (1.1% v. 0.4%); additional AEs included pyrexia (2.2% v. 1.0%), upper respiratory tract infection (1.2% v. 0.7%), nasopharyngitis (1.0% v. 0.9%), streptococcal pharyngitis (1.0% v. 0.9%), and vomiting (1.3% v. 0.1%).

Berdazimer gel, 10.3% has an acceptable risk-benefit profile for the treatment of MC and offers an alternative treatment option to a number of treatments available in the US for this condition.

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 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. It is estimated that < 5% of children in the US have clinical evidence of MCV infection (Isaacs et al. 2023). A retroactive chart review of 302 pediatric patients with MC found the following percentages of MC patients in each age group: 0-36 months (28%), 37-60 months (25%), 61-96 months (27%), > 96 months (20%) (Dohil et al. 2006). The prevalence of MC in pediatric patients < 6 months of age is considered low; consistent with a high prevalence (31%) of (maternally acquired) MCV seropositivity in this age group, compared to MCV seropositivity in patients between 6 months to < 2 years of age (3%) (Konya and Thompson 1999).MC has also been reported to be more common and more extensive in patients with atopic dermatitis (AD).	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 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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.	
Current Treatment Options	• YCANTH (cantharidin) is the only FDA-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.[1]	YCANTH (cantharidin) is the only FDA-approved drug products for the treatment of 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.
Benefit	• The primary efficacy endpoint results from Study NI-MC304 were statistically significant ($p<0.0001$; treatment difference of 12.8%, 95% CI (7.1%, 18.6%)), consistent across subgroups and sensitivity analyses, and supported by the findings on the key secondary endpoint at Week 8. Thus, efficacy has been demonstrated in Study NI-MC304.	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use.

[1] Analysis of Condition and Current Treatment Options in Section 1.3, 2.1, and 2.2 of this review were adapted from corresponding sections of the Multidisciplinary Review and Evaluation of NDA 212905, YCANTH (cantharidin) by Maryjoy Mejia, MD on 7/10/2020. Additional references to the literature Articles pertaining to the prevalence of MC was provided by this reviewer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In Study NI-MC302, although the results for the primary endpoint analysis at Week 12 just missed the significance threshold (p=0.0510), the point estimates and treatment effect estimate were similar to those observed in Study NI-MC304 (treatment difference of 9.2%, 95% CI (-0.04%, 18.4%)) and the secondary endpoint (complete clearance at Week 8) was supportive of the Week 12 result. The prespecified method of handling missing data in Study NI-MC302 was conservative, and many sensitivity analyses that used reasonable alternative methods of handling missing data had nominally significant findings. In addition, exploratory endpoints that evaluated change or percent change in lesion counts, rather than a dichotomized response endpoint, support an efficacy finding for Study NI-MC302. The complete evaluation of the efficacy results, including primary endpoint results, sensitivity and supplementary analyses, and secondary and exploratory endpoint results, were persuasive and confirm that efficacy had been demonstrated in Study NI-MC302. • While the third trial (Study NI-MC301) did not demonstrate efficacy on the primary endpoint, an imbalance in the amount of missing data on the two treatment arms along with a conservative method of handling missing data may have contributed to the attenuated treatment effect. Although the observed treatment effect in Study NI-MC301 was smaller than in the other two trials, the study did have a small trend in favor of the active treatment, and the results do not detract from an overall demonstration of efficacy in the development program.	Trials NI-MC-302 and NI-MC-304 were adequate and well-controlled; and the results are persuasive.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The results for the primary efficacy endpoint for the Phase 3 trials NI-MC304, NI-MC-302, and NI-MC301 for subjects treated with berdazimer gel, compared to vehicle, respectively, were the following: – Trial NI-MC-304: 32.4% v. 19.7% (treatment difference of 12.8%, 95% CI [7.1%, 18.6%]) – Trial NI-MC-302: 30.0% v. 20.3% (treatment difference of 9.2%, 95% CI [-0.04%, 18.4%]). – Trial NI-MC-301: 25.8% v. 21.6% (treatment difference of 4.3%, 95% CI [- 5.0%, 13.6%]). • The results for the key secondary efficacy endpoint (the proportion of subjects with complete clearance of all treatable MC lesions at Week 8) for the Phase 3 trials NI-MC304, NI-MC-302, and NI-MC301 for subjects treated with berdazimer gel, compared to vehicle, respectively, were the following: - Trial NI-MC-304: 19.6% v. 11.6% (treatment difference of 7.5%, 95% CI [3.0%, 12.0%]) - Trial NI-MC-302: 13.9% v. 5.9% (treatment difference of 7.8%, 95% CI [1.8%, 13.8%]). - Trial NI-MC-301: 15.3% v. 10.3% (treatment difference of 4.7%, 95% CI [- 2.2%, 11.5%]).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The primary safety database (ISS, comprised of the Phase 3 trials NI-MC301/ -302/ -304) consisted of 1596 subjects, including 916 subjects treated with berdazimer gel and 680 subjects treated with vehicle once daily for up to 12 weeks. Cumulative exposures to berdazimer gel was reported for 892 (≥7 Days), 815 (≥29 Days), 677 (≥57 Days), 393 (≥85 Days), and 81 (≥90 Days) subjects. • The safety database is adequate to characterize the safety profile of berdazimer gel, 10.3% for MC. The following adverse events were reported for the ISS: - SAEs occurred in 1/916 (0.1%) subject in the berdazimer group (not related to study drug) and 2/680 (0.3%) subject in the vehicle group. - Adverse drug reactions (possibly, probably, or likely related to study drug) occurred in 336/916 (36.7%) of subjects in the berdazimer group, compared to 81/680 (11.9%) subjects in the vehicle group. - The most common adverse events (reported in ≥1% of subjects in the berdazimer group, and greater than in vehicle group during weeks 0-12) included the following application site reactions: pain (18.7% v. 4.9%), erythema (11.7% v. 1.3%), pruritus (5.7% v. 1.0%), exfoliation (5.0% v. 0), dermatitis (4.9% v. 0.7%), swelling (3.5% v. 0.6%), erosion (1.6% v. 0.1%), discoloration (1.5% v. 0.1%), vesicles (1.5% v. 0.1%), irritation (1.2% v. 0), infection (1.1% v. 0.4%). Additional AEs included pyrexia (2.2% v. 1.0%), upper respiratory tract infection (1.2% v. 0.7%), nasopharyngitis (1.0% v. 0.9%), streptococcal pharyngitis (1.0% v. 0.9%), and vomiting (1.3% v. 0.1%). • The effects of berdazimer gel on pregnant or lactating women are unknown.	The safety profile of berdazimer gel, 10.3% has been adequately characterized by the premarket safety data for MC. Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the potential risks of the product.

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		
		x	Patient reported outcome (PRO)	Subject Global Severity Assessment and Subject Global Impression of Change
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	MC lesion count, Investigator Global Severity Assessment and Investigator Global Impression of Change, LSR, BOTE score, Scarring/Keloid assessment, Household status of MC
		□	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 was not submitted as part of this application.**			

Abbreviations: BOTE, beginning-of-the-end; LSR, local skin reaction; MC, molluscum contagiosum

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). It is estimated that < 5% of children in the US have clinical evidence of MCV infection (Isaacs et al. 2023). A retroactive chart review of 302 pediatric patients with MC found the following percentages of MC patients in each age group: 0-36 months (28%), 37-60 months (25%), 61-96 months (27%), > 96 months (20%) (Dohil et al. 2006). The prevalence of MC in pediatric patients < 6 months of age is considered low; consistent with a high prevalence (31%) of (maternally acquired) MCV seropositivity in this age group, compared to MCV seropositivity in patients between 6 months to < 2 years of age (3%) (Konya and Thompson 1999).

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 of molluscum contagiosum during the time period of 1966-1983 (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

YCANTH (cantharidin) is the only FDA-approved drug products for the treatment of 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			
YCANTH (Cantharidin) 7/2023	Topical: Apply a single application directly to each lesion every 3 weeks as needed	The primary efficacy Endpoint (proportion of patients achieving complete clearance of all treated MC lesions by Week 12) in 2 R, DB, PC trials were 29% and 40%.	Approved for patients ≥2 years of age. Adverse reactions were primarily local skin reactions at the application site (reported in 97% of subjects treated with YCANTH during both trials).
Not FDA-Approved			
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: Adapted from the Multidisciplinary Review and Evaluation of NDA 212905, YCANTH (cantharidin), Table 1 by Maryjoy Mejia, MD on 7/10/2020.
Abbreviations: CNS, central nervous system; IV, intravenous

The main goal of therapy is to alleviate discomfort, including itching; reduce autoinoculation; limit transmission of the virus to close contacts and reduce cosmetic concerns and prevent secondary infections (Hebert et al. 2023).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ZELSUVMI gel has not been approved for marketing in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed ZELSUVMI gel for topical treatment of MC under IND137015 and submitted their marketing application for NDA 217424 under 505(b)(1) regulatory pathway. Milestone interactions with the Applicant included the following:

- No Pre-IND meeting was held for IND 137015 (MC). (b) (4)
- IND 137015 was opened with study NI-MC201 submitted on 12/8/2017. A study may proceed letter was conveyed on 2/8/2018.
- Type B- EOP2 meeting on 3/6/2019- discussed:
  - Size of the safety database
  - Follow-up period of 12 weeks added after treatment period (Weeks 0-12)
  - Active assessment of dermal safety/photosafety for irritancy/sensitization (and patch testing as needed)
  - The proposed primary endpoint of complete clearance of mollusca at Week 12 is acceptable.
  - Comments related to inclusion/exclusion criteria
  - Inclusion of assessment of local skin reactions (LSRs) and scarring by investigators at all clinic visits.
  - Statistical comments related to Phase 3 trial design
- Advice letter- Protocols NI-MC301/-302 conveyed on 7/9/2019
- Agreed iPSP 8/9/2019, Amended Agreed iPSP conveyed on 12/30/2021
- Advice letter- SAP for NI-MC301 conveyed on 9/20/2019
- Type C Guidance meeting- review of efficacy for -301/-302 on 4/1/2020
- Advice letter- protocol NI-MC304 review on 8/25/2020
- Type C Guidance meeting WRO- content and format of ISE/ISS conveyed on 11/30/2021
- Type B pre-NDA meeting on 4/4/2022- discussed:
  - No provocative dermal safety or photosafety studies required
  - Adequacy of long-term safety data and size of safety database
  - Labeling restriction to 12 weeks and pharmacologic classification

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

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. All Phase 3 trials were conducted at sites in the U.S.

The Division requested that the Office of Scientific Investigations conduct clinical inspections of three (3) domestic sites (Drs. Gibson, Jackson, and Forsha) participating in trial NI-MC304 and the Applicant (Novan, Inc.). The criteria used to select these sites were high enrollment (all 3 sites), high efficacy (Drs. Gibson and Forsha), and follow-up of previous VAI inspection (Dr. Forsha).

In the Clinical Inspection Summary, the review team concluded that the conduct of the trials appeared to be adequate, and that the data generated appeared to be acceptable to support the use of this product for the proposed indication. In her Clinical Inspection Summary of 10/23/2023, Stephanie Coquia, MD, made the following overall assessment of findings and recommendations regarding the findings of the Clinical Site Inspections:

“Three clinical investigators (Drs. Gibson, Jackson, and Forsha) and the Applicant, Novan Inc., were inspected. The inspections did not find significant concerns regarding the study conduct, oversight, and management of the clinical trial or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, the data generated by the inspected clinical investigators and submitted by the applicant appear acceptable in support of the proposed indication”.

The Clinical Review Team for NDA 217424 concurs with the conclusions by the Office of Scientific Investigation clinical inspection team that the data quality from the inspected sites are acceptable in support of this application and did not identify any safety concerns that would preclude a recommendation for an “Approval Action” for this NDA.

4.2. Product Quality

Based on the OPQ evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall Manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements. The CDTL and the signatories agree with these conclusions and recommendations.

A shelf-life of 28 months is supported for the drug product when stored refrigerated at 2°C – 8°C (36°F – 46°F). Do not freeze. When dispensed from the pharmacy, patients should store the

drug product at room temperature 20°C – 25°C (68°F – 77°F). The product should be disposed of 60 days after being stored at room temperature.

4.3. Clinical Microbiology

Not applicable to berdazimer sodium gel drug product.

4.4. Devices and Companion Diagnostic Issues

Not applicable to berdazimer sodium gel drug product.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(1) application for their proposed product, SB206 (berdazimer) gel, 10.3% to treat molluscum contagiosum in adults and pediatric patients 1 year of age and older. The drug product consists of 1) the active ingredient, berdazimer sodium (NVN1000), a nitric oxide (NO) releasing agent, contained in a white to off-white (b) (4) isopropyl alcohol gel, and 2) a proton donating (b) (4) hydrogel. The NVN1000 is a new molecular entity (NME). The to-be-marketed formulation corresponds to the code name of SB206 gel.

The nonclinical studies submitted in this NDA include pharmacology, pharmacokinetics and toxicology studies of NVN1000.

During the development, NVN1000 was formulated as NVN1000 ointment, NVN1000 gel, SB204 gel and SB206 gel. The applicant was informed during the End-of-Phase 2 meeting dated 3/6/2019, that the completed dermal nonclinical studies for berdazimer sodium, SB206 gel and SB204 gel are adequate to support the NDA filing for SB206 gel for the treatment of molluscum contagiosum. In addition, since the Agency confirmed the lack of significant systemic exposure in the maximal use clinical pharmacokinetics study, then it was determined that the completed other nonclinical studies for berdazimer sodium, SB206 gel and SB204 gel are adequate to support the NDA filing for SB206 gel. In addition, the Agency granted waiver for the conduct of a systemic chronic rodent toxicity study, a pre-and post-natal development study, and a systemic carcinogenicity study also based on the lack of significant systemic exposure under the maximal clinical use conditions. Also, the Agency agreed that no juvenile toxicology studies were needed for SB206 gel based on the results of subnanomolar clinical exposure observed under clinical maximal use conditions.

NVN1000 did not display potential acute cardiovascular, central nervous system, or respiratory toxicity in the standard battery of safety pharmacology studies.

In minipigs, the test article was topically applied for 4 weeks (NVN1000 gel and NVN1000 ointment), 13 weeks (SB204 gel), 39 weeks (SB204 gel) and 4 weeks (SB206 gel). In rats, the test article was topically applied for 13 weeks (SB204 gel). The findings were limited to application site reactions. In mice, the test article was topically applied for 13 weeks (SB204 gel) and test article-related findings included application site reactions and microscopic findings in the esophagus (inflammation) and non-glandular stomach (squamous hyperplasia and inflammation). The systemic treatment related findings in mice were related to systemic exposure after oral grooming. Therefore, these systemic treatment related findings are not clinically relevant for SB206 gel since the clinical use conditions involve topical application.

Berdazimer sodium (NVN1000) was orally administered to rats for 4 weeks and 13 weeks. Test article-related findings included increases in methemoglobin levels and microscopic findings in non-glandular portion of the stomach. These systemic treatment related findings are not clinically relevant for SB206 gel since the clinical use conditions involve topical application.

NVN1000 demonstrated mutagenicity in an Ames assay. This is not a safety concern for the clinical use of SB206 gel due to the subnanomolar systemic exposure under maximal clinical use conditions. NVN1000 was not clastogenic in in vivo genotoxicity tests in two tissue types: bone marrow via intraperitoneal administration and skin via topical administration (non-standard test). NVN1000 was negative for induction of structural and numerical chromosome aberrations in the in vitro mammalian chromosome aberration test using human peripheral lymphocytes.

In a 2-year dermal mouse carcinogenicity study, topically applied SB204 gel at once daily doses up to 4% did not result in treatment related tumor findings.

In a fertility and early embryonic development study, oral administration of NVN1000 did not lead to adverse findings in fertility or reproductive parameters in either sex and the no-observed-adverse-effect-level (NOAEL) was 200 mg/kg/day in rats. In an oral embryo-fetal developmental study in rats, the maternal NOAEL was 30 mg/kg/day based on mortality and elevated methemoglobin levels at ≥100 mg/kg/day; and the fetal NOAEL was 100 mg/kg/day based on fetal skeletal and visceral malformations and decreased fetal body weights in litters from dams receiving 200 mg/kg/day. In an oral embryo-fetal developmental study in rabbits, the maternal NOAEL was 50 mg/kg/day based on mortalities, aborted fetuses, adverse clinical observations, and elevated methemoglobin levels in does receiving 150 and 300 mg/kg/day; and the fetal NOAEL was 150 mg/kg/day based on decreased fetal body weights in litters from does receiving 300 mg/kg/day.

Special toxicity studies with NVN1000 including skin sensitization and irritation, dermal irritation, ocular irritation, and phototoxicity were conducted. No safety concerns were identified for NVN1000 based on the results from these studies.

There are no safety concerns related to excipients and impurities in the proposed topical drug product.

In summary, the nonclinical assessment did not identify any safety concerns for the proposed SB206 gel formulation. This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA. The CDTL and the signatories agree with these conclusions and recommendations.

5.2. Referenced NDAs, BLAs, DMFs

Not applicable to berdazimer sodium gel drug product.

5.3. Pharmacology

SB206 gel is a two-component formulation being developed as a topical therapy for molluscum contagiosum. The active ingredient, NVN1000 (sodium berdazimer), is a nitric oxide (NO)-releasing (b) (4) The drug product, SB206 gel, is designed to release NO when the drug substance, NVN1000, is mixed 1:1 with a proton-donating source. The (b) (4) isopropyl alcohol-based gel contains the active component at

various strengths and an inactive (b) (4) hydrogel (aqueous) component that donates the proton necessary for release of NO.

Safety Pharmacology

Neurological Effects

Male Crl:CD(SD) rats (6 animals/group) received single oral gavage administration of berdazimer sodium at the doses of 0, 30, 100 and 200 mg/kg (19-NC-004). The Irwin test and body temperatures were evaluated. Observations were made prior to dosing (on the day of dosing) and at approximately (± 10 minutes) 30, 90, 150, and 300 minutes postdosing. A test article-related finding was decreased cutaneous blood flow, as qualitatively assessed by decreased coloration of hairless areas such as the ears, observed in the 200 mg/kg group in 3 of 6 animals at 30 minutes postdosing and in 2 of 6 animals at 90 minutes postdosing, returning to normal by 150 minutes postdosing. This finding is likely due to the known effect of berdazimer sodium in causing methemoglobinemia and was recovered by 150 minutes. Therefore, the finding is not considered adverse. The NOAEL was considered to be 200 mg/kg in this study.

Respiratory Effects

Male Crl:CD(SD) rats (8 animals/group) received single oral gavage administration of berdazimer sodium at the doses of 0, 30, 100 and 200 mg/kg (19-NC-005). Respiratory assessment was conducted at baseline (for at least 1 hour prior to administration of vehicle or test article) and following administration of vehicle or test article for at least 5 hours. Only male rats were used because no sex differences in exposure were anticipated. No treatment effects were noted on respiratory frequency, tidal volume, or minute volume. Therefore, the NOAEL was 200 mg/kg in this study.

Cardiovascular Effects

The in vitro effects of berdazimer sodium (0, 1.4, 3.3, 7 µg/mL) and hMAP3 (0, 1, 3 µg/mL) on the hERG (human ether-a-go-go-related gene) channel were evaluated in stably transfected human embryonic kidney cells (HEK-293) that express the hERG gene (19-NC-006). The vehicle consisted of HEPES-buffered physiological saline supplemented with 0.3% DMSO. Previous results document that 0.3% DMSO does not affect channel current. The IC_{50} for berdazimer sodium was not calculated, but was estimated to be >7 µg/mL. The IC_{50} for hMAP3 was not calculated, but was estimated to be >3 µg/mL. The positive control, terfenadine, inhibited hERG potassium current by (Mean ± SD; n=2) 86.0 ± 2.3% at 60 nM, confirming the sensitivity of the test system to hERG inhibition.

Berdazimer sodium (0 [PBS], 10, 30, or 100 mg/kg) was given via oral gavage to radiotelemetry-instrumented Göttingen minipigs (4 animals/group) to determine the potential acute effects on heart rate, arterial blood pressure, body temperature, and lead II electrocardiogram (19-NC-003). All doses were administered at a dose volume of 5 mL/kg. The same 4 animals were used for each treatment in a Latin square cross-over design with approximately 7 days between

doses. Testing was limited to male minipigs because no sex differences in exposure were anticipated. At the mid and high dose levels of NVN1000 administered, there was a decrease in pulse pressure from 1-6 hours following dosing; this effect persisted through 18 hours postdosing in the high dose (100 mg/kg NVN1000) animals. Following the highest dose administered (100 mg/kg), NVN1000 was associated with an increase in heart rate from approximately 1-5 hours postdosing. However, there were no observed changes in arterial blood pressure, body temperature, or ECG waveforms that were associated with NVN1000 administration at the mid and high dose levels. The low dose NVN1000 (10 mg/kg) resulted in no clinical signs as well as no changes to heart rat, arterial blood pressure, pulse pressure, body temperature, or ECG waveforms throughout the duration of the study.

Results from both studies indicate a low potential for cardiovascular effects.

In addition, repeat-dose dermal toxicity studies of various NVN1000 topical formulations (12 NC-017, 14-NC-001, 14-NC-004, and 14-NC-005) revealed no test article-related electrocardiogram findings in dermal studies up to 39 weeks in duration in minipigs.

5.4. ADME/PK

Table 2. ADME/PK Studies

Type of Study	Major Findings
Absorption	
Summary of major findings	Pharmacokinetic studies following dermal, intramuscular, and/or bolus intravenous dosing with NVN1000 were conducted in rats to determine the relative systemic exposure to NVN1000 following topical application of NVN1000 gel. Silicon, nitrate/nitrite and hMAP3 were measured in the blood as markers of NVN1000 exposure. Following topical administration of various NVN1000 topical formulations, silicon and nitrate were detected in blood only sporadically and mostly at the same frequency and levels found in pre-dose blood samples. Unlike silicon and nitrate, hMAP3 is not endogenous and is a more appropriate analyte to measure for demonstration of NVN1000 systemic exposure.

Type of Study	Major Findings
A Pharmacokinetic and Dose Finding Study of NVN1000 by Dermal Administration, Intravenous Bolus Injection, and Intramuscular Injection in Rats (ADME-12-001)	Systematic exposure to NVM1000 was measured by the concentration of nitrate ion in the blood. In this study, pre- dose concentrations of nitrate in blood were 9300±7100 ng/mL. Nitrate concentrations following most doses and routes of administration of NVN1000 were in the range of background levels of nitrate, although a somewhat elevated level of nitrate was seen following IV or IM injections of NVN1000. The level of nitrate in blood following dermal administration of NVN1000 gel did not increase. Nitrate AUC_{0-12} increased as NVN1000 dose increased following IM administration of NVM1000 on Day 1 and 5 and dermal administration of NVN ointment on Day 5. The mean bioavailability of nitrate following IM administration was ~48% on Day 1 and 6% on Day 5, reflecting the large variability in the background level of nitrate. The systemic availability of nitrate coming from NVN1000 gel was estimated to be ~2% and from NVN1000 ointment was ~5%. Topical bioavailability of silicon from NVN1000 Topical gel or ointment is essentially zero.
Pharmacokinetic and Bioavailability Evaluation of the Test Compound, NVN1000, Following IV and Topical Administration to Sprague-Dawley Rats (ADME-12-002)	The background concentration of nitrate in blood, determined in this study from pre-dose blood samples and blood samples following administration of vehicle, was 3280±3754 ng/mL in rats. Lack of significant increase in the levels of nitrate in blood above endogenous background levels was noted following dermal administration of NVN1000 gel and after IV administration of NVN1000. Nitrate AUC_{0-12} following most doses and routes of administration of NVN1000 were in the range of background levels of nitrate.
Pharmacokinetic and Bioavailability Evaluation of Nitrate and Silicon Following IV and Topical Administration of NVN1000 to Rats (ADME-12-003)	The level of nitrate determined in pre-dose blood samples and blood samples following administration of vehicle was 3441 ± 3168 ng/mL. Nitrate concentrations and nitrate AUC_{0-12} following most doses and routes of administration of NVN1000 were in the range of background levels of nitrate, although a somewhat elevated level of nitrate was seen following IV administration of NVN1000 and topical application of 200 mg/kg/day of NVN1000 ointment. Estimated bioavailability of 200 mg/kg/day of NVN1000 ointment was approximately 4% on Day 1 and approximately 21% on day 5. Topical bioavailability of silicon from NVN1000 ointment is essentially zero.

Type of Study	Major Findings
Topical Dosing and Pharmacokinetic Analysis of NVN1000 in an 8% Gel versus an 8% Gel + Hydrogel (ADME-12-005)	Following the administration of 8% NVN1000 with and without hydrogel, there was no significant differences observed in blood nitrate, skin nitrite and nitrate or skin silicon concentrations.
Topical Administration and Pharmacokinetic Analysis of NVN1000 Gels with Hydrogel in Male Sprague-Dawley Rats (ADME-12-011)	Comparing NVN1000 concentrations (4% versus 12% NVN1000 gel applied once daily), there was no significant difference observed in blood nitrate, skin nitrite or skin nitrate concentration. Of note, skin silicon did increase with increasing NVN1000 concentration. Comparing once daily versus twice daily application of 12% NVN1000 gel, there was no significant difference observed in blood nitrate, skin nitrite or skin nitrate concentration. Skin silicon did increase upon twice daily dosing compared to once daily dosing of 12% NVN1000 gel.
Comparative Oral and Intravenous Exposure Study of NVN1000 (Lot# 1400601) in Hanford Miniature Swine (ADME-14-003)	Following IV administration at 20 mg/kg, NVN1000 showed average half-life values for hMAP3, total silicon and nitrate of 2.6 ± 0.9, 2.3 ± 0.6 and 3.9 ± 1.2 hrs, respectively; C_{max} for hMAP3, total silicon and nitrate were 98433 ± 30497, 41010 ± 14462 and 31662 ± 9834 ng/mL, respectively; AUC_{last} for hMAP3, total silicon and nitrate were 115122 ± 4144, 60371 ± 3508 and 103351 ± 9161 ng/mL*hr, respectively. Following oral administration at 30 mg/kg, NVN1000 showed average half-life values for hMAP3, total silicon and nitrate of 10.9 ± 2.4, 4.9 ± 1.3 and 7.3± 4.1 hrs, respectively; C_{max} for hMAP3, total silicon and nitrate were 412 ± 90, 1546 ± 648 and 13324 ± 2777 ng/mL, respectively; AUC_{last} for hMAP3, total silicon and nitrate were 8146 ± 2392, 10765 ± 2402 and 160403 ± 23270 ng/mL*hr, respectively. Following oral administration at 100 mg/kg, NVN1000 showed average half-life values for hMAP3, total silicon and nitrate of 15.2, 9.4 and 3.7± 0.3 hrs, respectively; C_{max} for hMAP3, total silicon and nitrate were 1547 ± 180, 2760 ± 1485 and 37992 ± 5046 ng/mL, respectively; AUC_{last} for hMAP3, total silicon and nitrate were 25792 ± 2778, 43869 ± 6245 and 498619 ± 36413 ng/mL*hr, respectively. There was a significant trend and correlation between plasma hMAP3 concentration and plasma silicon concentration with an increase in plasma silicon concentration of 42 µg/mL for every 100 µg/mL increase in hMAP3 concentration (r=0.99). Additionally, there were significant trends and correlations between nitrate plasma concentrations and whole blood methemoglobin percentages for all

Type of Study	Major Findings
	doses of NVN1000 administered via IV and oral administration. When the results of all NVN1000 doses were combined, for every 1 ng/mL increase in plasma nitrate concentration, whole blood methemoglobin increased by 0.0007% (r=0.82).
Pharmacokinetic Analysis Following Dermal Administration of 24% NVN1000 Gel with Corresponding Hydrogels in Collared versus Uncollared Mice (ADME-18-001)	Plasma hMAP3 exposure is primarily through the oral route and is similar when NVN1000 gel is co-administered with either hydrogel A or hydrogel B. There was no appreciable accumulation of hMAP3 exposure after 5 daily topical administrations.
Distribution	
Not conducted	
Metabolism	
Not conducted	
Excretion	
Not conducted	
General Toxicology Studies	
Dermal Toxicology Studies	
One-month Dermal Toxicology Study of NVN1000 Ointment in Minipigs (12-NC-017)	<u>Minipig</u> TK calculations cannot be completed for all samples/groups because many samples were not quantifiable. Whole blood nitrate and silicon concentrations were widely distributed across all dose groups, including controls, on Day 1 and Day 28. The results indicated wide inter-individual variability that did not appear to be treatment related over the range of 2 to 20% NVN1000. This variability likely represents little or no systemic exposure to nitric oxide from NVN1000 compared to the presence of nitrate and silicon in the food and/or environment. The administration of NVN1000 in combination with hydrogel also did not appear to have an effect on blood concentrations of nitrate or silicon. Methemoglobin saturation was minimally elevated with treatment with ≥6% NVN1000. Of note, at the time of this study, the whole blood nitrate (nitric oxide metabolism) and silicon (polysiloxane polymer component) assays for systemic exposure were fairly insensitive with LLOQ of 5,000 ng/mL making it difficult to draw any conclusions of systemic absorption of test article.

Type of Study	Major Findings
13-week Dermal Toxicology Study of SB204 Gel in Hanford Miniature Swine (14-NC-001)	Hanford miniature swine TK calculations cannot be completed because many samples were not quantifiable. Repeated dermal application of SB204 gel at up to 8%, bid of NVN1000 for 13 consecutive weeks did not increase hMAP3, nitrate, or silicon exposure. There was no association between test article exposure level and methemoglobin levels at any time point.
39-week Dermal Toxicology Study of SB204 Gel in Hanford Miniature Swine (14-NC-004)	Hanford miniature swine During week 39, at 8%, bid (NOAEL) hMAP3: T_{max}: 0.4 hr C_{max}: 10.2 ng/mL AUC_{0-6}: 44.8 hr*ng/mL Accumulation: No Dose proportionality: No Nitrate: Plasma nitrate showed no increase in concentrations due to SB204 gel administration. Compared to post-dose values, pre-dose concentrations were higher on Day 1 and similar to the post-dose levels during weeks 20 and 39. During week 39, at 8%, bid (NOAEL) T_{max}: 3 hr C_{max}: 1125 ng/mL AUC_{0-6}: BLQ Accumulation: No Dose proportionality: No There was no clear dose response relationship between SB204 gel dose level and methemoglobin results at any time point.
4-week Toxicity Bridging Study of SB206 Gel in Hanford Miniature Swine (14-NC-005)	Hanford miniature swine TK calculations cannot be completed for plasma hMAP3 and nitrate. hMAP3: Minimal hMAP3 systemic exposure Nitrate: Plasma nitrate showed no increase in concentrations due to SB206 gel administration. Where quantifiable, pre-dose concentrations were similar to post-dose concentrations on both Day 1 and Day 28 in all treatment groups.

Type of Study	Major Findings
	Dose proportionality: No There was no clear dose response relationship between SB206 gel dose level and methemoglobin results at any time point.
13-week Dermal Toxicology Study of SB204 Gel in Sprague-Dawley Rats (14-NC-002)	Rat On Day 39, at 2% (dermal NOAEL was less than 2%) hMAP3: T_{max}: 4 hr C_{max}: 86.6 and 111 ng/mL for male and female, respectively AUC_{last}: 231 and 387 hr* ng/mL for male and female, respectively Accumulation: In males at all doses and only in female at 8% Dose proportionality: Yes Nitrate: Due to the large natural variations of the levels observed, it is inconclusive whether dermal SB204 gel administration increased nitrate level above the background. On Day 39, at 2% (dermal NOAEL was less than 2%) T_{max}: 4 and 1 hr for male and female, respectively C_{max}: 2920 and 3820 ng/mL for male and female, respectively AUC_{last}: 8610 and 12600 hr* ng/mL for male and female, respectively Accumulation: minimal Dose proportionality: No There was no clear dose response relationship between SB204 gel dose level and methemoglobin results at any time point.
13-week Dermal Toxicology Study of SB204 Gel in CD-1 Mice (15-NC-001)	CD-1 mice On Day 91, at 8% (dermal NOAEL) hMAP3: T_{max}: 4 hr C_{max}: 420 ng/mL AUC_{0-8}: 2300 hr* ng/mL Dose proportionality: Exposure increased in a linear fashion but in a less than dose proportional manner Nitrate: Dermal administration of SB204 gel increased nitrate level 1-hour post-dose in the 2 and 8% groups but returned to baseline by 8-hour post-dose. Nitrate level remained at the baseline in the vehicle and 0.5 % groups at any time point.

Type of Study	Major Findings
	On Day 91, at 8% (dermal NOAEL) T_{max}: 1 hr C_{max}: 23200 ng/mL AUC_{0-8}: 102200 hr* ng/mL Dose proportionality: Exposure increased in a linear fashion but in a less than dose proportional manner There was no clear dose response relationship between SB204 gel dose level and methemoglobin results at any time point.
Oral Toxicology Studies	
1-month Toxicology Study of NVN1000 in Sprague-Dawley Rats (16-NC-005)	<u>Rats</u> On Day 28, at 100 mg/kg (NOAEL) hMAP3: T_{max}: 1 hr C_{max}: 700 ng/mL AUC_{last}: 6050 hr*ng/mL Accumulation: No Dose proportionality: Yes Nitrate: Following oral administration up to 200 mg/kg, nitrate levels were higher than that of the sham and vehicle control groups which represent the background values. Peak plasma nitrate concentrations were observed at 1-hour post-dose in all berdazimer sodium-treated groups on Days 1 and 28 and declined to around background levels by 24 hours post-dose. On Day 28, at 100 mg/kg (NOAEL) T_{max}: 1 hr C_{max}: 27200 ng/mL AUC_{last}: 202000 hr*ng/mL Accumulation: No Dose proportionality: Yes On Day 1, at 30 mg/kg/day mean methemoglobin concentrations remained within the background level in both male and female animals. At 100 mg/kg/day, mean methemoglobin concentrations peaked at ~3% in male and 9% in female rats at 1- hour post-dose. At 200 mg/kg/day, mean methemoglobin concentrations reached 31% in male rats and 23% in female rats at 1-hour post-dose. The increased methemoglobin levels returned to background levels at 6-and 12-hour post-dose for animals treated with 100 and 200 mg/kg/day, respectively. On Day 28, blood methemoglobin concentrations followed a similar dose- and time-related pattern as on Day 1.

Type of Study	Major Findings
13-week Oral Toxicology Study of Berdazimer Sodium in Rats (19-NC-002)	Rat On Day 90, at 30 mg/kg/day (NOAEL less than 30 mg/kg/day) hMAP3: T_{max}: 1 and 3 hr for male and female, respectively C_{max}: 175 and 182 ng/mL for male and female, respectively AUC_{last}: 1540 and 1610 hr*ng/mL for male and female, respectively Accumulation: No Dose proportionality: Exposure increased as dose increased in a less than dose-proportional manner Nitrate: Following oral administration up to 200 mg/kg, nitrate levels were higher than that of the vehicle control group which represented the background values. Peak plasma nitrate concentrations were observed at 1-hour post-dose in all berdazimer sodium-treated groups on Days 1 and 90 and declined to around background levels by 24 hours post-dose. On Day 90, at 30 mg/kg/day (NOAEL less than 30 mg/kg/day) T_{max}: 1 hr for both sexes C_{max}: 8250 and 9050 ng/mL for male and female, respectively AUC_{last}: 54300 and 53300 hr*ng/mL for male and female, respectively Accumulation: No Methemoglobin demonstrated a dose-responsive increase on both Days 2 and 91 by the 1-hour sampling time point. Methemoglobin returned to baseline levels by the 6-hour time point.
Reproductive Toxicology Studies	
Study of Fertility and Early Embryonic Development in Sprague Dawley Rats after Daily Oral Administration of NVN1000 (14-NC-003)	Rat Females on Day 23, at 200 mg/kg/day (NOAEL) (No TK parameters were obtained on Day 85 due to death of all male in the 200 mg/kg/day group) hMAP3 (female): C_{max}: 1510 ng/mL AUC: 8310 hr*ng/mL Nitrate (female): Following oral administration of NVN1000 up to 200 mg/kg/day, mean nitrate concentrations were

Type of Study	Major Findings
	elevated (compared to concurrent controls) through at least 3-hour post-dose. Females on Day 23, at 200 mg/kg/day (NOAEL) (No TK parameters were obtained on Day 85 due to death of all male in the 200 mg/kg/day group) C_{max}: 51000 ng/mL AUC: 289000 hr*ng/mL Methemoglobin levels were elevated in a dose-dependent manner in both sexes at all NVN1000 dose levels.
An Oral Embryo-fetal Developmental Toxicity Study of NVN1000 in the Sprague Dawley Rat (15-NC-002)	<u>Rat</u> On GD17, at 30 mg/kg (maternal NOAEL) hMAP3: C_{max}: 153 ng/mL AUC_{last}: 1040 hr*ng/mL Nitrate: Following oral administration of NVN1000 up to 200 mg/kg/day, nitrate levels were higher than the pre-dose levels. On GD17, at 30 mg/kg (maternal NOAEL) C_{max}: 10700 ng/mL AUC: 89900 hr*ng/mL Elevated methemoglobin levels were seen at all NVN1000 dose levels at 1-and 3-hours post-dose on GD 6 and GD 17. Methemoglobin increases were at their highest at 1-hour post-dose and had decreased by 3 hours post-dose.
An Oral Embryo-fetal Developmental Toxicity Study of NVN1000 in the New Zealand White Rabbit (15-NC-003)	<u>Rabbit</u> On GD19, at 50 mg/kg (maternal NOAEL) hMAP3: C_{max}: 345 ng/mL AUC_{last}: 3630 hr*ng/mL Nitrate: Following oral administration of NVN1000 up to 300 mg/kg/day, nitrate levels were higher than the pre-dose levels. On GD19, at 50 mg/kg (maternal NOAEL) C_{max}: 24700 ng/mL AUC_{last}: 393000 hr*ng/mL Elevated mean methemoglobin levels were seen at all NVN1000 dose levels at 1 and 3-

Type of Study	Major Findings
	hour post-dose on GD 7 and 19. The highest methemoglobin levels were observed at 1 h post-dose on GD 19 for does receiving 150 or 300 mg NVN1000/kg/day, reaching means of 14.6% and 50.20%.
Carcinogenicity Studies	
SB204 Gel: A 104-Week Dermal Carcinogenicity Study in Mice (15-NC-004)	<u>Mice</u> On Day 181, at 4% (NOAEL) hMAP3: C_{max}: 202 and 398 ng/mL for male and female, respectively $AUC_{0\text{-}8hr}$: 1160 and 2140 hr*ng/mL for male and female, respectively Nitrate: Following dermal administration of SB204 gel, nitrate levels increased in the 2 and 4% groups at 1 hour post-dose but returned to the background level by 8-hour post-dose. The nitrate level in the 0.5% group remained at close to the background levels at all time points. On Day 181, at 4% (NOAEL) C_{max}: 17200 and 20200 ng/mL for male and female, respectively $AUC_{0\text{-}8hr}$: 48100 and 69100 hr*ng/mL for male and female, respectively

Source: NDA submission.

5.5. Toxicology

5.5.1. General Toxicology

5.5.1.1. Repeat-Dose Toxicity Studies Using Dermal Administration

5.5.1.1.1. Minipig Studies

28-Day Toxicity Study With Daily Topical Doses of NVN1000 Followed by a 7-Day, Drug-Free Recovery Period in Hanford Miniature Swine (GLP) (12-NC-011)

Following 28 consecutive days of daily administration of 0 (untreated control), 0 (vehicle control), 6, 12 and 20% of NVN1000 gel, there were no macroscopic or microscopic findings related to test article administration in Hanford Miniature Swine (4 animals/sex/group). Similarly, there were no NVN1000 gel-related findings through the seven-day recovery period. Under the conditions of this study, the NOAEL for NVN1000 gel was 180 mg/kg/day (20% NVN1000 gel; the highest dose tested) in male and female Hanford miniature swine.

NVN1000: 28-Day Dermal Toxicity Study in Minipigs (GLP) (12-NC-017)

Daily dermal administration of NVN1000 ointment concentrations up to 20% (60 mg/kg/day NVN1000) as NVN1000 ointment for up to 28 days resulted in no or very limited systemic exposure of NVN1000 in Göttingen minipigs (3-4 animals/sex/group). Persistent and worsening skin ulceration of the dose site at 20% (60 mg/kg/day NVN1000) required early study termination on Day 14 or 15 of dosing. Under the conditions of this study, the NOAEL was determined to be 6% NVN1000 ointment with and without hydrogel.

13-Week Toxicity Study With Twice Daily Topical Doses of SB204 Gel Followed by a 4-Week, Drug-Free Recovery Period in Hanford Miniature Swine (GLP) (14-NC-001)

SB204 gel [0 (untreated control), 0 (vehicle control), 2, 4 and 8%; 0, 0, 6, 12 and 24 mg/kg, respectively] was dermally applied twice daily for 13 weeks to ~ 10% of body surface area (BSA) of Hanford Miniature Swine (4 animals/sex/group). The NVN1000 and hydrogel were mixed prior to application onto the skin. Test article-related findings were limited to site reactions including hyperplastic changes of the epidermis and inflammatory response of the dermis. Partial recovery was noted. Under the conditions of this study, the NOAEL for SB204 gel was considered to be 8% SB204 gel, twice daily, the highest dose tested in Hanford Miniature Swine.

A complete review of the pivotal chronic dermal repeat dose general toxicity study conducted with SB204 gel is provided below.

39-Week Toxicity Study With Twice Daily Topical Doses of SB204 Gel Followed by a 4-Week, Drug-Free Recovery Period in Hanford Miniature Swine (GLP) (14-NC-004)

In minipigs, twice-daily dermal application of SB204 gel at concentrations at 0 (untreated control), 0 (vehicle control), 2, 4, and 8% (0, 0, 12, 24, and 48 mg/kg/day NVN1000) for 39

consecutive weeks resulted in no test article-related changes in clinical observations, physical examination findings, feed consumption, body weight change, clinical pathology or organ weight findings. Under the conditions of this study the NOAEL is determined to be SB204 gel, 8% bid, the highest dose level evaluated in this study.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Table 3. Methods for Study No. 14-NC-004

Methods	Details
Dose and frequency of dosing:	0 (untreated control), 0 (vehicle control), 2, 4 and 8% SB204 gel; 0, 0, 6, 12, 24 mg/kg/dose, twice daily
Route of administration:	Topical
Formulation/Vehicle:	Clinical formulation
Species/Strain:	Sus scrofa / Hanford miniature swine
Number/Sex/Group:	4
Age:	2 to 3 months at Day 1
Satellite groups/ unique design:	Recovery: 2/sex/group
Deviation from study protocol affecting interpretation of results:	None significant to the integrity of results. Results from mid-dose male replacing mid-dose male terminated on Day 20 were not included in statistical analysis, since dosing procedures were initiated 20 days later than in other animals.

Source: NDA submission.

Table 4. Observations and Results Changes From Control (Study No. 14-NC-004)

Parameters	Major Findings
Mortality	No treatment-related effects
Clinical Signs	No treatment-related effects
Body Weights	No treatment-related effects
Ophthalmoscopy	No treatment-related effects
ECG	No treatment-related effects
Hematology	No treatment-related effects
Clinical Chemistry	No treatment-related effects
Gross Pathology	No treatment-related effects
Organ Weights	No treatment-related effects
Histopathology Adequate battery: Yes	Test article-related microscopic findings were limited to dose-site skin tissues (skin lesions included erosion/pustules, crust formation, hyper/parakeratosis, epidermal hyperplasia, edema, mononuclear cell infiltration, and sweat gland dilation). Partial reversibility was noted in all SB204 gel-treated groups.

Parameters	Major Findings
Methemoglobin analyses	Methemoglobin % was variable amongst all treatment groups at Day 1 and this variability continued over time. There were no patterns or trends suggesting a clear dose response relationship between SB204 gel dose level and methemoglobin results at any time point.

Source: NDA submission.

A complete review for a 4-week dermal minipig toxicity study conducted with SB206 gel is provided below. This 4-week dermal minipig toxicity study was conducted to compare the toxicity provide of the SB206 gel to previously conducted repeat dose dermal minipig toxicity studies conducted with SB204 gel. The results for this 4-week dermal minipig study conducted with SB206 gel are similar to results from repeat dose dermal toxicity studies conducted with SB204 gel. Therefore, this study serves as a bridging study for SB206 gel and SB204 gel to allow use of the 9-month dermal minipig study conducted with SB204 gel to support the safety for chronic use of SB206 gel.

4-Week Toxicity Bridging Study With Twice Daily Topical Doses of SB206 Gel Followed by a 2-Week, Drug-Free Recovery Period in Hanford Miniature Swine (GLP) (14-NC-005)

In minipigs, once or twice daily application of SB206 gel (0% {vehicle control} bid, 8% bid, 16% qd; 0, 48, 48 mg/kg/day NVN1000) to a clipped dorsal surface area for 28 consecutive days resulted in no test article-related changes in clinical observations, physical examination findings, feed consumption, body weight change, clinical pathology or organ weight findings. A modest degree of erythema and/or edema was observed at the application site skin over the 28-day exposure period. Under the conditions of this study, the systemic NOAEL is determined to be 8% SB206 gel, bid and 16% SB206 gel, qd, the highest dose levels evaluated. A local NOAEL could not be determined based on microscopic changes in the superficial dermis and epidermis that had not completely resolved by the end of the 2-week recovery period.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Table 5. Methods for Study No. 14-NC-005

Methods	Details
Dose and frequency of dosing:	0 (vehicle control), bid, 8% SB206 gel, bid and 16% SB206 gel, qd; 0, 48, 48 mg/kg/day
Route of administration:	Topical
Formulation/Vehicle:	Clinical formulation
Species/Strain:	Sus scrofa / Hanford miniature swine
Number/Sex/Group:	4
Age:	4 to 5 months at Day 1

Methods	Details
Satellite groups/ unique design:	Recovery: 2/sex/group
Deviation from study protocol affecting interpretation of results:	None significant to the integrity of results.

Source: NDA submission.

Table 6. Observations and Results Changes From Control (Study No. 14-NC-005)

Parameters	Major Findings
Mortality	No treatment-related effects
Clinical Signs	Modest degree of erythema and/or edema at the application site in both vehicle gel and SB206 gel treated animals.
Body Weights	No treatment-related effects
Ophthalmoscopy	No treatment-related effects
ECG	No treatment-related effects
Hematology	No treatment-related effects
Clinical Chemistry	No treatment-related effects
Urinalysis	No treatment-related effects
Gross Pathology	No treatment-related effects
Organ Weights	No treatment-related effects
Histopathology Adequate battery: Yes	8% SB206 gel (bid) or 16% SB206 gel (qd): hyperkeratosis, epidermal hyperplasia and mononuclear dermal inflammation in the epidermis and superficial dermis at the application site. Partial reversibility was noted in all SB206 gel-treated groups.
Methemoglobin analyses	Methemoglobin % was variable amongst all treatment groups at most time points. There were no patterns or trends suggesting a clear dose response relationship between SB206 gel dose level and methemoglobin results at any time point.

Source: NDA submission.

5.5.1.1.2. Rat Studies

13-Week Repeat Dermal Dose Toxicology Study in Sprague-Dawley Rats With a 4-Week Recovery Period (GLP) (14-NC-002)

SB204 gel (0 (untreated control), 0 (vehicle control), 2, 4, or 8%) at 0.8 g/kg/dose was dermally applied once daily to an area of 10% BSA of Sprague-Dawley rats (15 animals/sex/group; 10 main study and 5 recovery animals) once a day for 13 weeks. The NVN1000 and hydrogel were mixed directly on the rat skin. The dose levels were equivalent to nominal 0, 0, 16, 32, or 64 mg/kg/day NVN1000.

In this study all active test article groups were terminated prior to the scheduled 13-week end date due to skin lesions (scabs, ulceration, crusts) within the treatment site at all dose levels tested. The development of skin lesions occurred in a time/dose dependent manner with the 8%, 4% and 2% SB204 gel dose groups showing a high frequency and severity of lesions approximately 3, 5, and 7 weeks after start of dosing, respectively. The lesions ranged from multifocal to coalescing crusts at the application site with underlying smooth, glistening,

erythematous dermis with scabbing. None of the animals in the vehicle or sham operated groups showed any dermal lesions evident in the active treatment arms. During the recovery phase, all affected rats recovered with no visible sign of erythema, lesions or residual scabbing after 1-2 weeks.

Under the conditions of this study, a local NOAEL for SB204 gel could not be determined in this study due to treatment site lesions observed at all doses. There were no other significant treatment-related adverse effects of SB204 gel detected in this study. The systemic NOAEL was 8% SB204 gel, the highest dose evaluated in this study.

5.5.1.1.3. Mouse Studies

13-Week Toxicity Study With Once Daily Topical Dosing of SB204 Gel Followed by a 4-Week, Drug-Free Recovery Period in CD-1 Mice (GLP) (15-NC-001)

Once daily dermal administration of 0 (vehicle control), 0.5, 2 or 8% SB204 gel (equivalent to nominal 0, 20, 80, 320 mg/kg/day NVN1000) to CD-1 mice (10 animals/sex/group) for 13 consecutive weeks was well tolerated on the skin at all dose levels. Microscopic observations of the skin were limited to minimal to mild epidermal hyperplasia and dermal inflammation which generally occurred in a dose dependent fashion. Following the 4-week recovery period all microscopic skin observations had resolved. Systemic toxicity included test article-related microscopic findings in the esophagus (inflammation) and non-glandular stomach (squamous hyperplasia and inflammation) at 8% SB204 gel in male and female animals. Following the 4-week recovery period, partial to complete recovery was observed for findings in the esophagus and stomach, respectively, in both male and female animals. Based on esophageal findings which did not fully reverse during the 4-week recovery period, the systematic NOAEL was 2% SB204 gel. The dermal NOAEL was 8% SB204 gel, the highest dose evaluated in this study.

5.5.1.2. Repeat-Dose Toxicity Studies Using Oral Administration

The Applicant was granted a waiver for conduct of the 6-month systemic rodent repeat dose toxicology study based on subnanomolar systemic exposure under maximal clinical use conditions.

28-Day Toxicity Study With Once Daily Oral Dosing of NVN1000 Followed by a 14-Day, Drug-Free Recovery Period in Sprague-Dawley Rats (GLP) (16-NC-005)

NVN1000 was orally administered to rats (10 animals/sex/group) at dose levels of 0 (untreated control), 0 (vehicle control), 30, 100, or 200 mg/kg/day for 28 days followed by a 14-day recovery period. The vehicle was phosphate buffered saline (PBS). Methemoglobin levels were significantly increased for all treatment groups receiving NVN1000. Mucosal hyperplasia in the non-glandular portion of the stomach was only partially reversible at 200 mg/kg/day. Based on reversible changes in hematology parameters and partially reversible histological changes in the stomach at 200 mg/kg/day, the NOAEL was determined to be 100 mg/kg/day.

Berdazimer Sodium: 13-Week Once Daily Oral Gavage Toxicity Study in Rats (19-NC-002)

Once daily oral gavage of berdazimer sodium (0 [vehicle control; PBS], 30, 100 or 200 mg/kg/day) to rats (10 animals/sex/group) for 13 weeks resulted in gross observations of an abnormal appearance in the stomach in female rats at ≥100 mg/kg/day and male rats at 200 mg/kg/day. Dose dependent microscopic findings of hyperplasia and hyperkeratosis of the squamous mucosa of the non-glandular portion of the stomach were observed at ≥30 mg/kg/day, precluding derivation of a NOAEL.

5.5.2. Genetic Toxicology

5.5.2.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Bacterial Reverse Mutation (Ames) Assay with NVN1000 Drug Substance (13-NC-003)

Key Study Findings: NVN1000 caused positive mutagenic responses for tester strains TA1535 and TA1537 in both the presence and absence of Aroclor-induced rat liver S9 Mix, and for tester strain WP2 uvrA in the presence of Aroclor-induced rat liver S9 Mix. The study was determined to be positive without the conduct of a confirmatory (independent repeat) assay because the results were unequivocally positive for multiple tester strains.

GLP Compliance: Yes

Test System:

- TA98, TA100, TA1535, WP2 uvrA (-S9): 2.0, 6.0, 20, 60, 200, 600 µg/plate
- TA98, TA100, WP2 uvrA (+S9): 20, 60, 200, 600, 1800, 5000 µg/plate
- TA1535 (+S9), TA1537 (±S9): 2.0, 6.0, 20, 60, 200, 500, 1500, 1800, 5000 µg/plate

Study is Valid: Yes. All criteria for a valid study as detailed in the protocol were met.

5.5.2.2. In Vitro Assays in Mammalian Cells

NVN1000 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes (15-NC-005)

Key Study Findings: Under the conditions of the assay, NVN1000 was negative for induction of structural and numerical chromosome aberrations in the non-activated and S9-activated test systems in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes.

GLP Compliance: Yes

Test System: Human peripheral lymphocytes from healthy male non-smokers with no history of chemotherapy or illicit drug use, 15.6, 31.3, 62.5, 125, 250, 500 µg/mL, -S9: 3 or 22 hours at 37±1°C, +S9: 3 hours at 37±1°C

Study is Valid: Yes. The concurrent positive controls induced significant increases in the percentage of cells with structural chromosome aberrations relative to the corresponding vehicle control groups, demonstrating the validity and sensitivity of the test system for detecting clastogens with and without metabolic activation.

5.5.2.3. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

In Vivo Bone Marrow Mouse Micronucleus Test (12-NC-010)

Key Study Findings: NVN1000 was not clastogenic or aneugenic in this assay.

GLP Compliance: Yes

Test System: CD-1 mouse (10 animals/sex/group); 6.3, 20.1, and 63.4 mg/kg; intraperitoneal injection; once; bone marrow

Study is Valid: Yes. The assay met the study validity criteria.

In Vivo Mouse Micronucleus Assay Using a Skin Model (GLP) (12-NC-018)

Key Study Findings: NVN topical gel was determined to not clastogenic under the conditions of this test.

GLP Compliance: Yes

Test System: Sprague-Dawley rats (despite the title) (5/sex/group); 0% (vehicle control), 2% and 20% NVN1000 gel; topical; once daily for 3 days; skin

Study is Valid: No. Although not yet validated, this assay evaluates the potential of a topically applied test article to induce micronuclei formation in basal cells present in the skin layer of young adult Sprague-Dawley rats.

5.5.2.4. Other Genetic Toxicity Studies

The genetic toxicity studies reviewed in this section were conducted to evaluate the mutagenic potential of impurities contained in the drug substance.

Bacterial Reverse Mutation Assay (b) (4)

Key Study Findings: (b) (4) an impurity identified in the drug substance did not cause a positive mutagenic response with any of the tester strains in either the presence or absence of Aroclor-induced rat liver S9.

GLP Compliance: Yes

Test System: TA98, TA100, TA1535, WP2 uvrA (+S9 and-S9): 125, 250, 500, 1250, 2500 and 5000 µg/plate

Study is Valid: Yes. All criteria for a valid study as detailed in the protocol were met.

Bacterial Reverse Mutation (Ames) Assay (b) (4)

Key Study Findings: (b) (4) an impurity identified in the drug substance did not cause a positive mutagenic response with any of the tester strains in either the presence or absence of Aroclor-induced rat liver S9.

GLP Compliance: Yes

Test System: TA98, TA100, TA1535, WP2 uvrA (+S9 and-S9): 12.5, 25.0, 75.0, 250, 500, 1250, 2500 and 5000 µg/plate

Study is Valid: Yes. All criteria for a valid study as detailed in the protocol were met.

5.5.3. Carcinogenicity

The Applicant was granted a waiver for conduct of the systemic carcinogenicity study based on subnanomolar systemic exposure under maximal clinical use conditions.

In a 2-year dermal mouse carcinogenicity study (15-NC-004), topical once daily doses of 0 (untreated control), 0 (vehicle control), 0.5%, 2%, and 4 % SB204 gel (16, 64 and 128 mg/kg/day NVN1000) were tested in CD-1 mice. No SB204 gel treatment related tumor findings were noted in this study.

Refer to Appendix 16.4 for full carcinogenicity study review.

5.5.4. Reproductive and Developmental Toxicology

The Applicant was granted a waiver request for conduct of the pre- and post-natal development study based on subnanomolar systemic exposure under maximal clinical use conditions.

5.5.4.1. Fertility and Early Embryonic Development

Study of Fertility and Early Embryonic Development in Sprague Dawley Rats After Daily Oral Administration of NVN1000 (14-NC-003)

Rats orally administered vehicle control (PBS) or NVN1000 (30, 100, or 200 mg/kg/day) for at least 81 days (males) and 23 days (females) had no significant changes in reproductive indices. NVN1000-related mortalities and adverse clinical observations seen in animals receiving 200 mg/kg/day were likely due to elevated methemoglobin levels (up to 80%). The surviving animals in the 200 mg/kg/day group were paired for mating. No treatment related effects were noted for fertility or reproductive parameters in this study. Based on no adverse findings in fertility or reproductive parameters in either sex, the NOAEL for effects on fertility and general reproductive performance was 200 mg/kg/day via oral gavage.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Table 7. Methods for Study No. 14-NC-003

Methods	Details
Dose and frequency of dosing:	0, 30, 100, 200 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	PBS
Species/Strain:	Rat/Sprague Dawley [Crl:CD®(SD)]
Number/Sex/Group:	25
Satellite groups:	Toxicokinetics (TK): 4 rats/sex/dose for low and mid dose groups, 4 males and 8 females for high dose group
Study design:	Males were dosed for at least 9 weeks prior mating and during mating. Females were dosed for at least 2 weeks prior to mating, during the mating phase, and through gestation day (GD) 7.
Deviation from study protocol affecting interpretation of results:	No (None significant to integrity of study results)

Source: NDA submission.

Table 8. Observations and Results (Study No. 14-NC-003)

Parameters	Major Findings
Mortality	Test article-related mortalities were observed in HD animals. Twelve males (8 in the toxicology group and 4 in the TK group) and 15 females (10 in the toxicology group and 6 in the TK group) were found dead or sacrificed moribund over the course of the study. The majority of the male deaths were at the end of the dosing period (Days 80-81).
Clinical Signs	HD: prostration, gasping, cold to touch and abnormal gait MD and HD: blue or pale mucosal membranes, dark eyes, and blue or pale body, which are attributed to high methemoglobin levels LD: pale mucous membranes and oral stain
Methemoglobin levels	Methemoglobin levels were elevated in a dose-dependent manner in both sexes at all NVN1000 dose levels.
Body Weights	HD: slight decrease in mean body weight in males (5-6%) from Days 7-56 of the premating phase
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	No treatment-related effects

Source: NDA submission.
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

5.5.4.2. Embryo-Fetal Development

An Oral Embryo-Fetal Developmental Toxicity Study of NVN1000 in the Sprague Dawley Rat (15-NC-002)

Key Study Findings: Timed-pregnant rats received vehicle control (PBS) or NVN1000 (30, 100, or 200 mg/kg/day) on GD 6-17. Based on mortality and elevated methemoglobin levels at ≥100 mg/kg/day, the maternal NOAEL is 30 mg/kg/day. Based on fetal skeletal and visceral malformations and decreased fetal body weights in litters from dams receiving 200 mg/kg/day,

the fetal NOAEL is 100 mg/kg/day. The fetal effects were noted in the presence of significant maternal toxicity.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Table 9. Methods For Study No. 15-NC-002

Methods	Details
Dose and frequency of dosing:	0, 30, 100, 200 mg/kg, once daily on gestation days (GD) 6-17
Route of administration:	Oral gavage
Formulation/Vehicle:	PBS
Species/Strain:	Rat/Sprague Dawley [Crl:CD®(SD)]
Number/Sex/Group:	25 pregnant females/group
Satellite groups:	Toxicokinetics (TK): 0 animal for control, 6 animals for low and mid dose, 12 for high dose (6 for GD 6 and 6 for GD 17)
Study design:	Pregnant rats underwent a caesarean examination on GD 21 with litter assessments
Deviation from study protocol affecting interpretation of results:	No (None significant to integrity of study results)

Source: NDA submission.

Table 10. Observations And Results (Study No. 15-NC-002)

Parameters	Major Findings
Mortality	MD: 1 female death HD: 9 females deaths or euthanasia due to moribund condition
Clinical Signs	HD: gasping, prostration/lying on side, dilated pupils, and or cold to touch prior to death MD and HD: dark eyes, pale or blue mucous membranes, and pale body, which were attributed to high methemoglobin levels in circulation LD: blue mucous membranes in 1 female on GD 15
Methemoglobin levels	Elevated methemoglobin levels were seen at all NVN1000 dose levels at 1-and 3-hours post-dose on GD 6 and GD 17. HD: 55.70% at 1 h post-dose on GD 17 MD: 22.4% at 1 h post-dose on GD 17
Body Weights	HD: Decreased body weight gain (18%) during the dosing period (GD 6-17) in dams
Necropsy findings Cesarean Section Data	HD: Decreased gravid uterine weights (7%), partially attributed to lower fetal weights
Necropsy findings Offspring	HD: Decreased fetal weights in males and both sexes combined; fetal visceral malformation of cleft palate was seen in 2 fetuses from 1 dam; skeletal malformations [changes in the lumbar and thoracic centra or arches: missing thoracic arches and centra in 1 fetus, additional bone in the thoracic arches in 1 fetus, missing lumbar centra and arches in 2 fetuses, and fused ribs (4th and 5th) in 1 fetus] from 3 litters from dams in the HD group

Source: NDA submission.
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

An Oral Embryo-fetal Developmental Toxicity Study of NVN1000 in the New Zealand White Rabbit (15-NC-003)

Key Study Findings: Timed-pregnant female rabbits received vehicle control (PBS) or NVN1000 (50, 150, or 300 mg/kg/day) on GD 7-19. Based on mortalities, aborted fetuses, adverse clinical observations, and elevated methemoglobin levels in does receiving 150 and 300 mg/kg/day, the maternal NOAEL is 50 mg/kg/day. Based on decreased fetal body weights in litters from does receiving 300 mg/kg/day, the fetal NOAEL is 150 mg/kg/day. The fetal effects were noted in the presence of significant maternal toxicity.

Conducting Laboratory and Location: (b) (4)

GLP Compliance: Yes

Table 11. Methods for Study No. 15-NC-003

Methods	Details
Dose and frequency of dosing:	0, 50, 150, or 300 mg/kg/day, once daily on gestation days (GD) 7-19
Route of administration:	Oral gavage
Formulation/Vehicle:	PBS
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	20 pregnant females/group
Satellite groups:	Toxicokinetic: 3/group (low, med, high)
Study design:	Does underwent a gross necropsy (C-section) on GD 29 with fetal assessments
Deviation from study protocol affecting interpretation of results:	Yes (Six does allocated to the 150 mg/kg/day dose group were given the 300 mg/kg/day (60 mg/mL) formulation on their respective GD 8, 9, or 10 (Deviation to Protocol #1). No doe received more than one incorrect dose. Three additional does were added to the 150 mg/kg/day dose group to maintain an acceptable group size. No deviations were significant to integrity of results. Due to decreased feed consumption and body weight loss in multiple does treated with 150 and 300 mg/kg/day, all rabbits at these dose levels were supplemented with a high-calorie gel supplement (Nutri-Cal®) from GD 11-21 until termination. It would have been more appropriate to supplement all dose groups or none of the dose groups.

Source: NDA submission.

Table 12. Observations and Results (Study No. 15-NC-003)

Parameters	Major Findings
Mortality	MD: 4 doe deaths or early euthanasia due to moribund condition HD: 15 doe deaths or early euthanasia due to moribund condition
Clinical Signs	MD and HD: lethargy/hypoactivity, lying on side, evidence of abortion (including aborted fetuses or tissue in bedding),

	discolored urine, vaginal discharge, thin body condition, high methemoglobin levels related clinical signs [discolored (blue, dark, or pale) mucosal membranes, eyes, and ears] and effects on fecal output LD: high methemoglobin levels related clinical signs (discolored (blue, dark, or pale) mucosal membranes, eyes, and ears) in three does on 1-2 occasions and effects on fecal output
Methemoglobin levels	Elevated mean methemoglobin levels were seen at all NVN1000 dose levels at 1 and 3 hours post-dose on GD 7 and 19. HD: 50.20% at 1 h post-dose on GD 19 MD: 14.6% at 1 h post-dose on GD 19
Body Weights	HD: decreased body weights (9-12%) from GD 21-29, mean body weight loss of 0.2 kg during GD 7-19 All groups: decreased body weight gain
Necropsy findings Cesarean Section Data	HD: decreased gravid uterine weights (36%), increased percent postimplantation loss (14.8% compared to 3.4% for controls) and percent early resorptions (14.8% compared to 1.3% for controls)
Necropsy findings Offspring	HD: decreased fetal weights (12-13%) in males, females and both sexes combined; decreased litter sizes (mean litter of 6.7 fetuses versus 8.3 fetuses for the controls); increased unossified posterior phalanges LD: increased unossified posterior phalanges

Source: NDA submission.
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

5.5.5. Other Toxicology Studies

5.5.5.1. Dermal Sensitization Studies

Closed patch skin sensitization studies were conducted in guinea pigs with NVN1000 gel 2%, 6%, and 12% (12-NC-008, 12-NC-007, and 12-NC-006, respectively). Ten treated animals (5 male, 5 female) and five control animals (3 male, 2 female) were used for each test article. Testing consisted of four phases: 1) primary irritancy testing to establish the Minimally Irritating Concentration (MIC) and the Highest Non-Irritating Concentration (HNIC); 2) Induction; 3) Challenge; and 4) Re-Challenge. During induction, animals received nine 6-hour topical applications of the test article at the MIC over the course of three weeks. Fourteen days after the ninth induction application, animals received a single occluded application of the HNIC at a naïve test site. If irritation was observed at challenge, animals were re-challenged at another naïve test site seven days later. Although the 6% and 12% gels caused irritation of increasing severity during the induction phase, none of the formulations were found to be skin sensitizers and none of them required re-challenge at a second naïve site. Based on this test, NVN1000 gel 2%, 6% and 12% did not elicit a sensitization response under the conditions of this test.

5.5.5.2. Ocular Irritation Studies

OECD Bovine Corneal Opacity and Permeability Test (BCOP) (17-NC-003)

An ex vivo BCOP assay was conducted to determine the ocular irritation potential of a 20% (200 mg/mL) preparation of NVN1000 in 0.9% sodium chloride. A 20% solution of imidazole in 0.9% sodium chloride was the positive control and 0.9% sodium chloride was the vehicle control. Following a 240-minute exposure, opacity measurements were made, sodium fluorescein permeability was determined, and the in vitro irritancy score (IVIS) was calculated as shown below:

Equation 1. Calculation of the In Vitro Irritancy Score

$$IVIS = corrected\ mean\ opacity\ score + (15 \times mean\ optical\ density\ score)$$

Source: NDA submission. .
Abbreviations: IVIS, in vitro irritancy score

Based on IVIS of 35.02, NVN1000 is not considered to be a severe ocular irritant, capable of causing serious eye damage.

OECD Bovine Corneal Opacity and Permeability Test (BCOP) (17-NC-005)

An ex vivo BCOP assay was conducted to determine the ocular irritation potential of SB206 12% gel and the corresponding vehicle. Following a 10-minute exposure, opacity measurements were made, sodium fluorescein permeability was determined, and the in vitro irritancy score (IVIS) was calculated using Equation 1.

Based on IVIS of 11.38 and 13.96, neither SB206 12% gel or vehicle, respectively, are considered to be a severe ocular irritant, capable of causing serious eye damage.

5.5.5.3. Phototoxicity Studies

Phototoxicity studies were not needed for the SB206 gel based on no absorbance in the range of 290 – 700 nm as indicated below.

UV-Spectrophotometer Development and Analysis of NVN1000 (DSAN-15-002)

Samples of NVN1000 (drug substance), 4% SB204 gel, hydrogel, 4% vehicle gel, 4% SB204 gel+hydrogel (1:1) and 4% vehicle gel+hydrogel (1:1) were dissolved in 30 mM potassium hydroxide and scanned for absorbance in the range of 290- 700 nm. There is no absorbance of NVN1000 drug substance or drug product in the range of natural sunlight (290- 700 nm). Since there were no absorbances observed in this range, a molecular extinction coefficient (MEC) was not calculated for NVN1000.

UV/Visible Spectroscopic Analysis and Photosafety Evaluation of SB206 Drug Product (RPT-0111)

The SB206 gel (24% berdazimer sodium gel), the (b) (4) buffered hydrogel, and SB206 gel+hydrogel (1:1) were dissolved in 30 mM potassium hydroxide and were scanned for absorbance in the range of 290- 700 nm. The monomeric species, MAP3-NONOate (N,N-methylaminopropyl diazeniumdiolate trimethoxysilane), which constitutes a majority of the polymeric sodium berdazimer and contributes the chromophore within the SB206 drug product was dissolved in methanol and was also evaluated. There was no significant absorbance within the range of natural sunlight (290- 700 nm) for each individual gel component as well as the SB206 drug product admixtures. The MEC for SB206 gel cannot be determined. In contrast, the MEC for MAP3-NONOate in the range of 290- 700 nm was calculated to be 180 M^{-1} cm^{-1} which is below the threshold of 1000 M^{-1} cm^{-1}.

5.5.5.1. Excipients and Impurities

Excipients

There are no novel excipients, nor any of animal or human origin. All inactive ingredients are compendial and within the limits of the Inactive Ingredient Database (IID), with the exception of carboxymethylcellulose sodium. The ingredient is used at (b) (4)% in the drug product and is minimally above the maximum previous topical use (i.e., (b) (4)%) listed in the IID. Its use has been qualified by the 28-day dermal minipig toxicity study conducted with SB206 (14-NC-005).

Impurities

(b) (4) were identified as alerting structures in the (Q)SAR analysis and their specifications are set (b) (4)%w/w, respectively. The levels are above the ICH Q3A qualification threshold of (b) (4)%. The Ames test was conducted for both impurities and has concluded both impurities have no mutagenic potential. Also, the higher levels were qualified by the 28-day dermal minipig toxicity study conducted with SB206 (14-NC-005). The specifications set for these two impurities are acceptable from a nonclinical perspective.

Another impurity, (b) (4) was identified as alerting structures in the (Q)SAR analysis and is controlled by the manufacturing process ICH M7 Option 4. This is acceptable from a nonclinical perspective.

Following literature review conducted by the Applicant, (b) (4) were considered not having potential mutagenic effects and are set at (b) (4) % w/w, respectively. This is acceptable from a nonclinical perspective.

Several extractables from the container closure system were identified and (b) (4) was confirmed in the leachable simulation. Following literature review conducted by the Applicant, a negative prediction from the Bacterial Mutation (Q)SAR model and the absence of an identified alert, (b) (4) is considered not mutagenic. In addition, the

potential Calculated Daily Exposure (CDE) of (b) (4) µg/day is well below the Threshold of Toxicological Concern (TTC) at (b) (4) µg/day for adults, children above 2 years-old and children between 6 months and <2 years-old, respectively as established by the Applicant. This is acceptable from a nonclinical perspective.

The applicant submitted the updated (b) (4) risk assessment including the information on the formation and presence of (b) (4) in SB206 gel. The levels of (b) (4) in SB206 gel, the active gel of SB206, and berdazimer sodium drug substance (NVN1000) were at levels above the limit of quantitation (b) (4) ng/mL). The applicant also conducted literature review to provide the estimate of dermal bioavailability of (b) (4) Based on an in vitro human skin penetration study (b) (4) the dermal bioavailability of (b) (4) appeared to be 4%. Using the maximum daily dose of the SB206 gel at 2 g and 4% of dermal bioavailability of (b) (4), the calculated intake levels of (b) (4) are shown in Table 13.

Table 13. Summary of Acceptable Intake Limits for Dermal Exposure to (b) (4) After Topical Application of SB206 Gel

(b) (4)

Source: NDA submission

Based on the (b) (4) levels measured in several lots of SB206 gel and accounting for 4% of dermal bioavailability, the calculated daily (b) (4) intake levels were (b) (4) ng/day. The calculated daily (b) (4) intake levels are below the (b) (4) Acceptable Intake Limits of (b) (4) ng/day (b) (4) Based on the updated (b) (4) risk assessment, the applicant does not propose further actions. From a pharmacology/toxicology perspective, the risks related to (b) (4) are very low because (1) the clinical route of administration for SB206 gel is topical, which provides very limited systemic exposure to this impurity; and (2) the dermal mouse carcinogenicity study conducted with SB204 gel, a slightly but not significantly different formulation from SB206 gel, showed no drug-related tumor findings. The applicant's approach is acceptable from a pharmacology/toxicology perspective.

6. Clinical Pharmacology

6.1. Executive Summary

Berdazimer sodium (also known as NVN1000) is a new molecular entity (NME), and it is a topical nitric oxide (NO) releasing agent developed for the topical treatment of molluscum contagiosum (MC) in adult and pediatric patients (b) (4) of age and older. The exact mechanism of action is unknown. Berdazimer sodium gel 10.3% (SB206 Gel; ZELSUVMI) is intended for self-administration by the patient or caregiver mixed and applied topically to MC lesions. The proposed dosing regimen is to apply admixed drug product (1 g) topically as an even thin layer once daily to MC lesions for up to 12 weeks.

The Applicant has developed a SB206 (berdazimer) Gel, 10.3% ("SB206"). The drug product consists of (1) the NME berdazimer sodium (NVN1000), an NO releasing agent, contained in a white to off-white (b) (4) isopropyl alcohol gel (Tube A), and (2) a proton donating hydrogel (Tube B). Mixing the two gels releases NO. The two gel components are stored in separate, identical aluminum tubes to preserve stability of the active gel and prevent unintended loss of NO. The individual component batches are manufactured and packaged separately, and then co-packaged together in a tertiary packaging. The two gels would need to be mixed before application.

Five clinical studies have been completed with the intended to-be-marketed formulation of SB206 Gel in MC: phase 1 maximal use safety and pharmacokinetic (PK) study (NI-MC101), Phase 2 dose-ranging study (NI-MC201), three phase 3 safety and efficacy studies (NI-MC301, NI-MC302, and NI-MC304). Studies, NI-MC301 (N=352) and NI-MC302 (N=355) did not meet statistical significance for the primary efficacy endpoint; however, Study NI-MC304 (N= 891) achieved statistical significance (treatment effect of 12.8%; p< 0.0001). See Section 8 for further details. The Applicant submitted the results of a maximal use study in patients with MC (N=34). Overall, the PK results indicate that the systemic exposure is low (below lower limit of quantification (LLOQ)) of berdazimer following topical application of SB206 Gel to subjects with molluscum lesions. The applicant also submitted results of a QT Study to support clinical pharmacology information of berdazimer gel (NI-AC104).

6.2. Summary of Clinical Pharmacology Assessment

Key review findings with specific recommendations and comments are summarized in Table 14.

Table 14. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy is established based on data from two phase 3 vehicle-controlled, safety and efficacy studies (NI-MC304; N=891 and NI-MC302; N=355). See section 8.1 for efficacy trials and their results.
General dosing instructions	The proposed dosing regimen is to dispense equal amounts (0.5 mL) of gel from Tube A containing berdazimer sodium gel and Tube B containing hydrogel on the dosing guide, mix together and apply topically as an even thin layer once daily to MC lesions for up to 12 weeks. The pivotal efficacy study used a dosing regimen of approximately 2 mL of SB206 Gel (10.3% berdazimer) applied QD to between 3 and 70 treatable MC lesions at baseline for 12 weeks (mean baseline lesion count=20). See section 8.1 and 8.2 for efficacy/safety trials and their results.
Dosing in patient subgroups (intrinsic and extrinsic factors)	There are no available data in pregnant women to inform the drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. Proposed product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There is no therapeutic individualization in this application
Summary of safety	The safety of berdazimer sodium gel, 10.3% applied once daily for up to 12 weeks for the treatment of MC was assessed in a pivotal phase 3 multicenter, randomized, double-blind, parallel-group, vehicle-controlled trial (NI-MC304) and two phase 3 studies (NI-MC301 and NI-MC302). In the three clinical trials with 1596 subjects 10.6 months to 76.6 years of age, there were 1020 TEAEs in the SB206 Gel group and 265 TEAEs in the Vehicle Gel group. The most commonly reported treatment-related AEs were application site pain (19%), erythema (12 %) and pruritis (6%). Most of the TEAEs were mild (17.4% Vehicle Gel subjects, 24.0% SB206 Gel subjects) or moderate (6.9% Vehicle Gel subjects, 21.0% SB206 Gel subjects) in severity. Methemoglobin levels were assessed in the maximal use PK study (Study NI-MC101) in subjects 2 to 12 years of age. Methemoglobin results were within the acceptable normal range throughout the study. Methemoglobin levels and PK in subjects less than 2 years of age were not studied.
Bridge between to-be-marketed and clinical trial formulations	To-be-marketed gel formulation of SB206 Gel in MC was used in phase 1 maximal-use safety and pharmacokinetic (PK) study, phase 2 dose-ranging study, two supportive phase 3 safety and efficacy trials, and one pivotal phase 3 safety and efficacy trial.

6.2.1. Recommendations

From a clinical pharmacology standpoint, data submitted in this NDA is acceptable to support the approval of SB206 gel (10.3% berdazimer) for the treatment of MC in in adult and pediatric patients 2 years of age and older. The adequacy of data and benefit-risk assessment to support approval down to 1 year of age are discussed in Section 8.2.11. The CDTL and the signatories agree with these conclusions and recommendations.

6.2.2. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Per the applicant, the proposed product is a nitric oxide (NO) releasing agent (b) (4) the exact mechanism of action is unknown.

Pharmacodynamics

The pharmacodynamics of ZELSUVMI are unknown.

QT Prolongation

A QT study was conducted in patients with moderate or severe acne vulgaris (Study NI-AC104) using a higher strength product (SB204 12%), covering up to 17% BSA (approximately 33x the expected average SB206 10.3% gel application area for MC indication). SB204 12% did not increase the QTc interval to any clinically relevant extent. Refer to the Interdisciplinary Review Team for Cardiac Safety Studies QT study review for IND 137015.[2]

Pharmacokinetics

Systemic exposure of SB206 Gel 10.3% has been characterized by plasma hMAP3 (hydrolyzed N-methylaminopropyl-trimethoxysilane), a specific structural marker of the berdazimer sodium backbone), methemoglobin, and nitrate in a phase 1 maximal use trial in subjects with MC (NI-MC101; N=34; 2-12 years old). In this study, subjects received berdazimer sodium gel applied on total treatment area of 484 cm^2 (mean lesion count=34) as field treatment for the first 15 days. No subjects had quantifiable plasma hMAP3 concentrations on Day 1; two subjects had quantifiable concentrations on Day 15. Mean plasma nitrate levels were similar on Days 1 and 15 and remained relatively flat during the PK sampling period (baseline through 1-, 3-, and 6-hours post-application).

Mean lesion count at baseline in the maximal use study was 34 as compared to the mean lesion count of 20.2 in phase 3 trials (NI-MC301, NI-MC302 and NI-MC304). The field treatment area was around 484 cm^2 (~5-fold higher than 98 cm^2 treatment area in phase 3 trials). The molluscum lesions treated in the maximal use PK study were within the upper range of the disease severity as compared to the phase 3 trials.

Summary of Safety

In three double-blind, vehicle-controlled clinical trials (NI-MC304, NI-MC301 and NI-MC302), 1598 subjects were enrolled out of which 917 received treatment with the SB206 Gel.

[2] DARRTS, IND 137015, CONSULT REV-QTIRT-01 (QT-IRT Review), date 04/07/2022

Treatment was completed by 1347 (84.3%) subjects (88.5% subjects in the Vehicle Gel group and 81.1% subjects in the SB206 Gel group). There was an increase in the occurrence of TEAEs when treated with SB206 Gel as compared to vehicle. Most commonly reported TEAEs were application site pain (mostly reported as burning or stinging sensation) (approximately 19%), application site erythema (approximately 12%), and application site pruritus (approximately 6%).

Methemoglobin is a biomarker for systemic exposure of nitric oxide (NO). Methemoglobin levels were assessed in NI-MC101 (max use PK study) and in phase 2 study NI-MC201. In study NI-MC101, methemoglobin levels were between 0 to 3.2 % throughout the duration of the study. For the two subjects with quantifiable plasma hMAP3 levels during the study, methemoglobin levels remained within 5% (Subject (b) (6) and Subject (b) (6) highest level was 2.1 % and 2.2 %). Comparable results were obtained for age groups 2-5 years and 6 years and older, however, there were no patients under 2-year-old enrolled in the study. Similarly, methemoglobin levels ranged from 0- to 3.2 % in study NI-MC201 in patients 2 to 62 years old.

6.2.3. General Dosing and Therapeutic Individualization

General Dosing

The dose used in phase 3 pivotal study was up to approximately 2 mL of SB206 Gel QD (between three and 70 treatable MC lesions at baseline) with a primary endpoint of complete clearance of MC lesions (defined as 0 lesions) at Week 12. dosing instructions The proposed dosing regimen is to dispense equal amounts (0.5 mL) of gel from Tube A containing berdazimer sodium gel and Tube B containing hydrogel on the dosing guide, mix together and apply topically as an even thin layer once daily to MC lesions for up to 12 weeks. The efficacy results in phase 3 trial overall support the acceptability of the proposed dosing regimen.

Therapeutic Individualization

There is no therapeutic individualization in this application because it is administered locally as topical gel with low systemic exposure.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this application from a Clinical pharmacology perspective. The considerations and recommendation to approve this product below the age of 2 years are discussed in Section 8.2.11.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, PK, and PD characteristics of berdazimer are summarized in Table 15.

Table 15. Summary of Clinical Pharmacology, Pharmacokinetics and Pharmacodynamics of Berdazimer

General Information	Characteristics
Bioanalysis	hMAP3 and nitrate ion concentrations in human plasma were quantified using high performance LC/MS/MS assays with sensitivity up to 5 ng/mL and 300 ng/mL, respectively. See section 19.4 for details of the method validation.
Exposure Response Analysis	No exposure response analysis was conducted as this is a topical product which is applied directly to the target site (skin). The systemic exposure in this case would inform only the systemic safety of this product and not efficacy.
Dose Proportionality	No studies were done to assess dose proportionality.
ADME	
Absorption	In the maximal use pharmacokinetic study (MUsT) in 34 subjects with MC, no subject had quantifiable concentrations of hMAP3 at any timepoint on Day 1, while 2 subjects had quantifiable concentrations on Day 15 (Cmax was 5.12 and 33.9 ng/mL; AUC was not calculated for one subject and AUC 0-3 was 75.5 h.ng/mL for the other). Tmax was around 2 h. There were no apparent differences in nitrate PK during the treatment.
Distribution	No distribution studies have been conducted. The plasma protein binding in human plasma was not determined.
Elimination	
Metabolism	No studies evaluating metabolism were conducted.
Excretion	No excretion studies have been conducted.
Drug-Drug Interaction	No drug-drug interactions (DDI) studies have been conducted. Due to low systemic exposure, the DDI studies are not deemed necessary.
Pediatric Subjects	Pediatric patients aged 6 months old or greater were enrolled in the pivotal phase 3 study.

Abbreviations: AUC, area under the curve to infinity; C_{max}, maximum concentration; T_{max}, time of C_{max}; LC/MS/MS, liquid chromatography with tandem mass spectrometry

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes. The overall efficacy data provide evidence that SB206 Gel is effective for the treatment of molluscum contagiosum. See Section 8 of this multi-discipline review for details of the study design and efficacy results of the Phase 3 trials.

Berdazimer is a topical gel for the treatment of MC which is directly applied to the target site (lesions on the skin). Therefore, the systemic exposure is not expected to inform the treatment effect and thus does not provide pivotal or supportive evidence for the effectiveness of berdazimer. The systemic exposure will inform the systemic safety of this product. In the Phase I MuST conducted in patients with MC, low systemic levels of hMAP3 were observed (4% of

samples had levels > LLOQ), while nitrate levels remained unchanged through the dosing period.

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Yes. The dose used in phase 3 pivotal study was up to approximately 2 mL of SB206 Gel QD (between three and 70 treatable MC lesions at baseline) with a primary endpoint of complete clearance of MC lesions (defined as 0 lesions) at Week 12. The efficacy results in phase 3 trial overall support the acceptability of the dosing regimen. See Section 8 for further details.

(b) (4) Across the three clinical studies (NI-MC301, NI-MC302 and NI-MC304), there was only 1 patient less than 1 year old and 44 patients out of 1596 who were between the age 1- 2-year-old. In the PK study NI-MC101, there were no patients enrolled under 2 years of age. Therefore, there is no PK and methemoglobin assessment in patients under 2 years of age. (b) (4) the indication will be revised to include patients who are 1 year old and older.

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 berdazimer is a topical gel. The applicant has not assessed drug interaction potential. Drug interaction assessment is not needed due to limited systemic absorption.

Refer to Individual Study Review in OCP appendices 16.5 for more details.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant conducted three (3) multicenter, randomized (R), double-blind (DB), vehicle-controlled (VC), parallel-group, Phase 3 clinical trials (NI-MC301, NI-MC302, and NI-MC304) of the efficacy and safety of SB206 (berdazimer) gel, 10.3% QD in subjects ≥6-months of age with 3 to 70 MC lesions at baseline, as presented in Table 16.

Table 16. Listing of Clinical Trials Relevant to NDA 217424

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
NI-MC301	NCT 03927716	R (2:1), DB, VC	SB206 gel, 10.3% or vehicle gel QD treatment x 12 weeks. DB, Observational safety follow-up x 12 weeks.	Primary: Proportion of subjects with complete clearance of all treatable MC lesions at Week 12 Secondary: Proportion of subjects with complete clearance of all treatable MC lesions at Week 8	Treatment period (Weeks 0-12). Safety follow-up (Weeks 12-24).	N=352	Male and female patients ≥ 6 months of age, with between 3 and 70 MC lesions (inclusive), at baseline	33 sites in the US
NI-MC302	NCT 03927703	R (2:1), DB, VC	Same as in -301	Same as in -301	Same as in -301	N=355	Same as in -301	33 sites in the US
NI-MC304	NCT 04535531	R (1:1), DB, VC	Same as in -301	Same as in -301. Additional secondary endpoints: Proportion of subjects achieving at least a 90% reduction from baseline in the number of all treatable MC lesions at W 12 Percent change from baseline (%CFB) in the number of all treatable MC lesions at W 4	Same as in -301	N=891	Same as in -301	55 sites in the US

Source: Clinical Overview (M 2.5), Table 1.

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of berdazimer gel, 10.3% included the Applicant's CSRs, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model (SDTM) and analysis datasets (ADaM) were submitted (LNHC 2023).

Data and Analysis Quality

A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS) on 2/6/2023. The OCS Clinical Services team performed exploratory safety analysis and data fitness analysis for trials NI-MC301, NI-MC302, NI-MC304, and the ISS for this NDA and found the data quality acceptable. In collaboration with the OCS Clinical Services team, the Statistical and Clinical reviewers held the following meetings:

- 1/25/2023 Annotated Core DF assessment
- 2/17/2023 ISS overview assessment
- 2/13/2023 SDTM to ADaM traceability assessment
- 2/15/2023 ISS traceability assessment
- 2/21/2023 Exploratory safety analysis bundles assessment

Assessments evaluated the data fitness, whether certain common analyses could be performed, and other data quality metrics including:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata

In general, the data submitted by the Applicant to support the efficacy and safety of berdazimer gel for the proposed indication appeared adequate.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies NI-MC301, NI-MC302, and NI-MC304

Trial Design

The Applicant conducted three multicenter, randomized, double-blind, vehicle controlled, Phase 3 trials (NI-MC301, NI-MC302, and NI-MC304) to evaluate the efficacy and safety of SB206 (berdazimer gel, 10.3%) in subjects with MC. The first two Phase 3 trials (NI-MC301 and NI-MC302) were conducted concurrently and followed the same trial design. The third Phase 3 trial (NI-MC304) generally followed the same study protocol as the first two except that the randomization schema and stratification factors of the third trial were different and which were adjusted based on the outcomes of the first two trials. The main differences between the third and the first two trials are as follows:

- For the first two trials (NI-MC301 and NI-MC302), eligible subjects were randomized in a 2:1 ratio to either SB206 or vehicle. For the third trial (NI-MC304), the randomization ratio was 1:1.
- For the first two trials (NI-MC301 and NI-MC302), randomization was stratified by investigator type (i.e., dermatologist versus other) and number of randomized subjects per household (i.e., 1 subject per household versus 2 subjects per household). For the third trial (NI-MC304), besides investigator type and number of randomized subjects per household, randomization was additionally stratified by the subject's "Beginning-of-the-End" (BOTE) score at baseline (i.e., no inflammation [BOTE = 0] vs. mild to very severe inflammation [BOTE ≥ 1]). In particular, subjects were stratified to 5 strata first by subjects per household. Subjects from 1-subject households were stratified by investigator type and baseline BOTE score. Subjects from 2-subject households were not further stratified with respect to investigator type and baseline BOTE score because the overall sample size that was expected for the stratum for households with 2 subjects was not large enough to support further stratification.

In all three trials, households randomizing 2 subjects received the same treatment assignment for both subjects.

Subjects or their caregivers applied treatment (SB206 or vehicle) once daily for a minimum of 4 weeks and up to 12 weeks to all active lesions identified at baseline and new lesions that arose during treatment. Subjects or their caregivers continued treating the area until the next scheduled visit even if the lesion(s) cleared. At Weeks 2, 4, 8, and 12, the investigator counted and recorded the number of active (raised, treatable) MC lesions per body area. If the investigator determined all lesions were cleared at a clinic visit, the treatment was stopped. If treatment was stopped due to clearance before Week 12, subjects continued regularly scheduled visits through Week 24. Study drug was dispensed through the Week 8 visit in case of

lesion recurrence between study visits. Prior to Week 12, if lesions recurred or new lesions appeared after the subject had cleared, treatment should have been resumed. No further treatment occurred after Week 12.

Subjects had clinic visits at screening/baseline and Weeks 2, 4, 8, 12, and 24. Subjects were also contacted via phone on Day 2 (to collect subject information on early dose reactions) and at Weeks 16 and 20 (to capture information regarding MC recurrence and AEs). For Study NI-MC304 that was conducted during COVID-19 pandemic, the subjects/caregivers were instructed on the technology to be used for remote visits during the baseline visit. The Week 4 visit may have been performed remotely or in clinic. Baseline, Week 2, Week 8, 12, and 24 visits should have been performed in clinic wherever possible. If a subject terminated early, an in-clinic visit was preferred, but a remote visit may have been performed with Applicant approval.

Study Endpoints

For all three studies, the primary efficacy endpoint was the proportion of subjects with complete clearance of all treatable MC at Week 12. Complete clearance was defined as having a total number of lesion count of 0 at assessment.

For Studies NI-MC301 and NI-MC302, the protocol specified one secondary efficacy endpoint, the proportion of subjects with complete clearance of all treatable MC at Week 8.

For Study NI-MC304, the protocol specified the following four secondary efficacy endpoints:

1. Proportion of subjects achieving a lesion count of 0 or 1 of all treatable MC at Week 12
2. Proportion of subjects achieving at least a 90% reduction from baseline in the number of all treatable MC at Week 12
3. Proportion of subjects with complete clearance of all treatable MC at Week 8
4. Percent change from baseline in the number of all treatable MC at Week 4

Statistical Reviewer's Comment: *In the written response to the Applicant's Type C meeting request submitted on September 17, 2021 (IND 137015), the Agency reiterated that secondary endpoints based on partial clearance of MC lesions are not considered clinically meaningful and would not be accepted for labeling claims. The Agency also noted that the endpoint of percent change from baseline in the number of all treatable MC at Week 4 may be not clinically meaningful for assessing efficacy, and thus claims based on findings from such endpoint are not expected to be included in the label. In this review, the statistical reviewer only analyzed the key secondary efficacy endpoint, the proportion of subjects with complete clearance of all treatable MC at Week 8, which is included in labeling.*

Statistical Analysis Plan

Analysis Populations

The SAP in the three studies defined the intent-to treat (ITT) population as all subjects who were randomized (Study NI-MC304 only: and had a signed informed consent or assent as

applicable), and the per-protocol (PP) population as all subjects in the ITT population who had no significant protocol deviations that impacted the analyses of efficacy endpoints. Treatment assignment was based on the randomized treatment.

The SAPs stated that the primary efficacy analysis was based on the ITT population, and additional supportive efficacy analyses were performed using the PP population.

Efficacy Analyses

The SAPs specified that the primary endpoint was analyzed using a generalized estimating equation (GEE) model for logistic regression with an exchangeable working correlation structure to account for the correlated subjects per household.

For Studies NI-MC301 and NI-MC302, the model for the primary efficacy included adjustments for the following covariates: investigator type (dermatologist vs. other), household number of randomized subjects (1 subject per household vs. 2 subjects per household), age (as a continuous variable), and baseline lesion count.

For Study NI-MC304, the model for the primary efficacy included adjustments for the following covariates: investigator type (dermatologist vs. other), household number of randomized subjects (1 subject per household vs. 2 subjects per household), baseline BOTE score (no inflammation [BOTE = 0] vs. mild to very severe inflammation [BOTE ≥ 1]), age (as a categorical variable: 0 to < 3, 3 to < 4, 4 to < 5, 5 to < 6, 6 to < 7, 7 to < 8, 8 to < 9, 9 to < 12, and 12+ years old), and baseline lesion count.

If there were not at least 3 responders and non-responders at each level of the stratification factors, then that stratification factor was removed from the model. If there were fewer than 10 responders/non-responders, then no stratification factor was included in the model.

The odds ratio between SB206 and vehicle, 95% confidence interval (CI) for the odds ratio, and p-value for the covariate-adjusted treatment comparison was presented, together with predicted proportions along with their associated 95% CI. The SAPs specified that the difference in proportion CI was calculated using the following formula:

Equation 2. Calculation of Difference in Proportion CI

$$(p_{SB206} - p_{Vehicle}) \pm z_{0.025} \cdot SE$$

Where $SE =$

$$\sqrt{\begin{array}{c} p^2{}_{SB206}(1-p_{SB206})^2 s^2{}_{SB206} + p^2{}_{Vehicle}(1-p_{Vehicle})^2 s^2{}_{Vehicle} \\ -2p_{SB206}(1-p_{SB206})p_{Vehicle}(1-p_{Vehicle})\left(\frac{s^2{}_{SB206} + s^2{}_{Vehicle} - s^2{}_{Odds\ Ratio}}{2}\right) \end{array}}$$

Source: Applicant's SAP [NI-MC304 SAP Version 2: page 22].
Note: The p_{SB206} and $p_{Vehicle}$ are the transformed predicted log odds at the mean of the covariates, s^2_{SB206} and $s^2_{Vehicle}$ are the standard errors of the predicted log odds for the two treatment groups and $s^2_{Odds\ Ratio}$ is the standard error of the odds ratio.
Abbreviations: CI, confidence interval; SAP, statistical analysis plan; SE, standard error

Statistical Reviewer's Comment:

- *In the IND 137015 Type B meeting (dated April 4, 2022), the Agency recommended the Applicant assess the population level summary of the difference in response rates (for the primary endpoint) at Week 12 between the treatment arms. The Agency stated that treatment effect as assessed by the difference in the response rates is easier to interpret and, consequently, is preferred for presentation in labeling.*
- *There is a typo in the Applicant's formula above for the 95% CI for the treatment difference with respect to the calculation of SE, i.e., $s^2_{Odds\ Ratio}$ should be corrected to $s^2_{Log\ Odds\ Ratio}$, which represents the standard error of the log odds ratio.*
- *In the Applicant's SAS code for calculating the 95% CI for the treatment difference, they used a wrong standard error for each treatment arm, i.e., they used the standard error of the predicted proportion rather than the standard error of the predicted log odds. The statistical reviewer corrected this error, which leads to minor differences in the statistical reviewer's results compared to the Applicant's results in three studies. The Applicant acknowledged this error in the labeling communication with the Agency, and the corrected results are included in labeling.*
- *Age was used as a continuous variable in Studies NI-MC301 and NI-MC302, but as a 9-level categorical variable in Study NI-MC304 in the statistical model. For Study NI-MC304, the statistical reviewer validated the results of the Applicant's model (with age as a 9-level categorical variable) by using age as a continuous variable and the study conclusion did not change.*

Multiplicity

The SAPs specified that the secondary endpoint(s) was/were analyzed in the same manner as the primary endpoint, and the familywise error rate with respect to the primary endpoint and secondary endpoint(s) was controlled at the alpha = 0.05 using a fixed-sequence method testing strategy. If the primary endpoint was not statistically significant at the alpha = 0.05 level, the secondary endpoint(s) was/were considered not significant. If the primary endpoint was statistically significant at the alpha = 0.05 level, then the secondary endpoint(s) was/were analyzed. For Study NI-MC304, the four secondary endpoints were tested in a hierarchical order as listed in the Study Endpoints section.

Statistical Reviewer's Comment: *The fixed-sequence method testing strategy is reasonable, but as discussed in the Study Endpoints section, only the key secondary endpoint, the proportion of subjects with complete clearance of all treatable MC at Week 8, was analyzed in this review for all three studies.*

Handling of Missing Data and Sensitivity Analyses

The primary method for handling of missing data was a non-responder imputation, that is, subjects with missing Week 12 lesion count data were counted as non-responders.

The Applicant conducted the following sensitivity analyses for the primary endpoint, most of which were conducted to evaluate alternative methods for handling of missing data. For

Studies NI-MC301 and NI-MC302, sensitivity analyses 1–4 were specified in SAP and sensitivity analyses 5–6 were post hoc analyses. For Study NI-MC304, all the following sensitivity analyses were specified in SAP. In this review, commonly used sensitivity analyses (Sensitivity Analyses 1, 2, 4, and 5) are reported.

1. Sensitivity analysis using the PP population
2. Sensitivity analysis where subjects with missing MC lesion count at Week 12 but who demonstrated complete clearance at the last collected lesion assessment were counted as responders, and other subjects with missing lesion count at Week 12 were counted as non-responders
3. Dropout sensitivity analysis where the complete clearance response probability for each dropout prior to Week 12 was independently generated under varying combinations of response probability in vehicle and SB206 (vehicle response probability, SB206 response probability) is described in Table 17.

Table 17. Complete Clearance Response Probability for Study Dropouts

(0.1, 0.1)	(0.1, 0.0)			
(0.2, 0.2)	(0.2, 0.1)	(0.2, 0.0)		
(0.3, 0.3)	(0.3, 0.2)	(0.3, 0.1)	(0.3, 0.0)	
(0.4, 0.4)	(0.4, 0.3)	(0.4, 0.2)	(0.4, 0.1)	(0.4, 0.0)

Source: Applicant's SAP [NI-MC304 SAP Version 2: page 23].

4. Sensitivity analysis using a logistic regression model in a subset of the ITT population where only 1 subject from each household was chosen to contribute to the model based on the subject with the highest number of baseline treatable MC, and the oldest to break ties, if needed
5. Sensitivity analysis using multiple imputation (MI) where subjects with a missing lesion count at Week 12 were imputed using a monotone imputation model
6. Subject reported response sensitivity analysis where "Lost to Follow-Up" subjects with missing lesion count at Week 12 who responded as having "Resolved (no lesions left)" or "Resolving (number of lesions decreasing)" patient reported outcome (PRO) of MC disease status at the end of their study participation were counted as responders, and other subjects with missing lesion count at Week 12 were counted as non-responders

Statistical Reviewer's Comment:

- *For the handling of missing data, although the SAPs specified a sensitivity analysis by counting subjects who had missing lesion count at Week 12 but demonstrated complete clearance at the last collected lesion assessment as responders, the Applicant did not fully follow this method as specified in their SAS code. According to their SAS code, they counted subjects who had missing lesion count at Week 12 but had achieved complete clearance at any time prior to Week 12 as responders. For example, if a subject achieved complete clearance at Week 4 and then relapsed at Week 8 and had missing lesion count at Week 12, that subject was also counted as a responder in their sensitivity analysis.*

Considering that a subject could still relapse after complete clearance, the statistical reviewer conducted a sensitivity analysis by counting subjects with missing MC lesion count at Week 12 but who demonstrated complete clearance at Week 8 as responders, and other subjects with missing lesion count at Week 12 as non-responders.

- *For the handling of missing data, the statistical reviewer conducted an additional sensitivity analysis using the observed data only.*
- *Study NI-MC304 allowed for different manners of lesion assessment (in-clinic vs. remote). In order to assess the impact of remote assessment on the primary endpoint, the statistical reviewer conducted a sensitivity analysis for Study NI-MC304 where the worst-case imputation was performed for subjects who had a remote assessment at Week 12, i.e., a non-responder imputation was performed for subjects in the SB206 arm with a remote Week 12 visit, and a responder imputation for those in the vehicle arm with a remote Week 12 visit.*
- *The Applicant stated that the baseline BOTE score may have an impact on the observed efficacy based on their post hoc sensitivity analyses for Studies NI-MC301 and NI-MC302. For Study NI-MC304, baseline BOTE status was one stratification factor in stratified randomization and was adjusted in the statistical model. Considering that Studies NI-MC301 and NI-MC302 were not stratified by baseline BOTE score, slight imbalance may have occurred between treatment arms in baseline BOTE status. In order to assess its impact on the primary endpoint, the statistical reviewer conducted a sensitivity analysis by additionally adjusting for baseline BOTE score for Studies NI-MC301 and NI-MC302, as for Study NI-MC304.*
- *The primary efficacy endpoint of complete clearance rate at Week 12 is considered inherently clinically meaningful. However, a binary endpoint is not as powerful as a continuous endpoint. The statistical reviewer conducted exploratory analyses based on the continuous endpoint, e.g., change from baseline in the number of all treatable MC at Week 12, or percent change from baseline in the number of all treatable MC at Week 12. For the continuous endpoint, MI or mixed model repeated measures (MMRM) was used to handle the missing data.*
- *To summarize, the statistical reviewer conducted four additional sensitivity analyses for the primary endpoint, the proportion of subjects with complete clearance of all treatable MC at Week 12, as below:*

1. *Subjects with missing MC lesion count at Week 12 but who demonstrated complete clearance at Week 8 were counted as responders, and other subjects with missing lesion count at Week 12 were counted as non-responders*
2. *Using the observed data only*

3. *Worst-case imputation for remote assessments for Study NI-MC304: a non-responder imputation was performed for subjects in the SB206 arm with a remote Week 12 visit, and a responder imputation for those in the vehicle arm with a remote Week 12 visit*
4. *Sensitivity analysis by additionally adjusting for baseline BOTE score for Studies NI-MC301 and NI-MC302*

In addition, the statistical reviewer conducted four more exploratory analyses based on the continuous endpoint, as listed below:

1. *Exploratory analysis of change from baseline in lesion count at Week 12 using MI*
2. *Exploratory analysis of percent change from baseline in lesion count at Week 12 using MI*
3. *Exploratory analysis of change from baseline in lesion count at Week 12 using MMRM*
4. *Exploratory analysis of percent change from baseline in lesion count at Week 12 using MMRM*

Protocol Amendments

For Studies NI-MC301 and NI-MC302, there were no protocol amendments during the study; however, an administrative letter was sent to the sites to clarify the definition of a scar on July 16, 2019. In the original protocol, only scars larger than 5 mm in diameter and/or >1 mm deep were considered reportable AEs because scars smaller than this are considered part of the normal healing process. The administrative letter instructed sites to capture all scars as AEs, regardless of size.

For Study NI-MC304, there were two protocol amendments. The first protocol amendment (version 2.0, dated July 15, 2020) was implemented to correct language regarding documenting AEs from 'related SAEs' to 'all SAEs' to align with regulations, to add questionnaire language to certain efficacy assessments (Investigator Global Severity Assessment, Subject Global Severity Assessment, Investigator Global Impression of Change, and Subject Global Impression of Change) to enhance clarity, and to make clarifying changes to the Schedule of Assessments. The second protocol amendment (version 3.0, dated September 30, 2020) was implemented to increase the sample size to approximately 850 patients and to permit remote or in-clinic visits at Week 4 and in-clinic visits at Week 8. Amendment version 2.0 was implemented prior to the initiation of the study on September 1, 2020. Amendment version 3.0 was implemented shortly after that date.

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant attested that the submitted clinical studies were conducted in accordance with Good Clinical Practice (GCP) as required by Food and Drug Administration regulations, International Council for Harmonisation (ICH) guidelines, and standard operating procedures (SOPs) for clinical investigation and documentation provided by the Applicant and contract

research organization (CRO). Compliance with these requirements also indicates conformity with the ethical principles that have their origins in the Declaration of Helsinki.

Financial Disclosure

Refer to Appendix 16.2.

Patient Disposition

Table 18 presents a summary of the subject disposition. Study NI-MC301 randomized a total of 352 subjects, 236 to SB206 and 116 to vehicle, from 33 centers. Study NI-MC302 randomized a total of 355 subjects, 237 to SB206 and 118 to vehicle, from 33 centers. Study NI-MC304 randomized a total of 891 subjects, 444 to SB206 and 447 to vehicle, from 55 centers. All centers were in the United States. The 1598 randomized subjects were all included in the ITT population, of which 1596 received at least one application of study treatment.

Across three studies, approximately 84–89% of subjects in the SB206 arm and 88–97% of subjects in the vehicle arm completed 12 weeks of study, and approximately 81–85% of subjects in the SB206 arm and 84–91% of subjects in the vehicle arm completed the entire study. In Study NI-MC301, a higher proportion of subjects discontinued in the SB206 arm (15.3%) than in the vehicle arm (3.4%) before Week 12. In Study NI-MC302, a slightly higher proportion of subjects discontinued in SB206 (15.6%) than in vehicle (11.9%) before Week 12. In Study NI-MC304, the proportion of discontinuations was similar in the two treatment arms. The most common reasons for discontinuation were lost to follow-up and withdrawn consent/assent.

Table 18. Subject Disposition (Studies NI-MC301, NI-MC302, and NI-MC304)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Subject	SB206 N=236	Vehicle N=116	SB206 N=237	Vehicle N=118	SB206 N=444	Vehicle N=447
ITT population	236	116	237	118	444	447
Received treatment	235 (99.6)	116 (100)	237 (100)	117 (99.2)	444 (100)	447 (100)
Completed 12 weeks of study (EOT)	200 (84.7)	112 (96.6)	200 (84.4)	104 (88.1)	394 (88.7)	400 (89.5)
Prematurely discontinued before Week 12	36 (15.3)	4 (3.4)	37 (15.6)	14 (11.9)	50 (11.3)	47 (10.5)
Completed study (24 weeks)	192 (81.4)	106 (91.4)	192 (81.0)	102 (86.4)	377 (84.9)	377 (84.3)
Prematurely discontinued	44 (18.6)	10 (8.6)	45 (19.0)	16 (13.6)	67 (15.1)	70 (15.7)

Subject	Study NI-MC301		Study NI-MC302		Study NI-MC304	
	SB206 N=236	Vehicle N=116	SB206 N=237	Vehicle N=118	SB206 N=444	Vehicle N=447
Primary Reason for Discontinuation Prior to Week 12						
Lost to follow-up	13 (5.5)	2 (1.7)	13 (5.5)	9 (7.6)	29 (6.5)	31 (6.9)
Withdrawn consent/assent	21 (8.9)	2 (1.7)	21 (8.9)	5 (4.2)	16 (3.6)	13 (2.9)
Adverse event	--	--	--	--	5 (1.1)	3 (0.7)
Other	2 (0.8)	--	3 (1.3)	--	--	--
Primary Reason for Study Discontinuation						
Lost to follow-up	16 (6.8)	4 (3.4)	17 (7.2)	10 (8.5)	43 (9.7)	46 (10.3)
Withdrawn consent/assent	26 (11.0)	4 (3.4)	25 (10.5)	6 (5.1)	19 (4.3)	21 (4.7)
Adverse event	--	--	--	--	5 (1.1)	3 (0.7)
Other	2 (0.8)	2 (1.7)	3 (1.3)	--	--	--

Source: reviewer analysis
Abbreviations: ITT, intent-to-treat; EOT, end of treatment
Percentages were calculated using the number of subjects randomized as the denominator.

Protocol Violations/Deviations

Table 19 presents a summary of the PP population and significant protocol deviations. Across three studies, approximately 81–88% of subjects in the SB206 arm and 87–92% of subjects in the vehicle arm were included in the PP population. In Studies NI-MC301 and NI-MC302, a higher proportion of subjects were excluded from the PP population in the SB206 arm than in the vehicle arm. In Study NI-MC304, the proportion of exclusions was similar in both treatment arms. The most common reason for exclusion from the PP population was Week 12 lesion count not performed. The significant protocol deviations that led to exclusion from the PP population included investigational medicinal product, GCP deviation, prohibited concomitant medication, inclusion/exclusion criteria and missed subject visit.

Table 19. PP Population (Studies NI-MC301, NI-MC302, and NI-MC304)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Subject	SB206 N=236	Vehicle N=116	SB206 N=237	Vehicle N=118	SB206 N=444	Vehicle N=447
PP population	192 (81.4)	107 (92.2)	194 (81.9)	103 (87.3)	389 (87.6)	396 (88.6)
Excluded from PP population	44 (18.6)	9 (7.8)	43 (18.1)	15 (12.7)	55 (12.4)	51 (11.4)
Primary Reason for Exclusion From the PP Population						
Significant deviation: investigational medicinal product	6 (2.5)	4 (3.4)	1 (0.4)	--	1 (0.2)	--
Significant deviation: GCP deviation	--	1 (0.9)	4 (1.7)	--	--	1 (0.2)
Significant deviation: prohibited concomitant medication	--	--	--	--	2 (0.5)	--
Significant deviation: Inclusion/Exclusion criteria	--	--	--	--	1 (0.2)	--
Significant deviation: missed subject visit & Week 12 lesion count not performed	3 (1.3)	--	1 (0.4)	1 (0.8)	--	1 (0.2)
Week 12 lesion count not performed	34 (14.4)	4 (3.4)	37 (15.6)	13 (11.0)	51 (11.5)	49 (11.0)
Didn't receive at least one application of study treatment	1 (0.4)	--	--	1 (0.8)	--	--

Source: reviewer analysis
Abbreviations: GCP, good clinical practice PP, per-protocol
Percentages were calculated using the number of subjects randomized as the denominator.

Table of Demographic Characteristics

Demographic characteristics of the ITT population are summarized in Table 20. Most of the subjects were between 2 and less than 12 years of age. There were 21 adult subjects in three studies and 1 subject (in Study NI-MC304) under 1 year of age. The proportion of subjects in the 6–12 year age group was similar across three studies. The proportion of subjects ≥ 12 years of age was slightly higher in Study NI-MC301 than in the other two studies. The majority of subjects were white and not Hispanic or Latino. Demographic characteristics were generally balanced between treatment groups among the three studies.

Table 20. Demographic Characteristics (Studies NI-MC301, NI-MC302, and NI-MC304; ITT)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Characteristic	**SB206 N=236**	**Vehicle N=116**	**SB206 N=237**	**Vehicle N=118**	**SB206 N=444**	**Vehicle N=447**
Age, Years						
Mean (SD)	7.3 (6.19)	6.7 (3.96)	6.3 (2.85)	6.8 (4.78)	6.6 (4.50)	6.5 (4.34)
Median	6.5	5.8	6.0	5.8	5.6	6.0
Min, Max	1.0, 76.6	1.6, 29.2	1.1, 17.3	1.2, 48.0	0.9, 47.5	1.3, 49.0
Age Categories, n (%)						
0 to < 1 year	0	0	0	0	1 (0.2)	0
1 to < 2 years	8 (3.4)	1 (0.9)	5 (2.1)	3 (2.5)	15 (3.4)	12 (2.7)
2 to < 6 years	99 (41.9)	59 (50.9)	116 (48.9)	61 (51.7)	220 (49.5)	213 (47.7)
6 to < 12 years	106 (44.9)	47 (40.5)	108 (45.6)	46 (39.0)	178 (40.1)	201 (45.0)
12 to < 18 years	17 (7.2)	7 (6.0)	8 (3.4)	7 (5.9)	24 (5.4)	15 (3.4)
≥ 18 years	6 (2.5)	2 (1.7)	0	1 (0.8)	6 (1.4)	6 (1.3)
Sex, n (%)						
Female	119 (50.4)	49 (42.2)	110 (46.4)	62 (52.5)	216 (48.6)	234 (52.3)
Male	117 (49.6)	67 (57.8)	127 (53.6)	56 (47.5)	228 (51.4)	213 (47.7)
Race, n (%)						
White	207 (87.7)	100 (86.2)	221 (93.2)	105 (89.0)	387 (87.2)	382 (85.5)
Black or African American	17 (7.2)	10 (8.6)	9 (3.8)	5 (4.2)	21 (4.7)	28 (6.3)
Asian	2 (0.8)	2 (1.7)	0	1 (0.8)	6 (1.4)	6 (1.3)
Am. Ind. or AK Native	0	0	0	0	2 (0.5)	2 (0.4)
Native HI or Pac. Isl.	0	0	1 (0.4)	1 (0.8)	4 (0.9)	2 (0.4)
More than one race	10 (4.2)	3 (2.6)	3 (1.3)	6 (5.1)	13 (2.9)	13 (2.9)
Not reported	0	1 (0.9)	3 (1.3)	0	11 (2.5)	14 (3.1)
Ethnicity, n (%)						
Not Hispanic or Latino	167 (70.8)	83 (71.6)	202 (85.2)	97 (82.2)	345 (77.7)	357 (79.9)
Hispanic or Latino	69 (29.2)	33 (28.4)	32 (13.5)	21 (17.8)	94 (21.2)	87 (19.5)
Not reported	0	0	3 (1.3)	0	4 (0.9)	1 (0.2)
Unknown	0	0	0	0	1 (0.2)	2 (0.4)

Source: Reviewer analysis
Abbreviations: AK, Alaska; Am. Ind., American Indian; HI, Hawaiian; ITT, intent-to-treat, Pac. Isl., Pacific Islander; SD, standard deviation

Other Baseline Characteristics

Baseline disease characteristics of the ITT population are summarized in Table 21. The average MC lesion count at baseline was 18.1 in Study NI-MC301, 18.3 in Study NI-MC302, and 21.8 in Study NI-MC304. The average baseline lesion count was similar between treatment groups in Studies NI-MC301 and NI-MC302, but slightly higher in the SB206 arm (23.1) than in the vehicle arm (20.5) in Study NI-MC304. A higher proportion of subjects in Study NI-MC304 had ≥ 20 lesions at baseline compared with the other two studies. The mean time since onset of

symptoms of the current episode was 10.3 months in Study NI-MC301, 9.8 months in Study NI-MC302, and 12.5 months in Study NI-MC304. A higher proportion of subjects in Study NI-MC301 had a current MC episode of ≤ 6 months compared with the other two studies. The majority of subjects had no AD/eczema history.

Table 21. Baseline Disease Characteristics (Studies NI-MC301, NI-MC302, and NI-MC304; ITT)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Characteristic	**SB206 N=236**	**Vehicle N=116**	**SB206 N=237**	**Vehicle N=118**	**SB206 N=444**	**Vehicle N=447**
Baseline Lesion Count						
Mean	17.9	18.6	18.9	17.1	23.1	20.5
SD	13.91	15.41	14.46	12.78	17.60	16.18
Median	13.0	13.0	15.0	13.0	18.5	15.0
Min, Max	3, 70	3, 68	3, 70	3, 68	3, 70	3, 69
Baseline Lesion Count Categories, n (%)						
0 to < 20 lesions	154 (65.3)	79 (68.1)	144 (60.8)	78 (66.1)	229 (51.6)	267 (59.7)
≥ 20 lesions	82 (34.7)	37 (31.9)	93 (39.2)	40 (33.9)	215 (48.4)	180 (40.3)
Age at Onset of Symptoms of Current Episode, Years						
Mean	6.4	5.9	5.5	6.0	5.6	5.5
SD	6.25	3.84	2.95	4.82	4.48	4.02
Median	5.5	5.1	4.9	5.1	4.8	4.9
Min, Max	0.2, 76.2	0.2, 23.9	0.1, 16.3	0.8, 47.5	0.2, 46.9	0.0, 37.3
Time Since Onset of Symptoms of Current Episode, Months						
Mean	10.2	10.6	9.9	9.7	12.0	13.1
SD	11.81	10.86	8.55	6.91	12.81	15.47
Median	6.5	6.7	7.0	8.0	8.4	8.6
Min, Max	0.03, 100.8	0.3, 63.1	0.03, 56.8	0.5, 42.7	0.2, 153.3	0.03, 192.8
Time Since Onset of Symptoms Categories, n (%)						
0 to ≤ 6 months	104 (44.1)	52 (44.8)	85 (35.9)	37 (31.4)	144 (32.4)	147 (32.9)
> 6 months	132 (55.9)	64 (55.2)	152 (64.1)	81 (68.6)	300 (67.6)	300 (67.1)
AD Medical History, n (%)						
AD/eczema	29 (12.3)	12 (10.3)	29 (12.2)	16 (13.6)	67 (15.1)	56 (12.5)
No AD/eczema	207 (87.7)	104 (89.7)	208 (87.8)	102 (86.4)	377 (84.9)	391 (87.5)

Source: Reviewer analysis
Abbreviations: AD, atopic dermatitis; ITT, intent-to-treat; SD, standard deviation

Baseline stratification factors of the ITT population are summarized in Table 22. The majority of subjects were from 1-subject household. The proportion of subjects from 2-subject household was higher in Study NI-MC301 (23.3%) and Study NI-MC302 (18.6%) than in Study NI-MC304 (9.2%). The investigator type was generally balanced between treatment groups among the three studies. A higher proportion of subjects in Study NI-MC304 (49.8%) had a mild to very severe baseline BOTE score compared with Study NI-MC301 (33.2%) and Study NI-MC302 (36.3%). The proportion of subjects with a mild to very severe baseline BOTE score was

balanced between treatment groups in Studies NI-MC302 and NI-MC304, but slightly higher in the vehicle arm (38.8%) than in the SB206 arm (30.5%) in Study NI-MC301.

Table 22. Baseline Stratification Factors (Studies NI-MC301, NI-MC302, and NI-MC304; ITT)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Stratification Factor	**SB206 N=236**	**Vehicle N=116**	**SB206 N=237**	**Vehicle N=118**	**SB206 N=444**	**Vehicle N=447**
Number of Subjects Randomized per Household, n (%)						
1-subject household	181 (76.7)	89 (76.7)	193 (81.4)	96 (81.4)	403 (90.8)	406 (90.8)
2-subject household	55 (23.3)	27 (23.3)	44 (18.6)	22 (18.6)	41 (9.2)	41 (9.2)
Number of Households, n						
1-subject household	179	88	193	96	403	406
2-subject household	29	13	22	11	21	22
3-subject household*	1	0	0	0	0	0
Investigator Type, n (%)						
Dermatologist	142 (60.2)	69 (59.5)	142 (59.9)	72 (61.0)	260 (58.6)	265 (59.3)
Other	94 (39.8)	47 (40.5)	95 (40.1)	46 (39.0)	184 (41.4)	182 (40.7)
Baseline BOTE Score, n (%)						
No inflammation [BOTE = 0]	160 (67.8)	69 (59.5)	151 (63.7)	75 (63.6)	225 (50.7)	222 (49.7)
Mild to very severe inflammation [BOTE ≥ 1]	72 (30.5)	45 (38.8)	86 (36.3)	43 (36.4)	219 (49.3)	225 (50.3)
Missing	4 (1.7)	2 (1.7)	0	0	0	0

Source: Reviewer analysis
Abbreviations: BOTE, beginning-of-the-end; ITT, intent-to-treat
Note: Number of subjects randomized per household was based on the stratification factor and number of households was based on the unique households randomized.
*In Study NI-MC301, Site 298 randomized a household of 3 subjects ([redacted] (b) (6)). These three subjects were included in the 2-subject household group for analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The safety population consisted of all subjects who received at least one application of study treatment. In Study NI-MC301, 1 subject [redacted] (b) (6) was randomized to SB206 but was never treated. In Study NI-MC302, 1 subject [redacted] (b) (6) was randomized to vehicle but was never treated. Therefore, the safety population consisted of 351 subjects in Study NI-MC301, 354 subjects in Study NI-MC302, and 891 subjects in Study NI-MC304.

Study drug compliance is summarized for the safety population in Table 23. In all three studies, the mean compliance in all subjects in the vehicle group (94.4% to 94.9%) was greater than in the SB206 group (86.7% to 91.4%). Subjects in the vehicle group had fewer modifications or interruptions than those in the SB206 group. Compliance when subjects required treatment modification or interruption was lower than the overall compliance across both groups and was also greater in the vehicle group than in the SB206 group.

Table 23. Study Drug Compliance (Studies NI-MC301, NI-MC302, and NI-MC304; Safety)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Compliance	SB206 N=235	Vehicle N=116	SB206 N=237	Vehicle N=117	SB206 N=444	Vehicle N=447
Compliance in all Subjects* (%)						
n	235	116	237	117	444	447
Mean	91.2	94.4	86.7	94.9	91.4	94.8
SD	12.53	9.10	16.90	8.46	13.81	10.83
Median	96.4	97.6	92.7	98.1	97.1	99.0
Min, Max	13, 100	40, 100	21, 100	47, 100	23, 100	6, 100
Compliance in Subjects who did not Require any Treatment Modifications or Interruption* (%)						
n	200	110	191	112	349	430
Mean	91.9	94.6	88.0	95.5	91.8	94.9
SD	12.35	8.90	15.58	7.03	13.04	10.84
Median	97.6	97.6	93.7	98.8	97.6	99.0
Min, Max	13, 100	40, 100	21, 100	59, 100	29, 100	6, 100
Compliance in Subjects Requiring a Treatment Modification or Interruption^ (%)						
n	35	6	46	5	95	17
Mean	85.0	89.1	76.0	75.0	88.8	93.5
SD	15.64	13.27	31.35	27.91	17.16	10.90
Median	90.1	94.5	87.4	87.4	95.5	97.7
Min, Max	29, 100	71, 100	-57#, 100	30, 100	18, 100	59, 100

Source: Applicant analysis [NI-MC301 CSR: Table 11-2 (page 53), NI-MC302 CSR: Table 11-2 (page 53), NI-MC304 CSR: Table 11-2 (page 70)]
Abbreviations: SD, standard deviation; CSR, clinical study report
*Compliance was defined as the total number of actual applications applied divided by the total number of planned applications (up to treatment completion or discontinuation) × 100.
^Adjusted compliance was defined as the total number of actual applications applied divided by the total number of planned applications (excluding the days of an Investigator-directed treatment interruption) × 100.
#Subject (b) (6) required eight interruptions for a total duration of 49 days and missed 55 doses according to the drug accountability log. Therefore, the adjusted compliance calculation for this subject resulted in a negative number (-57%).

Concomitant medications were generally similar between treatment groups in the ITT population among the three studies.

- In Study NI-MC301, 182 (51.7%) subjects received concomitant medications during the study. In the SB206 group, 125 (53.0%) subjects used a concomitant medication. In the vehicle group, 57 (49.1%) subjects used a concomitant medication. Antihistamines for systemic use and plain corticosteroids were the concomitant medications used most frequently.
- In Study NI-MC302, 180 (50.7%) subjects received concomitant medications during the study. In the SB206 group, 118 (49.8%) subjects used a concomitant medication. In the vehicle group, 62 (52.5%) subjects used a concomitant medication. Antihistamines for

systemic use, penicillins, multivitamins, and corticosteroids were the concomitant medications used most frequently.

- In Study NI-MC304, 371 (41.6%) subjects received concomitant medications during the study. In the SB206 group, 197 (44.4%) subjects used a concomitant medication. In the vehicle group, 174 (38.9%) subjects used a concomitant medication. The most common concomitant medications were vitamins, cetirizine hydrochloride, hydrocortisone, paracetamol, and loratadine. Two subjects (b) (6) used prohibited concomitant medication of ammonium lactate, which was discovered after unblinding.

Efficacy Results – Primary and Secondary Endpoints

The primary efficacy endpoint was the proportion of subjects achieving complete clearance at Week 12. The key secondary efficacy endpoint was complete clearance rate at Week 8. Table 24 shows the number and proportion of subjects who had missing lesion count at Week 12 and Week 8, respectively. For the primary endpoint at Week 12, approximately 12–16% of subjects in the SB206 arm and 3-13% of subjects in the vehicle arm had missing data across three studies. In Studies NI-MC301 and NI-MC302, a higher proportion of missing data was observed in the SB206 arm compared to the vehicle arm, especially in Study NI-MC301, where the proportion of missing data was highly imbalanced: 16.1% of SB206 subjects and 3.4% of vehicle subjects had missing data. In Study NI-MC304, the proportion of missing data was relatively balanced (11.5% of SB206 subjects and 11.2% of vehicle subjects). Among the three studies, Study NI-MC302 had the highest proportion of missing data (16.0% of SB206 subjects and 12.7% of vehicle subjects). Similar trends were also observed for the key secondary endpoint at Week 8.

Table 24. Subjects With Missing Lesion Count at Week 12 and Week 8 (Studies NI-MC301, NI-MC302, and NI-MC304; ITT)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Subject	SB206 N=236	Vehicle N=116	SB206 N=237	Vehicle N=118	SB206 N=444	Vehicle N=447
Subjects with missing lesion count at Week 12	38 (16.1)	4 (3.4)	38 (16.0)	15 (12.7)	51 (11.5)	50 (11.2)
Subjects with missing lesion count at Week 8	33 (14.0)	4 (3.4)	34 (14.3)	11 (9.3)	51 (11.5)	47 (10.5)

Source: reviewer analysis
Abbreviations: ITT, intent-to-treat

Table 25 presents the statistical reviewer's results for the primary and key secondary endpoints, which are slightly different from the Applicant's results as discussed in Section 8.1.1 (Statistical Analysis Plan) due to the Applicant's acknowledgement that they used the incorrect standard error in calculations, but the study conclusions remain the same. Non-responder imputation was used for the handling of missing data. For the primary endpoint, the complete clearance rate in the SB206 arm was statistically significantly higher than that in the vehicle arm in Study NI-MC304 ($p < 0.0001$); however, the statistical significance just missed the cutoff in Study NI-MC302 ($p = 0.0510$) and was not achieved in Study NI-MC301 ($p = 0.3637$). For the key

secondary endpoint, efficacy of the SB206 arm compared to the vehicle arm was demonstrated in Study NI-MC304 (p = 0.0012); in Study NI-MC302, the p-value was nominally significant (p = 0.0114), but the endpoint was not formally tested because the primary endpoint was not significant; in Study NI-MC301, the statistical significance was not achieved (p = 0.1801).

Statistical Reviewer's Comment: *As shown in Table 24, the proportion of missing data for the primary endpoint was highly imbalanced between two treatment groups in Study NI-MC301 (16.1% of SB206 subjects vs. 3.4% of vehicle subjects) and slightly imbalanced in Study NI-MC302 (16.0% of SB206 subjects vs. 12.7% of vehicle subjects). Since non-responder imputation was pre-specified as the primary method for handling of missing data, the resulting treatment effect was in favor of the vehicle arm which had much less missing data (3.4%) than the SB206 arm (16.1%) in Study NI-MC301, and less (12.7% vs. 16.0%) in Study NI-MC302. Hence, imbalanced missing data between treatment groups and non-responder imputation were considered to largely contribute to the inadequate efficacy in Study NI-MC301 and contribute to the borderline failed efficacy in Study NI-MC302.*

Table 25. Primary and Key Secondary Efficacy Results – Complete Clearance Rate at Week 12 and Week 8 (Studies NI-MC301, NI-MC302, and NI-MC304; ITT)

	Study NI-MC301		Study NI-MC302		Study NI-MC304	
Endpoint	**SB206 N = 236**	**Vehicle N = 116**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
Week 12 (Primary Endpoint)						
Complete Clearance Rate	61/236 (25.8%)	25/116 (21.6%)	71/237 (30.0%)	24/118 (20.3%)	144/444 (32.4%)	88/447 (19.7%)
Treatment Difference (95% CI) p-value*	4.3% (-5.0%, 13.6%) 0.3637		9.2% (-0.04%, 18.4%) 0.0510		12.8% (7.1%, 18.6%) < 0.0001^	
Week 8 (Key Secondary Endpoint)						
Complete Clearance Rate	36/236 (15.3%)	12/116 (10.3%)	33/237 (13.9%)	7/118 (5.9%)	87/444 (19.6%)	52/447 (11.6%)
Treatment Difference (95% CI) p-value*	4.7% (-2.2%, 11.5%) 0.1801		7.8% (1.8%, 13.8%) 0.0114		7.5% (3.0%, 12.0%) 0.0012^	

Source: Reviewer analysis
Abbreviations: CI, confidence interval; ITT, intent-to-treat
Note: Subjects with missing lesion count data at the endpoint visit were counted as non-responders.
*P-values for the individual studies were obtained from a generalized estimating equation for logistic regression with an exchangeable working correlation structure to account for the correlated subjects per household. The model included treatment, investigator type (dermatologist vs. other), household number of randomized subjects (1 subject per household vs. 2 subjects per household), age, and baseline lesion count as factors. For Study NI-MC304, baseline beginning-of-the-end status as randomized was additionally included as a factor in the model.
^Statistically significant under the multiplicity control scheme

Efficacy Results – Sensitivity Analyses of Primary Endpoint

Table 26 presents the results of the Applicant's sensitivity analyses for the primary endpoint as described in Section 8.1.1 (Statistical Analysis Plan), most of which were conducted to evaluate alternative methods for handling of missing data. Table 26 shows that Study NI-MC302 changed from non-significant in the primary analysis to statistically significant in most of the Applicant's sensitivity analyses. The one that was not significant was sensitivity analysis 5 using MI based on the ITT population. Considering that MI adds more variation than single imputation, it is not

surprising that the p value of MI (p = 0.1383) was not significant. Studies NI-MC304 and NI-MC301 had consistent results in the Applicant's sensitivity analyses as in the primary analysis, that is, Study NI-MC304 remained statistically significant and Study NI-MC301 remained non-significant.

Table 26. Applicant's Sensitivity Analysis Results of Primary Endpoint* – Complete Clearance Rate at Week 12 (Studies NI-MC301, NI-MC302, and NI-MC304)

Sensitivity Analysis 1	Study NI-MC301		Study NI-MC302		Study NI-MC304	
	SB206 N = 192	Vehicle N = 107	SB206 N = 194	Vehicle N = 103	SB206 N = 389	Vehicle N = 396
PP Population						
Complete Clearance Rate	60/192 (31.3%)	23/107 (21.5%)	70/194 (36.1%)	24/103 (23.3%)	142/389 (36.5%)	88/396 (22.2%)
Odds Ratio (95% CI)	1.637 (0.922, 2.908)		1.813 (1.065, 3.087)		2.082 (1.501, 2.887)	
p-value	0.0927		0.0284		< 0.0001	
Sensitivity Analysis 2	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 236	**Vehicle N = 116**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
ITT Population, Adapted Non-Responder Imputation with Responder Imputation for Complete Clearance Prior to Week 12^						
Complete Clearance Rate	63/236 (26.7%)	25/116 (21.6%)	73/237 (30.8%)	24/118 (20.3%)	145/444 (32.7%)	89/447 (19.9%)
Odds Ratio (95% CI)	1.333 (0.781, 2.276)		1.703 (1.013, 2.862)		1.983 (1.455, 2.704)	
p-value	0.2924		0.0444		< 0.0001	
Sensitivity Analysis 4	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 207	**Vehicle N = 103**	**SB206 N = 215**	**Vehicle N = 107**	**SB206 N = 424**	**Vehicle N = 428**
One Subject per Household						
Complete Clearance Rate	54/207 (26.1%)	20/103 (19.4%)	64/215 (29.8%)	20/107 (18.7%)	139/424 (32.8%)	86/428 (20.1%)
Odds Ratio (95% CI)	1.429 (0.798, 2.561)		1.812 (1.024, 3.207)		1.987 (1.441, 2.740)	
p-value	0.2302		0.0414		< 0.0001	
Sensitivity Analysis 5	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 236	**Vehicle N = 116**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
ITT Population, MI						
Complete Clearance Rate (Average)	26.7%	21.7%	30.6%	20.7%	32.8%	20.0%
Odds Ratio (95% CI)	1.320 (0.610, 2.029)		1.657 (0.788, 2.526)		2.012 (1.369, 2.655)	
p-value	0.3772		0.1383		0.0020	

Source: Applicant analysis [NI-MC301 CSR: Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.8, Table 14.2.1.11.a, NI-MC302 CSR: Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.8, Table 14.2.1.11, NI-MC304 CSR: Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.8, Table 14.2.1.11]
Abbreviations: CI, confidence interval; ITT, intent-to-treat; MI, multiple imputation; CSR, clinical study report
*As discussed in Section 8.1.1 (Statistical Analysis Plan), commonly used sensitivity analyses were reported herein.
^Subjects with missing MC lesion count at Week 12 but who demonstrated complete clearance prior to Week 12 were counted as responders (Study NI-MC301: 2 in SB206, Study NI-MC302: 2 in SB206, Study NI-MC304: 1 in SB206 and 1 in vehicle), and other subjects with missing lesion count at Week 12 were counted as non-responders.

Table 27 presents the results of the statistical reviewer's sensitivity analyses as discussed in Section 8.1.1 (Statistical Analysis Plan). In summary, the first reviewer's sensitivity analysis counted subjects with missing MC lesion count at Week 12 but who demonstrated complete clearance at Week 8 as responders, and other subjects with missing lesion count at Week 12 as non-responders, while the Applicant's sensitivity analysis 2 counted subjects who had missing lesion count at Week 12 but had achieved complete clearance at any time prior to Week 12 as responders. The second reviewer's sensitivity analysis was an observed case analysis. For Study NI-MC304, a sensitivity analysis was conducted where the worst-case imputation was performed for subjects who had a remote assessment at Week 12. Finally, for Studies NI-MC301 and NI-MC302, a sensitivity analysis was conducted adjusted for baseline BOTE score. In Study NI-MC302, the p-value turned significant in all of the reviewer's sensitivity analyses, similar to what was observed in the Applicant's sensitivity analyses, where the p-value turned significant in most of the Applicant's sensitivity analyses. In Studies NI-MC304 and NI-MC301, the conclusions of all the reviewer's sensitivity analyses were consistent with that of the primary analysis.

Statistical Reviewer's Comment:

- *In all of the statistical reviewer's sensitivity analyses and most of the Applicant's sensitivity analyses, the p-value of the primary endpoint changed from non-significant in the primary analysis to statistically significant in Study NI-MC302. The sensitivity analysis that was not significant was the Applicant's sensitivity analysis 5 (using MI based on the ITT population). Considering that MI adds more variation than single imputation, it is not surprising that the p-value of MI (p = 0.1383) was not significant. Hence, how the missing data was handled did make a difference in the study conclusion in Study NI-MC302.*
- *In Study NI-MC301, the p-value from the reviewer's sensitivity analysis 2 (using the observed data only) reduced from 0.3637 in the primary analysis to 0.1058. This indicates that imbalanced missing data between treatment groups and non-responder imputation in the primary analysis did make the treatment effect in favor of the vehicle arm in Study NI-MC301.*

Table 27. Statistical Reviewer's Sensitivity Analysis Results of Primary Endpoint – Complete Clearance Rate at Week 12 (Studies NI-MC301, NI-MC302, and NI-MC304)

Sensitivity Analysis 1	Study NI-MC301		Study NI-MC302		Study NI-MC304	
	SB206 N = 236	Vehicle N = 116	SB206 N = 237	Vehicle N = 118	SB206 N = 444	Vehicle N = 447
ITT Population, Adapted Non-Responder Imputation with Responder Imputation for Complete Clearance at Week 8*						
Complete Clearance Rate	62/236 (26.3%)	25/116 (21.6%)	72/237 (30.4%)	24/118 (20.3%)	144/444 (32.4%)	88/447 (19.7%)
Treatment Difference (95% CI)	5.3% (-4.0%, 14.7%)		9.5% (0.3%, 18.7%)		12.8% (7.1%, 18.6%)	
p-value	0.2631		0.0432		< 0.0001	

Sensitivity Analysis 2	Study NI-MC301		Study NI-MC302		Study NI-MC304	
	SB206 N = 198	Vehicle N = 112	SB206 N = 199	Vehicle N = 103	SB206 N = 393	Vehicle N = 397
Observed Data Only						
Complete Clearance Rate	61/198 (30.8%)	25/112 (22.3%)	71/199 (35.7%)	24/103 (23.3%)	144/393 (36.6%)	88/397 (22.2%)
Treatment Difference (95% CI) p-value	8.4% (-1.8%, 18.7%) 0.1058		12.0% (1.5%, 22.4%) 0.0248		14.8% (8.4%, 21.1%) < 0.0001	
Sensitivity Analysis 3	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 236	**Vehicle N = 116**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
ITT Population, Non-Responder Imputation for Missing Data, Worst-Case Imputation for Remote Assessment at Week 12^						
Complete Clearance Rate					142/444 (32.0%)	89/447 (19.9%)
Treatment Difference (95% CI) p-value					12.1% (6.4%, 17.8%) < 0.0001	
Sensitivity Analysis 4	**Study NI-MC301#**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 232	**Vehicle N = 114**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
ITT Population, Additionally Adjusted for Baseline BOTE Score, Non-Responder Imputation						
Complete Clearance Rate	60/232 (25.9%)	24/114 (21.1%)	71/237 (30.0%)	24/118 (20.3%)	144/444 (32.4%)	88/447 (19.7%)
Treatment Difference (95% CI) p-value	5.3% (-3.9%, 14.5%) 0.2602		9.3% (0.1%, 18.5%) 0.0476		12.8% (7.1%, 18.6%) < 0.0001	

Source: reviewer analysis
Abbreviations: BOTE, beginning-of-the-end; CI, confidence interval; ITT, intent-to-treat
*Subjects with missing MC lesion count at Week 12 but who demonstrated complete clearance at Week 8 were counted as responders (Study NI-MC301: Subject (b) (6) in SB206, Study NI-MC302: Subject (b) (6) in SB206), and other subjects with missing lesion count at Week 12 were counted as non-responders.
^This analysis applies only to Study NI-MC304. Subjects with missing lesion count data at Week 12 were counted as non-responders. 2 subjects ((b) (6)) in the SB206 arm with a remote Week 12 visit were counted as non-responders, and 1 subject ((b) (6)) in the vehicle arm with a remote Week 12 visit was counted as responder.
#There were 6 subjects (4 in SB206 and 2 in vehicle) had missing baseline BOTE score in Study NI-MC301.

Efficacy Results – Exploratory Analyses of Continuous Endpoint

Table 28 presents the statistical reviewer's results of the exploratory analyses based on the continuous endpoint as discussed in Section 8.1.1 (Statistical Analysis Plan). As shown in Table 28, by using either MI or MMRM, absolute change from baseline in lesion count at Week 12 was statistically significantly larger in the SB206 arm compared to the vehicle arm in Studies NI-MC302 and NI-MC304, but not in Study NI-MC301. Similar results were also observed for percent change from baseline in lesion count at Week 12. Figure 1, Figure 2, and Figure 3 illustrate mean change from baseline in lesion count over time up to Week 12 by treatment group in each study, respectively. Both studies NI-MC302 and NI-MC304 showed no overlap in error bars between the two treatment arms, with the SB206 arm performing better.

Statistical Reviewer's Comment:

- *Consistent with the observed results from the sensitivity analyses based on the primary endpoint (complete clearance rate at Week 12), the results of the exploratory analyses based on the continuous endpoint (change or percent change from baseline in lesion count at Week 12) were statistically significant in Study NI-MC302, regardless of whether MI or MMRM was used. In addition, the p-values for the continuous endpoint were much more significant than those for the primary endpoint, which is expected given that a continuous endpoint is more powerful than a binary one.*
- *Supplementary analyses (result not shown) were performed to compare the continuous endpoint (change or percent change from baseline in lesion count at Week 12) between treatment arms over time using MMRM. Continuous endpoint over time also revealed significant p-values throughout Studies NI-MC302 and NI-MC304, further supporting the findings on the primary endpoint.*

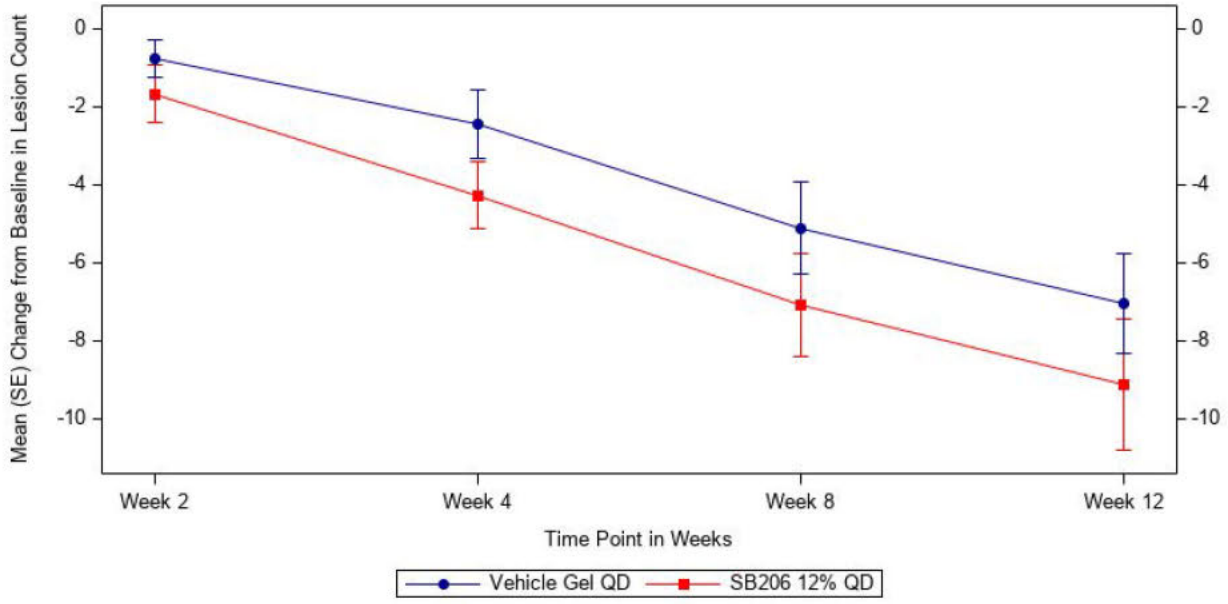
Table 28. Exploratory Analysis Results of Continuous Endpoint – Change and Percent Change From Baseline in Lesion Count at Week 12 (Studies NI-MC301, NI-MC302, and NI-MC304; ITT)

Exploratory Analysis 1	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 236	**Vehicle N = 116**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
Change from Baseline in Lesion Count at Week 12, MI						
Treatment Difference (95% CI) p-value	-1.9 (-6.01, 2.23) 0.3687		-5.7 (-8.80, -2.50) 0.0004		-5.9 (-7.70, -4.11) < 0.0001	
Exploratory Analysis 2	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 236	**Vehicle N = 116**	**SB206 N = 237**	**Vehicle N = 118**	**SB206 N = 444**	**Vehicle N = 447**
Percent Change from Baseline in Lesion Count at Week 12, MI						
Treatment Difference (95% CI) p-value	-4.5 (-28.60, 19.70) 0.7181		-27.9 (-47.23, -8.66) 0.0045		-24.3 (-38.34, -10.19) 0.0007	
Exploratory Analysis 3	**Study NI-MC301**		**Study NI-MC302**		**Study NI-MC304**	
	SB206 N = 198	**Vehicle N = 112**	**SB206 N = 199**	**Vehicle N = 103**	**SB206 N = 393**	**Vehicle N = 397**
Change from Baseline in Lesion Count at Week 12, MMRM*						
LS Mean (SE)	-8.9 (1.38)	-6.6 (1.87)	-11.5 (1.10)	-6.0 (1.48)	-14.2 (1.13)	-7.4 (1.15)
Treatment Difference (95% CI) p-value	-2.4 (-6.84, 2.14) 0.3033		-5.6 (-9.02, -2.15) 0.0015		-6.8 (-8.83, -4.77) < 0.0001	

Exploratory Analysis 4	Study NI-MC301#		Study NI-MC302		Study NI-MC304	
	SB206 N = 198	Vehicle N = 112	SB206 N = 199	Vehicle N = 103	SB206 N = 393	Vehicle N = 397
Percent Change from Baseline in Lesion Count at Week 12, MMRM*						
LS Mean (SE)	-42.5 (6.35)	-27.6 (8.55)	-53.2 (6.05)	-28.3 (8.08)	-59.5 (4.54)	-33.2 (4.63)
Treatment Difference (95% CI)	-14.9 (-35.35, 5.50)		-24.9 (-43.60, -6.28)		-26.3 (-33.40, -19.21)	
p-value	0.1514		0.0090		< 0.0001	

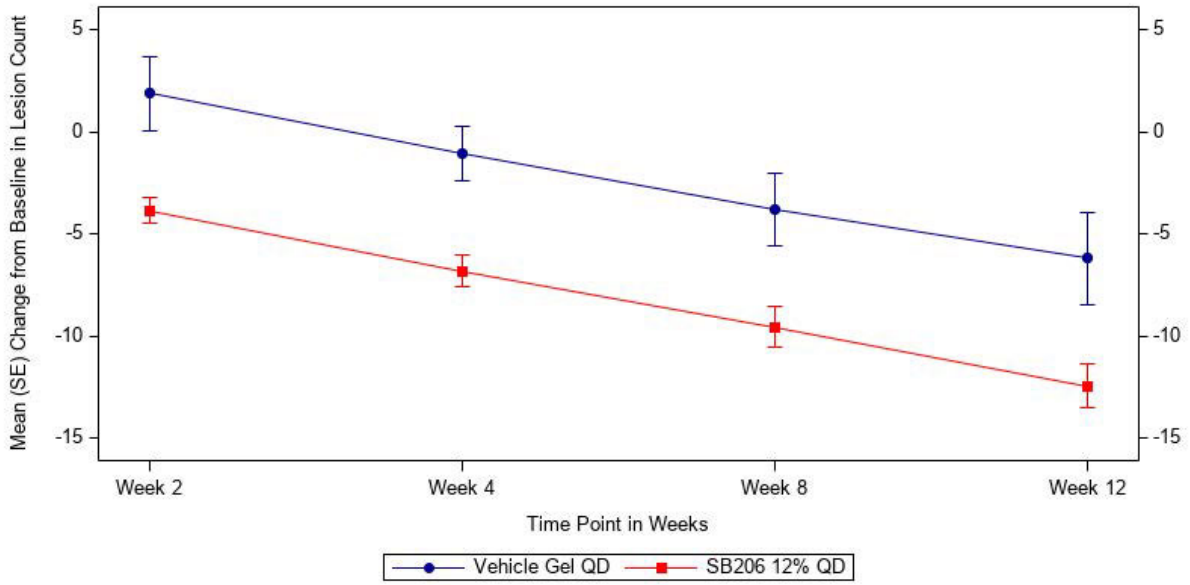
Source: reviewer analysis
Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; MI, multiple imputation; MMRM, mixed model repeated measures; SE, standard error
*MMRM refers to analyzing the continuous endpoint using a repeated measures mixed model for the respective visits with the same covariates as the primary model together with visit and treatment by visit interaction with an unstructured covariance matrix. If the calculated percent change from baseline was greater than 100%, then it would be censored to 100% so that all values were in the range of -100% to 100%.

Figure 1. Mean Change From Baseline in Lesion Count Over Time by Treatment Group (Study NI-MC301; ITT)



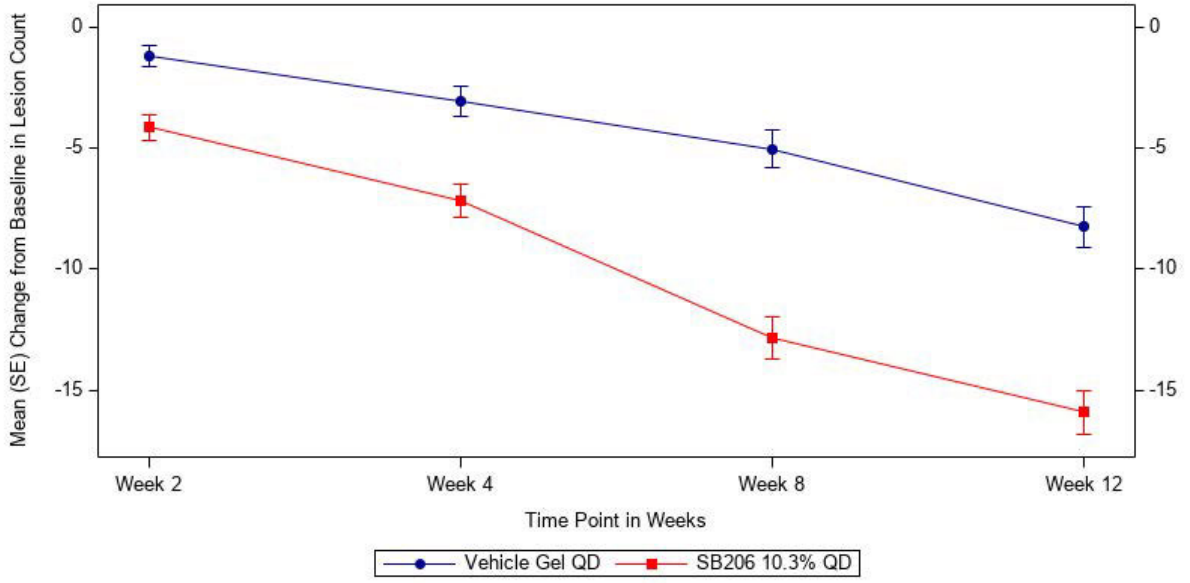
Source: Applicant analysis [NI-MC301 CSR: Figure 11-2 (page 65)], validated by reviewer analysis
Abbreviations: ITT, intent-to-treat; QD, once daily; SE, standard error; CSR, clinical study report

Figure 2. Mean Change From Baseline in Lesion Count Over Time by Treatment Group (Study NI-MC302; ITT)



Source: Applicant analysis [NI-MC302 CSR: Figure 11-2 (page 65)], validated by reviewer analysis
Abbreviations: ITT, intent-to-treat; QD, once daily; SE, standard error; CSR, clinical study report

Figure 3. Mean Change From Baseline in Lesion Count Over Time by Treatment Group (Study NI-MC304; ITT)



Source: Applicant analysis [NI-MC304 CSR: Figure 11-1 (page 78)], validated by reviewer analysis
Abbreviations: ITT, intent-to-treat; QD, once daily; SE, standard error; CSR, clinical study report

Findings in Special/Subgroup Populations

The Applicant performed subgroup analyses of the primary endpoint using the same GEE model as that for the main analysis of all subjects in the ITT population, additionally including both an indicator variable for the subgroup outcome and the interaction of the subgroup indicator with

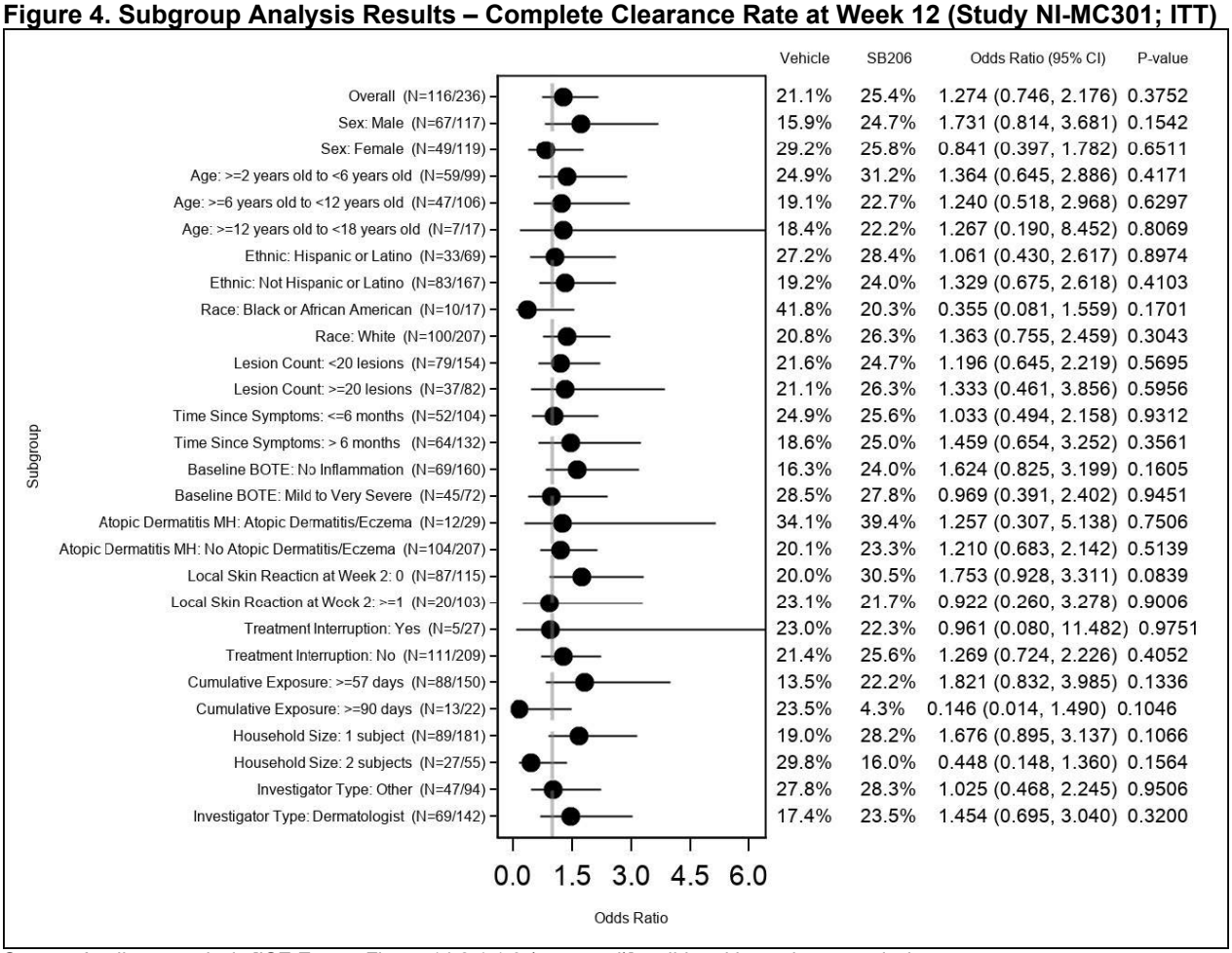
the treatment group as fixed factors and considering an independent correlation structure instead of exchangeable correlation structure. The subgroup summaries were presented for the following subgroups that had meaningful sample size for review, suitable number of responses and minimal convergence issues:

- Sex (Male vs. Female)
- Age (≥ 2 to 6 years old vs ≥ 6 to 12 years old vs ≥ 12 to 18 years old)
- Ethnicity (Hispanic or Latino vs Not Hispanic or Latino)
- Race (Black or African American vs White)
- Number of subjects randomized per household (1-subject household vs 2-subject household)
- Investigator type (dermatologist vs other)
- Lesion counts at baseline (< 20 lesions vs ≥ 20 lesions)
- Time since onset of symptoms of current MC episode (≤ 6 months vs > 6 months)
- Baseline BOTE score (no inflammation [score=0] vs mild to very severe inflammation [score 1 to 4])
- AD medical history (AD/eczema vs no AD/eczema)
- Local skin reaction (LSR) composite score at Week 2 (LSR composite = 0 vs LSR composite ≥1)
- Subject experienced treatment interruption (Yes vs No)
- Cumulative subject exposure (≥57 days and ≥90 days)

Note that the groupings based on LSR composite, treatment interruption, and cumulative subject exposure are improper subgroups based on post-randomization outcomes that are likely to be impacted by treatment assignment.

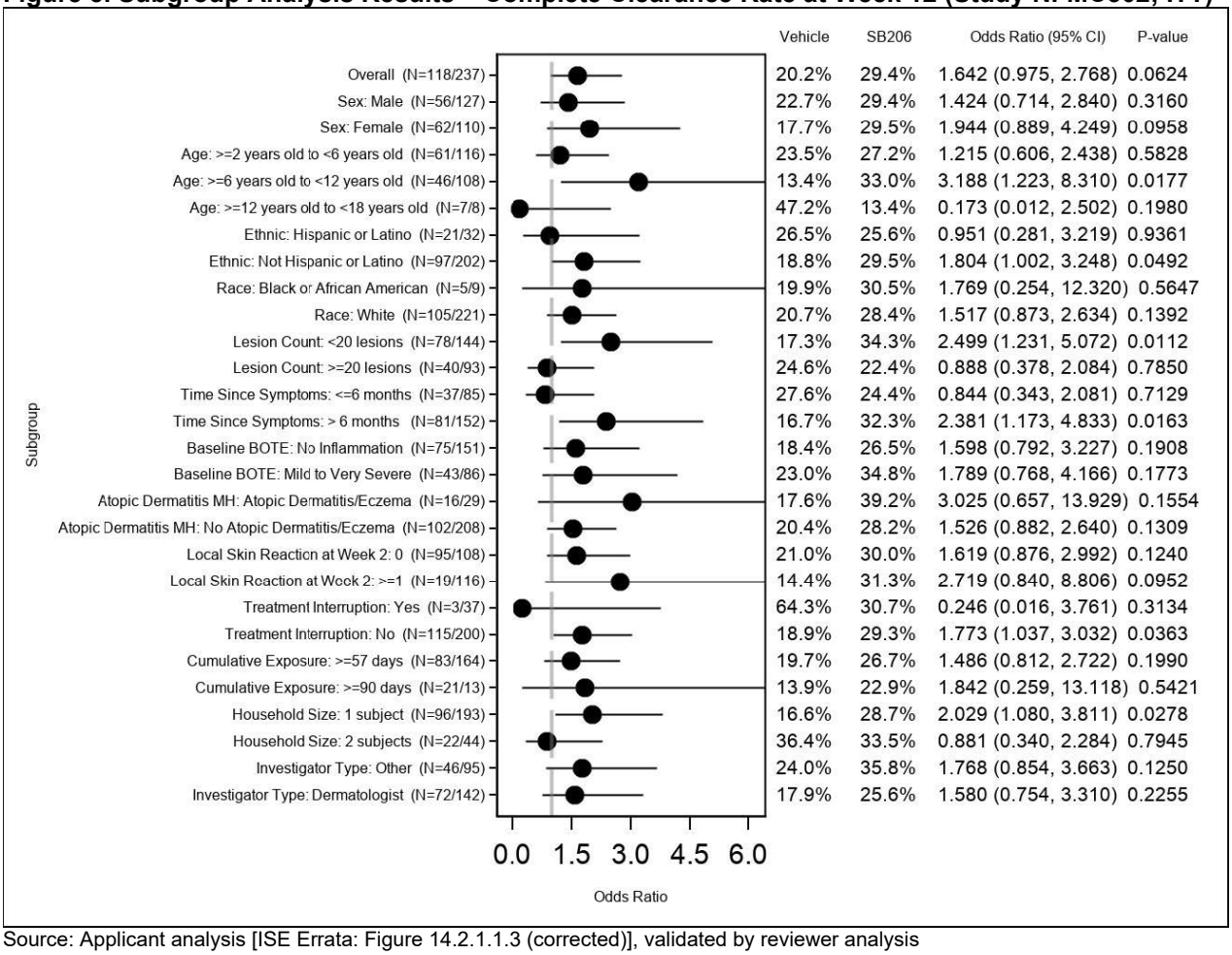
Figure 4, Figure 5, and Figure 6 present the efficacy results of the primary endpoint by subgroup in each study, respectively. In Study NI-MC304, the SB206 arm demonstrated a higher complete clearance rate than the vehicle arm in all of subgroups. In Study NI-MC302, the efficacy of the SB206 arm was generally consistent across subgroups. Notably, the 12–18 year age group had a trend favoring the vehicle arm, however, due to the small sample size, the treatment effect may not be reliably estimated with sufficient precision in this subgroup. Similar results were also observed in Study NI-MC301.

Figure 4. Subgroup Analysis Results – Complete Clearance Rate at Week 12 (Study NI-MC301; ITT)



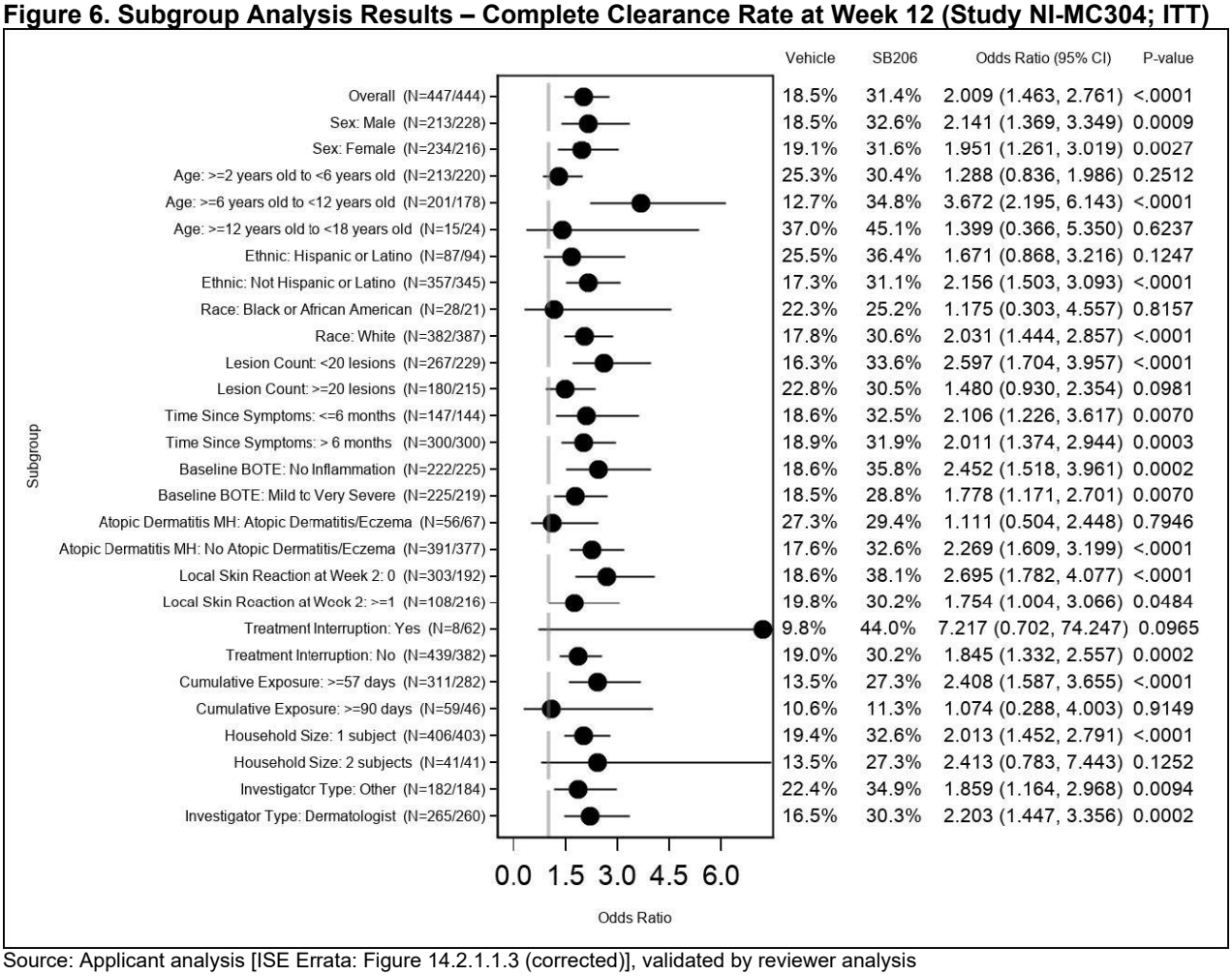
Source: Applicant analysis [ISE Errata: Figure 14.2.1.1.3 (corrected)], validated by reviewer analysis
Abbreviations: CI, confidence interval; ITT, intent-to-treat; ISE, integrated summary of efficacy
Note: Subjects with missing lesion count data at Week 12 were counted as non-responders.

Figure 5. Subgroup Analysis Results – Complete Clearance Rate at Week 12 (Study NI-MC302; ITT)



Source: Applicant analysis [ISE Errata: Figure 14.2.1.1.3 (corrected)], validated by reviewer analysis
Abbreviations: CI, confidence interval; ITT, intent-to-treat; ISE, integrated summary of efficacy
Note: Subjects with missing lesion count data at Week 12 were counted as non-responders.

Figure 6. Subgroup Analysis Results – Complete Clearance Rate at Week 12 (Study NI-MC304; ITT)



Source: Applicant analysis [ISE Errata: Figure 14.2.1.1.3 (corrected)], validated by reviewer analysis
Abbreviations: CI, confidence interval; ITT, intent-to-treat; ISE, integrated summary of efficacy
Note: Subjects with missing lesion count data at Week 12 were counted as non-responders.

Efficacy Results by Center

Study NI-MC301 randomized a total of 352 subjects from 33 centers. Study NI-MC302 randomized a total of 355 subjects from 33 centers. Study NI-MC304 randomized a total of 891 subjects from 55 centers. All centers were in the United States. Results were generally consistent across sites for the primary endpoint. It does not appear that any single or few sites drove the efficacy results.

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoint

For the primary endpoint, the complete clearance rate at Week 12 in the SB206 arm was statistically significantly higher than that in the vehicle arm in Study NI-MC304 ($p < 0.0001$); the statistical significance just missed the cutoff in Study NI-MC302 ($p = 0.0510$) and was not achieved in Study NI-MC301 ($p = 0.3637$).

In Study NI-MC302, the higher proportion of missing data in the SB206 arm (16.0%) than that in the vehicle arm (12.7%), as well as the non-responder imputation, made the treatment effect in favor of the vehicle arm in the primary analysis and contributed to the borderline failure of Study NI-MC302. In all of the statistical reviewer's sensitivity analyses and most of the Applicant's sensitivity analyses where missing data were handled in alternative ways other than non-responder imputation, the results of Study NI-MC302 became nominally statistically significant. Exploratory analyses based on the continuous endpoint (change or percent change from baseline in lesion count at Week 12) revealed the same results with higher statistical significance due to the higher power of a continuous endpoint than a binary endpoint.

In Study NI-MC301, missing data was highly imbalanced between treatment groups: the vehicle arm had a much lower proportion of missing data (3.4%) than the SB206 arm (16.1%). Similar as Study NI-MC302, non-responder imputation in the primary analysis made the resulting treatment effect in favor of the vehicle arm. Hence, the highly imbalanced missing data and non-responder imputation were considered to largely contribute to the inadequate efficacy in Study NI-MC301.

Secondary and Other Endpoints

For the key secondary endpoint, efficacy of the SB206 arm compared to the vehicle arm was demonstrated in Study NI-MC304 ($p = 0.0012$) and the p-value was nominally significant in Study NI-MC302 ($p = 0.0114$); the statistical significance was not achieved in Study NI-MC301 ($p=0.1801$).

Exploratory analyses based on the continuous endpoint of change or percent change in MC lesion count were supportive of the primary endpoint of complete clearance. In Studies NI-MC302 and NI-MC304, the results for change in lesion count from baseline to Week 12 using MMRM were nominally statistically significant ($p=0.0015$ and $p < 0.0001$, respectively), lending support to the findings on the primary endpoint. The results in Study NI-MC301 were not nominally significant ($p=0.3033$). The results for percent change in lesion count from baseline to Week 12 were similar with supportive findings in Studies NI-MC302 and NI-MC304 ($p=0.0090$ and $p < 0.0001$) and non-significant findings in Study NI-MC301 ($p=0.1514$).

Subpopulations

In Study NI-MC304, the SB206 arm demonstrated a higher complete clearance rate than the vehicle arm in all of subgroups. In Study NI-MC302, the efficacy of the SB206 arm was generally consistent across subgroups. Notably, the 12–18 year age group had a trend favoring the vehicle arm, however, due to the small sample size, the treatment effect may not be reliably estimated with sufficient precision in this subgroup. Similar results were also observed in Study NI-MC301.

Conclusions

Both studies NI-MC302 and NI-MC304 are adequate and well-controlled trials that support the efficacy of SB206 in the treatment of MC. The results from Study NI-MC304 were robust and consistent across subgroups and sensitivity analyses. In Study NI-MC302, the results of the primary endpoint analysis just missed the significance cutoff with p-value of 0.0510. However, the point estimates and treatment effect were similar to those observed in Study NI-MC304, many sensitivity analyses had nominally significant findings, the key secondary endpoint (complete clearance at Week 8) and exploratory endpoints that evaluated change or percent change in MC lesion count all supported an efficacy finding for Study NI-MC302. Thus, Study NI-MC302 is an adequate and well-controlled trial that supports the evidence of effectiveness. While it is not possible to determine why Study NI-MC301 did not demonstrate efficacy, the fact that the amount of missing data on the vehicle arm was much smaller compared to the SB206 arm may have contributed to the attenuated treatment effect. Although the observed treatment effect in Study NI-MC301 was smaller than in the other two trials, the study did have a small treatment effect trending in favor of the SB206 arm. Thus, the findings of Studies NI-MC302 and NI-MC304 provide for the demonstration of substantial evidence of effectiveness through two adequate and well-controlled trials.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of berdazimer gel, 10.3% QD for topical treatment of subjects with MC relied on pooled safety data from three phase 3 randomized, double-blind, placebo-controlled trials (NI-MC301/-302/-304 which shared similar inclusion/exclusion criteria, study designs, dosing regimen, and primary and secondary efficacy endpoints) included in the ISS and comprised the safety population. The Phase 3 trials included a treatment duration of 12 weeks followed by a double-blind, off-treatment follow-up period of 12 weeks. Treatment-related Adverse Events (ARs) ongoing at the Week-24 visit were followed to their resolution, or up to one year after last study drug application, whichever occurred first. No long-term safety study was conducted for this drug product given the finite treatment period and a single treatment course of MC.

Additionally, the Applicant submitted supportive safety data from a phase 2a, dose-ranging trial (NI-MC201) in subjects with MC, and two provocative Phase 1 dermal safety studies (NI-AC105/-106) conducted with SB204 gel, 3.4% in their acne drug development program.

The safety population (ISS) included 1596 randomized subjects who used the study drug at least once, including 680 subjects who received the vehicle gel and 916 subjects who received berdazimer gel with a mean number of drug applications of 69.6.

To determine the safety profile of berdazimer gel, 10.3% QD for the treatment of MC, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs [including severe TEAEs, SAEs, adverse events leading to discontinuation (AELDs)], local skin reactions (LSRs), Scarring/keloid assessments, physical examinations, urine pregnancy tests for

female subjects of child-bearing potential ≥9 years of age), and recurrence of MC lesions.

An endpoint (not safety-related) of the "beginning-of-the-end (BOTE)" inflammation scores (0-4) was collected and distinguished from the LSRs. Adverse events of special interest (AESIs) were not prespecified in the Phase 3 protocols (refer to the AESI section of this review under Section 8.2.4).

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure to berdazimer gel, 10.3% in terms of frequency, duration and target population was adequate for the evaluation of safety. In the combined Phase 3 trials (ISS) safety population, 744/916 (81.2%) subjects in the berdazimer group and 603/680 (88.7%) subjects in the vehicle group completed treatment with the study drug (at Week 12 or at the time of achievement of complete clearance of all MC lesions prior to Week 12). AEs led to discontinuation from treatment in 52/916 (5.7%) subjects in the berdazimer group and 7 (1.0%) subjects in the vehicle group during treatment period (Weeks 0-12).

The Demographic Characteristics of the safety population at baseline were well-balanced across treatment groups and representative of the target population. Refer to Section 8.1 of this review for details of Subject Disposition.

Adequacy of the Safety Database

The safety database presented by the Applicant is adequate to characterize the safety profile of Berdazimer gel for the treatment of subjects with MC. Safety assessments were reasonable and consistent with known adverse events for berdazimer in the target population:

- The size of safety database is adequate. A total of 916 subjects received at least one dose of berdazimer gel, 10.3% QD; including cumulative exposures for 892 (≥7 Days), 815 (≥29 Days), 677 (≥57 Days), 393 (≥85 Days), and 81 (≥90 Days) subjects. subjects required. Treatment interruption or modification was required for 176/916 (19.2%) subjects.
- The total subject exposure to berdazimer gel, 10.3% QD in the safety population provides adequate data for the evaluation of safety. The Mean (SD) for the number of study drug applications were 71.2 (22.4) in the berdazimer group and 77.3 (18.5) in the vehicle group.
- The demographics of the study population are sufficiently representative of the target population as presented in Table 29.

Table 29. Demographic and Baseline Disease Characteristics-ISS (Safety Population)

Treatment Group	Vehicle Gel, QD (N=680)	Berdazimer Gel, 10.3% QD (N=916)	Total (N=1596)
Demographic Characteristics			
Age (years)			
Mean (SD)	6.6 (4.4)	6.7 (4.7)	6.7 (4.5)
Median	5.8	6.0	5.9
Minimum to maximum	1.2, 49.0	0.9, 76.6	0.9, 76.6
Age Group, n (%)			
<1 year	0	1 (0.1)	1 (0.1)
≥1 to <2 years	16 (2.4%)	28 (3.1%)	44 (2.8%)
≥2 to <6 years	332 (48.8%)	435 (47.5%)	767 (48.1%)
≥6 to <12 years	294 (43.2%)	391 (42.7%)	685 (42.9%)
≥12 to <18 years	29 (4.3%)	49 (5.3%)	78 (4.9%)
≥18 years to < 65 years	9 (1.3%)	12 (1.3%)	21 (1.3%)
≥65 years	0	1 (0.1%)	1 (0.1%)
Sex, n (%)			
Male	336 (49.4%)	471 (51.4%)	807 (50.6%)
Female	344 (50.6%)	445 (48.6%)	789 (49.4%)
Race, n (%)			
American Indian or Alaska native	2 (0.3%)	2 (0.2%)	4 (0.3%)
Asian	9 (1.3%)	8 (0.9%)	17 (1.1%)
Black or African American	43 (6.3%)	47 (5.1%)	90 (5.6%)
Native Hawaiian or Other Pacific Islander	3 (0.4%)	5 (0.5%)	8 (0.5%)
White	586 (86.2%)	814 (88.9%)	1400 (87.7%)
multiple/unreported	37 (5.4%)	40 (4.3%)	77 (4.8%)
Ethnicity, n (%)			
Hispanic or Latino	141 (20.7%)	195 (21.3%)	336 (21.1%)
Not Hispanic or Latino	536 (78.8%)	713 (77.8%)	1249 (78.3%)
Unknown/unreported	3 (0.4)	8 (0.9%)	11 (0.7%)
Baseline Disease Characteristics			
MC Lesion Counts at Baseline			
Mean (SD)	19.6 (15.6)	20.7 (16.1)	20.2 (15.9)
Median	15.0	16.0	15.0
Minimum to maximum	3, 69	3, 70	3, 70
BOTE Score at Baseline, n (%)			
BOTE score=0	365 (53.7%)	536 (58.5%)	901 (56.5%)
1≤ BOTE score≤ 4	313 (46.0%)	376 (41.0%)	689 (43.2%)

Source: adapted from NDA 217424, M 5.3.5.3 (ISS) Section 2.2, Table 4. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.
Abbreviations: BOTE, beginning-of-the-end [No Inflammation (BOTE=0), Mild to Very Severe Inflammation (BOTE 1 to 4)]; SD, standard deviation; QD, once daily

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of Berdazimer gel, 10.3% for the treatment of MC. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs were recorded from the time of the first application of study drug (TEAEs) through the end of subject's last visit. AEs that occurred after the signing of the informed consent and before the first administration of the study drug were recorded as medical history. AEs that are not resolved at the time of the last scheduled study visit (Week 24/ET2) were recorded in the study database as ongoing/not recovered/not resolved/resolving. Treatment related adverse events (Adverse Reactions, ARs) and serious adverse events (SAEs), including local skin reactions (LSRs) and scars/keloids, were followed until resolution or up to 1 year after last treatment, whichever is sooner.

The investigators categorized AEs by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities version 23.1. The Applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of Medical Dictionary for Regulatory Activities summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for Phase 3 trials included in the ISS, and there was good correlation between the verbatim and preferred terms used. No new safety signals emerged from the review of TEAEs.

Investigators categorized AEs for seriousness, causality, severity, preferred term (PT), duration, action taken regarding the study drug and study participation (including any treatment given), and outcome of AEs.

SAEs were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators according to the following definitions:

- Mild: AE may be noticeable to subject; does not influence daily activities; usually does not require intervention

- Moderate: AE may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- Severe: AE may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed.

Causality of AEs were assessed by investigators as Related (including definitely related, probably related, or possibly related) or Unrelated (including unlikely related and unrelated) Based on positive temporal relationship to the study drug, reasonable possibility of association of AE with underlying or concomitant illness or therapy, whether the AE was related to study procedures or lack of efficacy, and existence of a likely alternative etiology.

Adverse events of special interests (AESIs) were not pre-specified in Phase 3 protocols. However, the statistical analysis plan (SAP) for ISS (which includes Phase 3 trials NI-MC301/-302/-304) specifies AESIs as any (on-treatment) TEAEs with a PT which contains "application site", or recurrence of MC recorded after Week 12 (defined where the PT contained "molluscum" and complete clearance of molluscum lesions was previously achieved for the subject).

The Applicant's assessment of adverse events conducted for the ISS safety data pool appears reasonable and appropriate. The Applicant reported accurate definitions of treatment emergent adverse events, serious adverse events, and severity of adverse events.

Routine Clinical Tests

During Phase 3 trials, the Applicant conducted urine pregnancy tests at screening, baseline, and Week 12 visits. However, no clinical laboratory evaluations (chemistry, hematology, or urinalysis) were conducted. No clinically significant changes in laboratory measurements or any TEAEs related to laboratory parameters were reported for the Phase 1, MuST NI-MC101 (for hematology, chemistry, coagulation, or urinalysis) or for the Phase 2, dose-ranging study NI-MC201 (chemistry, hematology, or methemoglobin).

8.2.4. Safety Results

Deaths

No deaths were reported during Phase 3 trials.

Serious Adverse Events

The following (on-treatment) SAEs were reported for 2/680 (0.3%) subjects in the placebo group and 1/916 (0.1%) subject in the SB206 group (the outcomes of all SAEs were reported as Recovered/Resolved and all SAEs were deemed as unrelated to the study drug):

- Subject (b) (6) (Placebo Group), SAE of Humerus Fracture: A 5-year-old white female subject was hospitalized for closed reduction of right humerus supracondylar fracture. The SAE was reported as resolved on D 36.

- Subject (b) (6) (Placebo Group), 3 SAEs of Nephrotic Syndrome: A 5-year-old white male subject with history of nephrotic syndrome, atopic dermatitis, seasonal and food allergies was reported with 3 SAEs of nephrotic syndrome which required hospitalization on D 11 (resolved on D12), D 56 (resolved on D 57), D 124 (resolved on D 128).
- Subject (b) (6) (SB206 Group), SAE of Cellulitis: A 3-year-old white male subject with history of eczema was hospitalized with right lower extremity cellulitis (not near study drug application site) on D 63. Study drug was interrupted, and he was treated with clindamycin. The SAE was reported as resolved on D 65.

Dropouts and/or Discontinuations Due to Adverse Effects

The following TEAEs leading to drug discontinuations (AELDs) were reported in 5/680 (0.7%) subjects in the placebo group, compared to 42/916 (4.6%) subjects in the SB206 group. Most frequent AELDs were reported in the SOC of General Disorders and Administration Site Conditions for 37 (4.0%) subjects in the SB206 group, compared to 4 (0.6%) subjects in the placebo group. Application site pain and application site dermatitis were the most frequently reported AELDs for subjects in the SB206 group, as summarized in Table 30.

Table 30. Summary of TEAEs Leading to Discontinuation (AELD)s in Phase 3 Trials- ISS (Safety Population)

	SB206 10.3% QD (N=916)		Vehicle Gel QD (N=680)		Risk Difference	
System Organ Class - Preferred Term	n	(%)	n	(%)	RD	(95% CI)
General disorders and administration site conditions	37	(4.0)	4	(0.6)	3.45	(2.05, 4.85)
Application site pain	15	(1.6)	3	(0.4)	1.20	(0.24, 2.16)
Application site dermatitis	13	(1.4)	0	(0.0)	1.42	(0.65, 2.19)
Application site erythema	3	(0.3)	1	(0.1)	0.18	(-0.29, 0.65)
Application site eczema	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)
Application site pruritus	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)
Application site discolouration	1	(0.1)	1	(0.1)	-0.04	(-0.40, 0.32)
Application site inflammation	1	(0.1)	0	(0.0)	0.11	(-0.10, 0.32)
Application site vesicles	1	(0.1)	0	(0.0)	0.11	(-0.10, 0.32)
Skin and subcutaneous tissue disorders	4	(0.4)	0	(0.0)	0.44	(0.01, 0.86)
Dermatitis contact	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)
Rash	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)

	SB206 10.3% QD		Vehicle Gel QD		
	(N=916)		(N=680)		Risk Difference
System Organ Class - Preferred Term	n	(%)	n	(%)	RD (95% CI)
Infections and infestations	2	(0.2)	1	(0.1)	0.07 (-0.35, 0.49)
Application site cellulitis	1	(0.1)	0	(0.0)	0.11 (-0.10, 0.32)
Molluscum contagiosum	1	(0.1)	0	(0.0)	0.11 (-0.10, 0.32)
Impetigo	0	(0.0)	1	(0.1)	-0.15 (-0.44, 0.14)

Source: Clinical Reviewer's OCS Analysis Studio, Safety Explorer. Unadjusted proportions reported in this table are consistent with both unadjusted proportions and study-weight-adjusted proportions in ISS, M 2.7.4, Table 9.
Filters: TRT01A = "SB206 10.3% QD" and SAFFL = "Y" (SB206 10.3% QD); TRT01A = "Vehicle Gel QD" and SAFFL = "Y" (Vehicle Gel QD); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events). Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Significant Adverse Events

Severe TEAEs

During Phase 3 trials pooled as the ISS, the following (on-treatment) severe TEAEs were reported in 2/680 (0.3%) subjects in the placebo group and 16/916 (1.7%) subject in the SB206.

- Placebo group: abscess limb (1), impetigo (1).
- SB206: Application site erythema (4), Application site dermatitis (3), Application site erosion (3), Application site exfoliation (2), Application site pain (2), Application site pruritus (1), Application site rash (1), Application site swelling (1), Application site infection (2), bronchitis (1), Adenoidal hypertrophy (1), Sleep apnea syndrome (1), Tonsillar hypertrophy (1).

Adverse Events of Special Interest (AESI)

AESIs were not pre-specified in Phase 3 protocols. However, the statistical analysis plan (SAP) for ISS (which includes Phase 3 trials NI-MC301/-302/-304) specifies AESIs as any (on-treatment) TEAEs with a preferred term (PT) which contains "application site", or recurrence of MC recorded after Week 12 (defined where the PT contained "molluscum" and complete clearance of molluscum lesions was previously achieved for the subject).

Two subjects in the SB206 group, compared to no subjects in the vehicle group, were reported with recurrence of MC lesions following complete clearance of all MC lesions at Week 12.

Application site pain and application site erythema were the most frequently reported AESIs for subjects in the SB206 group, as summarized in Table 31

Table 31. Summary of AESIs in Phase 3 Trials- ISS (Safety Population)

	SB206 10.3% QD (N=916)		Vehicle Gel QD (N=680)		Risk Difference	
System Organ Class - Preferred Term	**n**	**(%)**	**n**	**(%)**	**RD**	**(95% CI)**
General disorders and administration site conditions	340	(37.1)	100	(14.7)	22.41	(18.30, 26.52)
Application site pain	171	(18.7)	33	(4.9)	13.82	(10.82, 16.81)
Application site erythema	107	(11.7)	9	(1.3)	10.36	(8.11, 12.61)
Application site pruritus	52	(5.7)	7	(1.0)	4.65	(2.97, 6.33)
Application site exfoliation	46	(5.0)	0	(0.0)	5.02	(3.61, 6.44)
Application site dermatitis	45	(4.9)	5	(0.7)	4.18	(2.64, 5.72)
Application site scar	37	(4.0)	47	(6.9)	-2.87	(-5.17, -0.58)
Application site swelling	32	(3.5)	4	(0.6)	2.91	(1.58, 4.23)
Application site erosion	15	(1.6)	1	(0.1)	1.49	(0.62, 2.36)
Application site discolouration	14	(1.5)	1	(0.1)	1.38	(0.54, 2.23)
Application site vesicles	14	(1.5)	1	(0.1)	1.38	(0.54, 2.23)
Application site irritation	11	(1.2)	0	(0.0)	1.20	(0.50, 1.91)
Application site scab	6	(0.7)	1	(0.1)	0.51	(-0.09, 1.10)
Application site dryness	5	(0.5)	0	(0.0)	0.55	(0.07, 1.02)
Application site discharge	4	(0.4)	0	(0.0)	0.44	(0.01, 0.86)
Application site eczema	4	(0.4)	3	(0.4)	0.00	(-0.66, 0.65)
Application site inflammation	4	(0.4)	0	(0.0)	0.44	(0.01, 0.86)
Application site haemorrhage	3	(0.3)	0	(0.0)	0.33	(-0.04, 0.70)
Application site fissure	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)
Application site oedema	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)
Application site rash	2	(0.2)	2	(0.3)	-0.08	(-0.58, 0.43)
Application site ulcer	2	(0.2)	1	(0.1)	0.07	(-0.35, 0.49)
Application site discomfort	1	(0.1)	0	(0.0)	0.11	(-0.10, 0.32)
Application site laceration	1	(0.1)	0	(0.0)	0.11	(-0.10, 0.32)
Application site wound	1	(0.1)	0	(0.0)	0.11	(-0.10, 0.32)
Application site lymphadenopathy	0	(0.0)	1	(0.1)	-0.15	(-0.44, 0.14)
Application site urticaria	0	(0.0)	1	(0.1)	-0.15	(-0.44, 0.14)

	SB206 10.3% QD (N=916)		Vehicle Gel QD (N=680)		Risk Difference	
System Organ Class - Preferred Term	**n**	**(%)**	**n**	**(%)**	**RD**	**(95% CI)**
Infections and infestations	22	(2.4)	6	(0.9)	1.85	(0.58, 3.11)
Application site infection	10	(1.1)	3	(0.4)	0.65	(-0.19, 1.49)
Application site pustules	7	(0.8)	1	(0.1)	0.62	(-0.02, 1.25)
Molluscum contagiosum	2	(0.2)	0	(0.0)	0.22	(-0.08, 0.52)
Application site cellulitis	3	(0.3)	1	(0.1)	0.18	(-0.29, 0.65)
Application site folliculitis	0	(0.0)	1	(0.1)	-0.15	(-0.44, 0.14)

Source: OCS Analysis Studio, Safety Explorer by Clinical Reviewer. Consistent with M 2.5, Table 11.
Filters: TRT01A = "SB206 10.3% QD" and SAFFL = "Y" (SB206 10.3% QD); TRT01A = "Vehicle Gel QD" and SAFFL = "Y" (Vehicle Gel QD); TRTEMFL = "Y" and AEDECOD = "Application site exfoliation" or "Application site erythema" or "Application site swelling" or "Application site pain" or "Application site pruritus" or "Molluscum contagiosum" or "Application site scar" or "Application site papules" or "Application site erosion" or "Application site pustules" or "Application site ulcer" or "Application site vesicles" or "Application site dermatitis" or "Application site discolouration" or "Application site infection" or "Application site rash" or "Application site eczema" or "Application site scab" or "Application site wound" or "Application site discharge" or "Application site discomfort" or "Application site cellulitis" or "Application site inflammation" or "Application site abscess" or "Application site haemorrhage" or "Application site fissure" or "Application site laceration" or "Application site oedema" or "Application site lymphadenopathy" or "Application site dryness" or "Application site urticaria" or "Application site folliculitis" or "Application site irritation" (Adverse Events).
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Post-Treatment AEs

Post-treatment AEs are defined as AEs that occurred after the last application of the study drug (after Week 12 or early termination from treatment). For the berdazimer group compared to the vehicle group, respectively:

- A similar proportion of subjects were reported with any AE (203/916 (22.2%) vs. 138/680 (20.3%))
- The AE of MC was reported at a higher frequency in 17/916 (1.9%) subjects vs. 3/680 (0.4%) subjects

AEs reported with a frequency of ≥1% are summarized in Table 32

Table 32. Summary of Post-Treatment AEs With a Frequency of (≥1%) in any Group- ISS (Safety Population)

Counts Table

Tabulate

		Actual Treatment for Period 01				
		SB206 10.3% QD (N = 916)		Vehicle Gel QD (N = 680)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Infections and infestations	Nasopharyngitis	12	1.3%	13	1.9%	25
	Upper respiratory tract infection	15	1.6%	8	1.2%	23
	Molluscum contagiosum	17	1.9%	3	0.4%	20
	Pharyngitis streptococcal	9	1.0%	8	1.2%	17
General disorders and administration site conditions	Application site scar	44	4.8%	28	4.1%	72
	Application site erythema	9	1.0%	.	.	9
Respiratory, thoracic and mediastinal disorders	Cough	6	0.7%	8	1.2%	14

Source: JMP Clinical 8.1 Analysis by Clinical Reviewer. Consistent with M 2.5, Table 12.

During the post-treatment period, 3 SAEs (appendicitis, forearm fracture, and lower limb fracture) were reported in the vehicle group and 1 SAE in the SB206 group, as follows:

- Subject (b) (6) (SB206 Group), SAE of Pneumonia: A 4-year-old white male subject hospitalized with SAE of pneumonia (moderate severity) on D 99 and received treatment with ceftriaxone and methylprednisolone. The SAE was considered as not related to study drug by the investigators and was reported as resolved with sequelae on D 101.

During the post-treatment period, 4 severe AEs (vomiting, appendicitis, forearm fracture, and lower limb fracture) were reported in 4 subjects in the vehicle group and 6 severe AEs were reported in 5 subjects in the SB206 group (application site erythema (2), application site dermatitis (1), tonsillar hypertrophy (1), adenoidal hypertrophy (1), otorrhea (1)).

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events (TEAEs) were reported at a higher frequency for 428/916 (46.7%) subjects in the berdazimer group, compared to 169/680 (24.9%) subjects in the placebo group. Adverse Reactions (ARs) (TEAEs related to the study drug) were also reported at a higher frequency for 336/916 (36.7%) subjects in the berdazimer group, compared to 81/680 (11.9%) subjects in the placebo group.

In general, the proportion of subjects with SAEs were similar between the two groups, and the proportion of subjects with severe TEAEs, AELDs, and AESIs were higher in the berdazimer group than their corresponding proportions in the vehicle group as presented in Table 33

Table 33. Overall Summary of TEAEs- ISS- Unadjusted (Safety Population)

Subject TEAEs	Vehicle Gel QD (N=680), n (%)	SB206 10.3% Gel QD (N=916), n (%)
Any TEAE	169 (24.9)	428 (46.7)
Any drug-related TEAE (AR)	81 (11.9)	336 (36.7)
Any severe TEAE	4 (0.6)	16 (1.7)
Any serious TEAE (SAE)	2 (0.3)	1 (0.1)
Any TEAE leading to drug withdrawal (AELD)	5 (0.7)	42 (4.6)
Any TEAE leading to death	0	0

Source: Adapted from M 2.5, Table 7, consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.

The most frequently reported (on-treatment) TEAEs (in ≥1% of subjects in any treatment group) for combined Phase 3 trials (ISS) were application site pain, application site erythema, application site pruritus, application site exfoliation, and application site scar as summarized in Table 34

Table 34. Summary of TEAEs by SOC and PT (Weeks 0-12)- ISS (Unadjusted)- Reported in ≥1% of Subjects in any Group (Safety Population)

	SB206 10.3% QD (N=916)		Vehicle Gel QD (N=680)		Risk Difference	
System Organ Class - Preferred Term	n	(%)	n	(%)	RD	(95% CI)
General disorders and administration site conditions	346	(37.8)	105	(15.4)	22.33	(18.18, 26.48)
Application site pain	171	(18.7)	33	(4.9)	13.82	(10.82, 16.81)
Application site erythema	107	(11.7)	9	(1.3)	10.36	(8.11, 12.61)
Application site pruritus	52	(5.7)	7	(1.0)	4.65	(2.97, 6.33)
Application site exfoliation	46	(5.0)	0	(0.0)	5.02	(3.61, 6.44)
Application site dermatitis	45	(4.9)	5	(0.7)	4.18	(2.64, 5.72)
Application site scar	37	(4.0)	47	(6.9)	-2.87	(-5.17, -0.58)
Application site swelling	32	(3.5)	4	(0.6)	2.91	(1.58, 4.23)
Pyrexia	20	(2.2)	7	(1.0)	1.15	(-0.06, 2.37)
Application site erosion	15	(1.6)	1	(0.1)	1.49	(0.62, 2.36)
Application site discolouration	14	(1.5)	1	(0.1)	1.38	(0.54, 2.23)
Application site vesicles	14	(1.5)	1	(0.1)	1.38	(0.54, 2.23)
Application site irritation	11	(1.2)	0	(0.0)	1.20	(0.50, 1.91)
Infections and infestations	98	(10.7)	56	(8.2)	2.46	(-0.41, 5.34)
Upper respiratory tract infection	11	(1.2)	5	(0.7)	0.47	(-0.49, 1.42)
Application site infection	10	(1.1)	3	(0.4)	0.65	(-0.19, 1.49)
Nasopharyngitis	9	(1.0)	6	(0.9)	0.10	(-0.85, 1.05)
Pharyngitis streptococcal	9	(1.0)	6	(0.9)	0.10	(-0.85, 1.05)

Skin and subcutaneous tissue disorders	31	(3.4)	14	(2.1)	1.33	(-0.26, 2.91)
Gastrointestinal disorders	26	(2.8)	4	(0.6)	2.25	(1.03, 3.47)
Vomiting	12	(1.3)	1	(0.1)	1.16	(0.37, 1.95)
Injury, poisoning and procedural complications	20	(2.2)	8	(1.2)	1.01	(-0.24, 2.25)
Respiratory, thoracic and mediastinal disorders	16	(1.7)	14	(2.1)	-0.31	(-1.68, 1.05)

Source: OCS Analysis Studio, Safety Explorer. Consistent with M 2.5, Table 8.
Filters: TRT01A = "SB206 10.3% QD" and SAFFL = "Y" (SB206 10.3% QD); TRT01A = "Vehicle Gel QD" and SAFFL = "Y" (Vehicle Gel QD); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Laboratory Findings

Clinical laboratory measurements were not included in the safety assessments for the Phase 3 trials, and negative urine pregnancy test results were reported for all female subjects ≥9 years of age.

The Clinical laboratory tests conducted during the Phase 1 MuST, NI-MC101 (hematology, chemistry, coagulation, methemoglobin, and urinalysis), and the Phase 2 dose-ranging trial, NI-MC201 (hematology, chemistry, and methemoglobin) were reported within normal range for most subjects; no TEAES related to laboratory measurements were reported (5 subjects treated with berdazimer in trial NI-MC201 were reported with abnormal laboratory results of mild severity; all deemed as not related to the study drug by the investigators.

Vital Signs

Vital signs measurements were not included in the safety assessments for the Phase 3 trials.

No TEAEs related to vital signs were reported during the Phase 1 MuST, NI-MC101. During Phase 2 trial, NI-MC201, TEAEs related to vital signs were reported in 9 subjects [increased heart rate (1), pyrexia (8)] treated with berdazimer gel; all were non-severe, unrelated to study drug, and resolved by the next day.

Electrocardiograms (ECGs)

No clinically significant changes in ECG measurements were reported in the Phase 1 MuST NI-MC101. ECG measurements were not included in the safety assessments for the Phase 2 and Phase 3 trials.

QT

The Applicant submitted the clinical study report for the thorough QTc study in subjects with acne NI-AC104 treated with berdazimer gel (SB204), 12% single dose applied to 17 %BSA (IND 137015, SDN 74, on 1/28/2022).

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

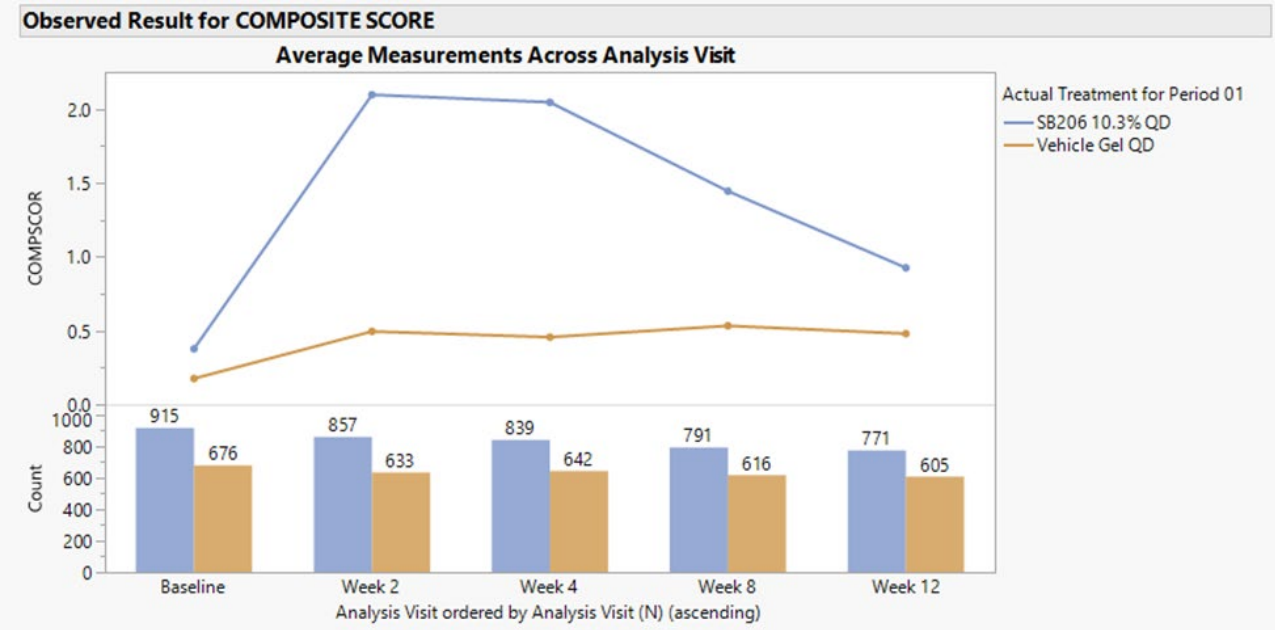
8.2.5.1. Local Skin Reactions (LSR)

The Applicant developed and used a scoring system to measure local skin reactions (LSRs) during Phase 3 trials. Each of the following 6 LSRs was rated (0-4) at each visit:

- Erythema
- Flaking/Scaling
- Crusting
- Swelling
- Vesiculation/Pustulation
- Erosion/Ulceration

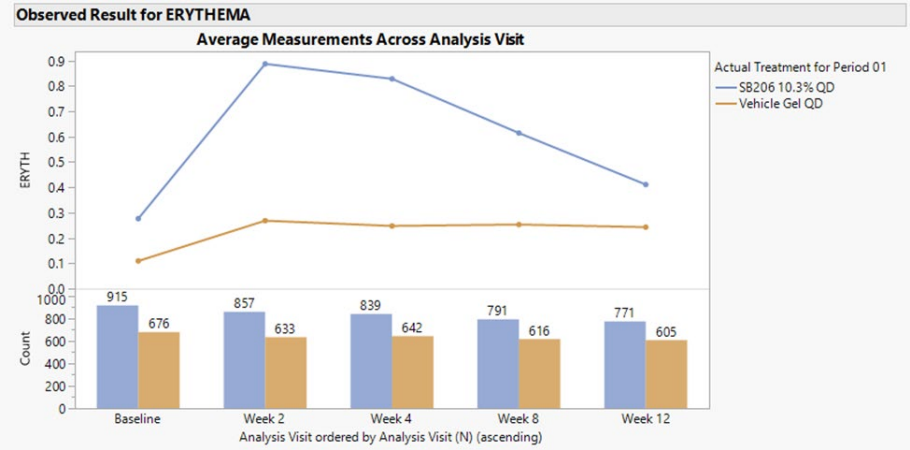
The composite LSR score (0-24) was calculated by summing all responses across the 6 LSRs. The LSR score was mainly driven by erythema, and was higher in the SB206 group compared to the vehicle group, as depicted in the following graphs:

Figure 7. Composite LSR Score (Weeks 0-12)- ISS (Unadjusted)- (Safety Population)



Source: Clinical Reviewer's analysis by JMP Clinical 8.1. Consistent with M 2.5, Figure 3.

Figure 8. Erythema LSR Score (Weeks 0-12)- ISS (Unadjusted)- (Safety Population)



Source: Clinical Reviewer's analysis by JMP Clinical 8.1.

The average values for both the composite and the erythema LSR scores in the berdazimer group peaked at Week 2 and trended towards similar average score values for the corresponding vehicle groups during Weeks 4 to 12.

8.2.5.2. Scarring

The Applicant conducted assessments of Application site scar (temporary epidermal atrophy following the resolution of an MC lesion), and hypertrophic scars and keloids as cosmetic outcomes. The only incidence of hypertrophic scars was reported for 1 subject in each group at Week 24 visit. No keloids were reported for any subject at any visit. Subjects in both berdazimer and vehicle groups demonstrated a higher frequency of reported temporary scars in the post-treatment period (Week 24) compared to on-treatment period (Weeks 0-12) as summarized in Table 35.

Table 35. Summary of Subjects Reported With Application Site Scar (Weeks 0-24), ISS (Unadjusted) (Safety Population)

Analysis Visit (Week)	SB206 10.3% QD (N=916) n (%)	Vehicle QD (N=680) n (%)
Week 4	20 (2.2)	17 (2.5)
Week 8	23 (2.5)	29 (4.3)
Week 12	31 (3.4)	26 (3.8)
Week 24	45 (4.9)	43 (6.3)

Source: M 2.5, Table 13. Consistent with Clinical Reviewer's analysis by JMP.

8.2.5.3. Allergic Contact Dermatitis (ACD)

For subjects (in the ISS safety population) included in the berdazimer group compared to the vehicle group, respectively:

- TEAE of Application site dermatitis was reported in 45/916 (4.9%) vs. 5/680 (0.7%).
- AELDs of Application site dermatitis was reported in 13 (1.4%) vs. 0.

Among subjects who were reported with application site dermatitis and suspected allergic contact dermatitis, patch testing was conducted for two subjects ([redacted] and [redacted]). A positive patch testing result was confirmed in one subject ([redacted]).

Application site reactions (including allergic contact dermatitis) will be included in Sec. 5.1 of the proposed label.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Refer to the "Analysis of Submission-Specific Safety Issues" section of this review above for a discussion of the COAs related to the LSRs and scarring.

8.2.7. Safety Analyses by Demographic Subgroups

In view of the small sample sizes, the utility of analyzing TEAEs by demographic subgroups is limited. The review of safety data revealed no substantial differences in the risk of adverse reactions in demographic subgroups. However, because the trials were not powered for these analyses, the data must be interpreted with caution.

Age

Analysis of TEAEs (reported in ≥ 1% of subjects in any treatment group during Weeks 0- 12) by age indicated a similar frequency of TEAEs by treatment group reported for subjects < 2 years of age compared to subjects ≥ 2 years of age as summarized in Table 36.

Table 36. Summary of TEAEs by Age Category and by SOC and PT (Weeks 0-12)- ISS (Unadjusted)- Reported in ≥1% of Subjects in Any Group (Safety Population)

	SB206 10.3% QD < 2 YO (N=29)		SB206 10.3% QD >= 2 YO (N=887)		Vehicle Gel QD < 2 YO (N=16)		Vehicle Gel QD >= 2 YO (N=664)	
System Organ Class - Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
General disorders and administration site conditions	10	(34.5)	336	(37.9)	3	(18.8)	102	(15.4)
Application site pain	4	(13.8)	167	(18.8)	0	(0.0)	33	(5.0)
Application site erythema	3	(10.3)	104	(11.7)	1	(6.3)	8	(1.2)
Application site dermatitis	2	(6.9)	43	(4.8)	0	(0.0)	5	(0.8)
Application site irritation	2	(6.9)	9	(1.0)	0	(0.0)	0	(0.0)
Application site swelling	2	(6.9)	30	(3.4)	0	(0.0)	4	(0.6)
Application site eczema	1	(3.4)	3	(0.3)	0	(0.0)	3	(0.5)
Application site exfoliation	1	(3.4)	45	(5.1)	0	(0.0)	0	(0.0)
Application site pruritus	1	(3.4)	51	(5.7)	0	(0.0)	7	(1.1)
Application site rash	1	(3.4)	1	(0.1)	0	(0.0)	2	(0.3)

System Organ Class - Preferred Term	SB206 10.3% QD < 2 YO (N=29) n	(%)	SB206 10.3% QD >= 2 YO (N=887) n	(%)	Vehicle Gel QD < 2 YO (N=16) n	(%)	Vehicle Gel QD >= 2 YO (N=664) n	(%)
Pyrexia	1	(3.4)	19	(2.1)	0	(0.0)	7	(1.1)
Application site discolouration	0	(0.0)	14	(1.6)	0	(0.0)	1	(0.2)
Application site erosion	0	(0.0)	15	(1.7)	0	(0.0)	1	(0.2)
Application site scar	0	(0.0)	37	(4.2)	2	(12.5)	45	(6.8)
Application site vesicles	0	(0.0)	14	(1.6)	0	(0.0)	1	(0.2)
Infections and infestations	5	(17.2)	93	(10.5)	2	(12.5)	54	(8.1)
Nasopharyngitis	2	(6.9)	7	(0.8)	0	(0.0)	6	(0.9)
Bronchitis	1	(3.4)	1	(0.1)	0	(0.0)	2	(0.3)
Fungal skin infection	1	(3.4)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis media	1	(3.4)	5	(0.6)	0	(0.0)	2	(0.3)
Upper respiratory tract infection	1	(3.4)	10	(1.1)	1	(6.3)	4	(0.6)
Application site infection	0	(0.0)	10	(1.1)	0	(0.0)	3	(0.5)
Pharyngitis streptococcal	0	(0.0)	9	(1.0)	0	(0.0)	6	(0.9)
Rhinovirus infection	0	(0.0)	0	(0.0)	1	(6.3)	0	(0.0)
Skin and subcutaneous tissue disorders	2	(6.9)	29	(3.3)	0	(0.0)	14	(2.1)
Rash	2	(6.9)	4	(0.5)	0	(0.0)	3	(0.5)
Gastrointestinal disorders	1	(3.4)	25	(2.8)	0	(0.0)	4	(0.6)
Diarrhoea	1	(3.4)	5	(0.6)	0	(0.0)	0	(0.0)
Teething	1	(3.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	12	(1.4)	0	(0.0)	1	(0.2)
Injury, poisoning and procedural complications	0	(0.0)	20	(2.3)	0	(0.0)	8	(1.2)
Respiratory, thoracic and mediastinal disorders	0	(0.0)	16	(1.8)	0	(0.0)	14	(2.1)

Source: OCS Analysis Studio, Safety Explorer by the Clinical Reviewer. Consistent with M 2.5, Table 14 and ISS Table 14.3.1.2.4.
Filters: TRT01A = "SB206 10.3% QD" and AGEGR1 = "<1 year old" or ">=1 to < 2 years old" and SAFFL = "Y" (SB206 10.3% QD < 2 YO); TRT01A = "SB206 10.3% QD" and AGEGR1 = ">=2 years old to < 6 years old" or ">=6 years old to < 12 years old" or ">=12 years old to < 18 years old" or ">=18 years old" and SAFFL = "Y" (SB206 10.3% QD >= 2 YO); TRT01A = "Vehicle Gel QD" and AGEGR1 = "<1 year old" or ">=1 to < 2 years old" and SAFFL = "Y" (Vehicle Gel QD < 2 YO); TRT01A = "Vehicle Gel QD" and AGEGR1 = ">=2 years old to < 6 years old" or ">=6 years old to < 12 years old" or ">=12 years old to < 18 years old" or ">=18 years old" and SAFFL = "Y" (Vehicle Gel QD >= 2 YO); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Sex

Analysis of TEAEs (reported in ≥ 1% of subjects in any treatment group during Weeks 0-12) by sex indicated a similar frequency of TEAEs by treatment group reported for male and female subjects as summarized in Table 37.

Table 37. Summary of TEAEs by Sex Category and by SOC and PT (Weeks 0-12)- ISS (Unadjusted)- Reported in ≥1% of Subjects in Any Group (Safety Population)

	SB206 10.3% QD Male (N=471)		SB206 10.3% QD Female (N=445)		Vehicle Gel QD Male (N=336)		Vehicle Gel QD Female (N=344)	
System Organ Class - Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
General disorders and administration site conditions	173	(36.7)	173	(38.9)	47	(14.0)	58	(16.9)
Application site pain	86	(18.3)	85	(19.1)	13	(3.9)	20	(5.8)
Application site erythema	49	(10.4)	58	(13.0)	3	(0.9)	6	(1.7)
Application site exfoliation	22	(4.7)	24	(5.4)	0	(0.0)	0	(0.0)
Application site dermatitis	22	(4.7)	23	(5.2)	3	(0.9)	2	(0.6)
Application site pruritus	31	(6.6)	21	(4.7)	3	(0.9)	4	(1.2)
Application site scar	17	(3.6)	20	(4.5)	23	(6.8)	24	(7.0)
Application site swelling	14	(3.0)	18	(4.0)	3	(0.9)	1	(0.3)
Pyrexia	5	(1.1)	15	(3.4)	2	(0.6)	5	(1.5)
Application site vesicles	5	(1.1)	9	(2.0)	1	(0.3)	0	(0.0)
Application site erosion	7	(1.5)	8	(1.8)	1	(0.3)	0	(0.0)
Application site discolouration	8	(1.7)	6	(1.3)	0	(0.0)	1	(0.3)
Application site irritation	6	(1.3)	5	(1.1)	0	(0.0)	0	(0.0)
Infections and infestations	43	(9.1)	55	(12.4)	24	(7.1)	32	(9.3)
Otitis media	0	(0.0)	6	(1.3)	0	(0.0)	2	(0.6)
Pharyngitis streptococcal	3	(0.6)	6	(1.3)	2	(0.6)	4	(1.2)
Application site pustules	2	(0.4)	5	(1.1)	1	(0.3)	0	(0.0)
Upper respiratory tract infection	6	(1.3)	5	(1.1)	2	(0.6)	3	(0.9)
Nasopharyngitis	5	(1.1)	4	(0.9)	3	(0.9)	3	(0.9)
Application site infection	7	(1.5)	3	(0.7)	1	(0.3)	2	(0.6)
Gastrointestinal disorders	9	(1.9)	17	(3.8)	2	(0.6)	2	(0.6)
Vomiting	4	(0.8)	8	(1.8)	1	(0.3)	0	(0.0)
Skin and subcutaneous tissue disorders	16	(3.4)	15	(3.4)	8	(2.4)	6	(1.7)
Injury, poisoning and procedural complications	9	(1.9)	11	(2.5)	4	(1.2)	4	(1.2)
Arthropod bite	1	(0.2)	5	(1.1)	0	(0.0)	1	(0.3)
Respiratory, thoracic and mediastinal disorders	5	(1.1)	11	(2.5)	9	(2.7)	5	(1.5)

Source: OCS Analysis Studio, Safety Explorer by the Clinical Reviewer. Consistent with M 2.5, Table 14 and ISS Table 14.3.1.2.4.
Filters: TRT01A = "SB206 10.3% QD" and SEX = "M" and SAFFL = "Y" (SB206 10.3% QD Male); TRT01A = "SB206 10.3% QD" and SEX = "F" and SAFFL = "Y" (SB206 10.3% QD Female); TRT01A = "Vehicle Gel QD" and SEX = "M" and SAFFL = "Y" (Vehicle Gel QD Male); TRT01A = "Vehicle Gel QD" and SEX = "F" and SAFFL = "Y" (Vehicle Gel QD Female); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Race

The number of subjects in each race subgroups for non-white subjects were too small for meaningful analysis. Analysis of TEAEs (reported in ≥ 1% of subjects in any treatment group during Weeks 0-12) by race shows a trend towards a higher frequency of application site pain, application site erythema, and application site exfoliation in white subjects, compared to non-white subjects treated with berdazimer. For vehicle-treated subjects, a trend towards a higher frequency of application site scar was reported in non-white subjects as summarized in Table 38.

Table 38. Summary of TEAEs by Race Category and by SOC and PT (Weeks 0-12)- ISS (Unadjusted)- Reported in ≥1% of Subjects in Any Group (Safety Population)

	SB206 10.3% QD White (N=814)		SB206 10.3% QD Non-white (N=88)		Vehicle Gel QD White (N=586)		Vehicle Gel QD Non-white (N=79)	
System Organ Class - Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
General disorders and administration site conditions	316	(38.8)	25	(28.4)	90	(15.4)	14	(17.7)
Application site pain	157	(19.3)	11	(12.5)	29	(4.9)	3	(3.8)
Application site erythema	100	(12.3)	5	(5.7)	7	(1.2)	1	(1.3)
Application site exfoliation	44	(5.4)	2	(2.3)	0	(0.0)	0	(0.0)
Application site pruritus	44	(5.4)	6	(6.8)	7	(1.2)	0	(0.0)
Application site dermatitis	41	(5.0)	3	(3.4)	5	(0.9)	0	(0.0)
Application site scar	34	(4.2)	3	(3.4)	38	(6.5)	9	(11.4)
Application site swelling	31	(3.8)	1	(1.1)	3	(0.5)	1	(1.3)
Pyrexia	20	(2.5)	0	(0.0)	7	(1.2)	0	(0.0)
Application site erosion	14	(1.7)	1	(1.1)	0	(0.0)	1	(1.3)
Application site vesicles	13	(1.6)	1	(1.1)	0	(0.0)	1	(1.3)
Application site discolouration	11	(1.4)	3	(3.4)	1	(0.2)	0	(0.0)
Application site irritation	10	(1.2)	1	(1.1)	0	(0.0)	0	(0.0)
Application site scab	5	(0.6)	1	(1.1)	1	(0.2)	0	(0.0)
Application site dryness	4	(0.5)	1	(1.1)	0	(0.0)	0	(0.0)
Application site ulcer	2	(0.2)	0	(0.0)	0	(0.0)	1	(1.3)
Application site rash	1	(0.1)	1	(1.1)	1	(0.2)	1	(1.3)
Infections and infestations	90	(11.1)	5	(5.7)	49	(8.4)	6	(7.6)
Upper respiratory tract infection	11	(1.4)	0	(0.0)	4	(0.7)	0	(0.0)
Application site infection	9	(1.1)	1	(1.1)	2	(0.3)	0	(0.0)
Pharyngitis streptococcal	9	(1.1)	0	(0.0)	6	(1.0)	0	(0.0)
Nasopharyngitis	8	(1.0)	0	(0.0)	6	(1.0)	0	(0.0)
Application site pustules	7	(0.9)	0	(0.0)	0	(0.0)	1	(1.3)
Gastroenteritis	4	(0.5)	1	(1.1)	0	(0.0)	0	(0.0)

System Organ Class - Preferred Term	SB206 10.3% QD White (N=814) n	(%)	SB206 10.3% QD Non-white (N=88) n	(%)	Vehicle Gel QD White (N=586) n	(%)	Vehicle Gel QD Non-white (N=79) n	(%)
Ear infection	3	(0.4)	1	(1.1)	2	(0.3)	1	(1.3)
Bronchitis	2	(0.2)	0	(0.0)	1	(0.2)	1	(1.3)
Hand-foot-and-mouth disease	1	(0.1)	0	(0.0)	0	(0.0)	1	(1.3)
Abscess limb	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Hordeolum	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.5)
Influenza	0	(0.0)	1	(1.1)	2	(0.3)	0	(0.0)
Ophthalmic herpes zoster	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	28	(3.4)	3	(3.4)	13	(2.2)	1	(1.3)
Dermatitis	3	(0.4)	1	(1.1)	0	(0.0)	0	(0.0)
Keratosis pilaris	1	(0.1)	0	(0.0)	0	(0.0)	1	(1.3)
Alopecia areata	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
Hand dermatitis	0	(0.0)	1	(1.1)	1	(0.2)	0	(0.0)
Gastrointestinal disorders	23	(2.8)	3	(3.4)	4	(0.7)	0	(0.0)
Vomiting	10	(1.2)	2	(2.3)	1	(0.2)	0	(0.0)
Malocclusion	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	19	(2.3)	1	(1.1)	7	(1.2)	1	(1.3)
Skin abrasion	4	(0.5)	1	(1.1)	2	(0.3)	0	(0.0)
Skin laceration	2	(0.2)	0	(0.0)	0	(0.0)	1	(1.3)
Respiratory, thoracic and mediastinal disorders	15	(1.8)	1	(1.1)	11	(1.9)	3	(3.8)
Cough	4	(0.5)	1	(1.1)	4	(0.7)	1	(1.3)
Nasal congestion	2	(0.2)	0	(0.0)	1	(0.2)	1	(1.3)
Asthma	1	(0.1)	0	(0.0)	1	(0.2)	1	(1.3)

Source: OCS Analysis Studio, Safety Explorer by the Clinical Reviewer. Consistent with M 2.5, Table 14 and ISS Table 14.3.1.2.4.
Filters: TRT01A = "SB206 10.3% QD" and RACE = "WHITE" and SAFFL = "Y" (SB206 10.3% QD White); TRT01A = "SB206 10.3% QD" and RACE = "BLACK OR AFRICAN AMERICAN" or "MULTIPLE" or "ASIAN" or "NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER" or "AMERICAN INDIAN OR ALASKA NATIVE" and SAFFL = "Y" (SB206 10.3% QD Non-white); TRT01A = "Vehicle Gel QD" and RACE = "WHITE" and SAFFL = "Y" (Vehicle Gel QD White); TRT01A = "Vehicle Gel QD" and RACE = "BLACK OR AFRICAN AMERICAN" or "MULTIPLE" or "ASIAN" or "NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER" or "AMERICAN INDIAN OR ALASKA NATIVE" and SAFFL = "Y" (Vehicle Gel QD Non-white); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Ethnicity

Analysis of TEAEs (reported in ≥ 1% of subjects in any treatment group during Weeks 0-12) by ethnicity indicated a similar frequency of TEAEs by treatment group reported for Hispanic and Non-Hispanic subjects as summarized in Table 39.

Table 39. Summary of TEAEs by Ethnicity Category and by SOC and PT (Weeks 0-12)- ISS (Unadjusted)- Reported in ≥1% of Subjects in Any Group (Safety Population)

	SB206 10.3% QD Hispanic (N=195)		SB206 10.3% QD Non-Hispanic (N=713)		Vehicle Gel QD Hispanic (N=141)		Vehicle Gel QD Non-Hispanic (N=536)	
System Organ Class - Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
General disorders and administration site conditions	67	(34.4)	274	(38.4)	14	(9.9)	91	(17.0)
Application site pain	33	(16.9)	134	(18.8)	4	(2.8)	29	(5.4)
Application site erythema	17	(8.7)	88	(12.3)	4	(2.8)	5	(0.9)
Application site dermatitis	12	(6.2)	32	(4.5)	1	(0.7)	4	(0.7)
Application site exfoliation	10	(5.1)	35	(4.9)	0	(0.0)	0	(0.0)
Application site swelling	7	(3.6)	25	(3.5)	2	(1.4)	2	(0.4)
Application site pruritus	6	(3.1)	46	(6.5)	2	(1.4)	5	(0.9)
Application site scar	6	(3.1)	31	(4.3)	3	(2.1)	44	(8.2)
Application site erosion	4	(2.1)	10	(1.4)	1	(0.7)	0	(0.0)
Application site irritation	4	(2.1)	7	(1.0)	0	(0.0)	0	(0.0)
Pyrexia	4	(2.1)	15	(2.1)	1	(0.7)	6	(1.1)
Application site discolouration	3	(1.5)	10	(1.4)	0	(0.0)	1	(0.2)
Application site vesicles	2	(1.0)	11	(1.5)	1	(0.7)	0	(0.0)
Infections and infestations	22	(11.3)	76	(10.7)	7	(5.0)	49	(9.1)
Nasopharyngitis	4	(2.1)	5	(0.7)	0	(0.0)	6	(1.1)
Application site infection	3	(1.5)	7	(1.0)	1	(0.7)	2	(0.4)
Molluscum contagiosum	3	(1.5)	2	(0.3)	0	(0.0)	0	(0.0)
Application site pustules	2	(1.0)	5	(0.7)	1	(0.7)	0	(0.0)
Ear infection	2	(1.0)	2	(0.3)	0	(0.0)	3	(0.6)
Otitis media	2	(1.0)	4	(0.6)	0	(0.0)	2	(0.4)
Pharyngitis streptococcal	2	(1.0)	7	(1.0)	1	(0.7)	5	(0.9)
Upper respiratory tract infection	2	(1.0)	9	(1.3)	1	(0.7)	4	(0.7)
Skin and subcutaneous tissue disorders	7	(3.6)	22	(3.1)	2	(1.4)	12	(2.2)
Gastrointestinal disorders	6	(3.1)	19	(2.7)	0	(0.0)	4	(0.7)
Diarrhoea	3	(1.5)	3	(0.4)	0	(0.0)	0	(0.0)
Vomiting	3	(1.5)	9	(1.3)	0	(0.0)	1	(0.2)
Abdominal pain upper	2	(1.0)	4	(0.6)	0	(0.0)	1	(0.2)
Injury, poisoning and procedural complications	3	(1.5)	16	(2.2)	1	(0.7)	7	(1.3)
Musculoskeletal and connective tissue disorders	2	(1.0)	1	(0.1)	0	(0.0)	1	(0.2)
Arthralgia	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)

System Organ Class - Preferred Term	SB206 10.3% QD Hispanic (N=195) n	(%)	SB206 10.3% QD Non-Hispanic (N=713) n	(%)	Vehicle Gel QD Hispanic (N=141) n	(%)	Vehicle Gel QD Non-Hispanic (N=536) n	(%)
Reproductive system and breast disorders	2	(1.0)	1	(0.1)	0	(0.0)	0	(0.0)
Genital rash	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	1	(0.5)	3	(0.4)	2	(1.4)	1	(0.2)
Headache	1	(0.5)	3	(0.4)	2	(1.4)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	1	(0.5)	14	(2.0)	2	(1.4)	12	(2.2)

Source: OCS Analysis Studio, Safety Explorer by the Clinical Reviewer. Consistent with M 2.5, Table 14 and ISS Table 14.3.1.2.4
Filters: TRT01A = "SB206 10.3% QD" and ETHNIC = "HISPANIC OR LATINO" and SAFFL = "Y" (SB206 10.3% QD Hispanic); TRT01A = "SB206 10.3% QD" and ETHNIC = "NOT HISPANIC OR LATINO" and SAFFL = "Y" (SB206 10.3% QD Non-hispanic); TRT01A = "Vehicle Gel QD" and ETHNIC = "HISPANIC OR LATINO" and SAFFL = "Y" (Vehicle Gel QD Hispanic); TRT01A = "Vehicle Gel QD" and ETHNIC = "NOT HISPANIC OR LATINO" and SAFFL = "Y" (Vehicle Gel QD Non-hispanic); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

8.2.8. Specific Safety Studies/Clinical Trials

Dermal Safety and Photosafety Studies

The Applicant conducted proactive dermal safety assessments in subjects with MC treated with berdazimer gel, 10.3% QD during Phase 3 clinical trials.

Additionally, the Applicant submitted the results of two provocative dermal safety studies previously conducted for berdazimer gel, 3.4% (SB204) in healthy adult subjects in their acne drug development program. In general, the number of subjects enrolled and the design and conduct of these studies were consistent with the typical requirements for dermal safety studies. The repeat insult patch test (NI-AC105) found no subject to be sensitized during challenge reading, and the cummulative irritation patch test (NI-AC106) found berdazimer gel, 3.4% (SB204) to be slightly irritating (under the exaggerated conditions of semi-occlusive patch applications for 21 consecutive days). FDA granted a waiver for conducting provocative dermal photosafety studies based on the lack of significant absorbance of either the NVN1000 drug substance or the drug product (SB206 gel) in the 290-700 nm range (7/12/2019).

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable to berdazimer sodium gel drug product.

Human Reproduction and Pregnancy

Not applicable to berdazimer sodium gel drug product.

Pediatrics and Assessment of Effects on Growth

Not applicable to berdazimer sodium gel drug product.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable to berdazimer sodium gel drug product.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Berdazimer gel has not been marketed in any country, and there are no postmarketing safety data available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the berdazimer gel, 10.3% safety data for treatment of MC identified no safety signals. There are no safety concerns that are expected to change the favorable benefit/risk assessment or lead to increased risk with administration of berdazimer gel, 10.3% in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The safety profile of berdazimer gel, 10.3% was adequately characterized during the drug development program. The primary review of safety of the drug product for topical treatment of molluscum contagiosum relied on the evaluation of the ISS pooled safety data from 1596 subjects enrolled in three Phase 3, vehicle-controlled trials (NI-MC301/-302/-304); which were similar in design, trial population, dosing regimen, and key primary and secondary efficacy endpoints. Eligible subjects were randomized in a 2:1 ratio in trials NI-MC301/-302 or a 1:1 ratio in trial NI-MC304 to receive berdazimer gel or vehicle gel once daily for up to 12 weeks.

Additionally, the Applicant submitted supportive safety data from a phase 2a, dose-ranging trial (NI-MC201) in subjects with MC, and two provocative Phase 1 dermal safety studies (NI-AC105/-106) conducted with SB204 gel, 3.4% in their acne drug development program.

No death was reported during berdazimer development program. For the ISS safety pool, the following safety results were reported:

- SAEs were reported in 1/916 (0.1%) subject treated with berdazimer (resolved, not related), compared to 2/680 (0.3%) subject treated with vehicle.
- AELDs were reported at a frequency of 42/916 (4.6%) subjects treated with berdazimer, compared to 5/680 (0.7%) subjects treated with vehicle.
- TEAEs were reported in 428/916 (46.7%) subjects treated with berdazimer, compared to 169/680 (24.9%) subjects treated with vehicle. The PTs reported as TEAEs in ≥1% of subjects treated with berdazimer (and at a higher frequency than for vehicle), compared to vehicle,

respectively, included the following application site reactions: pain (18.7% v. 4.9%), erythema (11.7% v. 1.3%), pruritus (5.7% v. 1.0%), exfoliation (5.0% v. 0), dermatitis (4.9% v. 0.7%), swelling (3.5% v. 0.6%), erosion (1.6% v. 0.1%), discoloration (1.5% v. 0.1%), vesicles (1.5% v. 0.1%), irritation (1.2% v. 0), and infection (1.1% v. 0.4%); additional AEs included pyrexia (2.2% v. 1.0%), upper respiratory tract infection (1.2% v. 0.7%), nasopharyngitis (1.0% v. 0.9%), streptococcal pharyngitis (1.0% v. 0.9%), and vomiting (1.3% v. 0.1%).

- Severe AEs were reported in 16/916 (1.7%) subjects treated with berdazimer, compared to 2/680 (0.3%) of subjects treated with the vehicle.
- ADRs: Adverse Drug Reactions (possibly, probably, or likely related to the study drug) were reported in 336/916 (36.7%) subjects treated with berdazimer, compared to 81/680 (11.9%) of subjects treated with vehicle.
- Recurrence of MC lesions following complete clearance of all MC lesions at Week 12 was reported by 2 subjects treated with berdazimer, compared to no subjects treated with vehicle.
- Local skin reactions (LSR) were assessed by a composite LSR score (mainly driven by the erythema score) which was slightly higher in the berdazimer group compared to the vehicle group during Weeks 2-4. Both the composite LSR score and the erythema LSR score in berdazimer group trended towards scores similar to the vehicle group during Weeks 4-12.
- A potential risk for methemoglobinemia in subjects with MC treated with topical berdazimer gel in the phase 1, maximal use study (NI-MC101) and the phase 2, dose ranging trial NI-MC201 was assessed by the Clinical Pharmacology review team in subjects 2 years of age and older; and was determined as not clinically significant. No subjects between 1 to less than 2 years of age were enrolled in either study and no methemoglobin measurements are available in the age group less than 2 years of age. However, based on the overall similar safety profiles observed in subjects between 1 to less than 2 years of age and subjects 2 years of age and older, the Clinical and Clinical Pharmacology review teams concluded that a dedicated PK/safety study to include methemoglobin measurements in the age group between 1 to less than 2 years of age as a postmarketing requirement (PMR) would not be necessary, and a PMR will not be issued.

The available data from the clinical trials demonstrated that berdazimer gel, 10.3% once daily was safe in the treatment of subjects ≥1 year of age with MC. Postmarketing risk management will include professional labeling and routine pharmacovigilance. No PMRs will be issued for berdazimer gel.

120-Day Safety Update

Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-Day Safety Update Report (SDN 12 on 4/18/2023). The review team identified no new safety signals in the safety update report.

8.3. Statistical Issues

The primary efficacy endpoint achieved statistical significance in Study NI-MC304 and just missed the cutoff in Study NI-MC302. Although Study NI-MC301 did not achieve statistical significance for the primary endpoint, a positive trend was observed. The findings in Study NI-MC304 were robust to the handling of missing data and consistent across subgroups. Studies NI-MC301 and NI-MC302 had imbalanced missing data with a greater portion of subjects on the active arm than the vehicle arm having missing data. Non-responder imputation magnified the impact of the missing data pattern and attenuated the treatment effect. Many of the sensitivity analyses that used alternate assumptions for the handling of missing data in Study NI-MC302 led to nominally significant findings.

The primary efficacy endpoint of complete clearance rate at Week 12 is considered inherently clinically meaningful, however, analyzing continuous variable using a binary outcome may result in loss of power and precision. The statistical reviewer conducted exploratory analyses based on the continuous endpoint to improve the power. The results of exploratory analyses based on continuous endpoint of change or percent change in MC lesion count from baseline to Week 12 were supportive of the findings on the binary primary endpoint.

In the Applicant's SAS code for calculating the 95% CI for the treatment difference, they used a wrong standard error for each treatment arm, i.e., they used the standard error of the predicted proportion rather than the standard error of the predicted log odds. The statistical reviewer corrected this error, which leads to minor differences in the statistical reviewer's results compared to the Applicant's results in three studies. The Applicant acknowledged this error in the labeling communication with the Agency, and the corrected results are included in labeling.

8.4. Conclusions and Recommendations

To establish the safety and efficacy of berdazimer gel, 10.3% in the treatment of MC, the Applicant submitted data from three similarly designed, randomized, double-blind, vehicle-controlled, parallel-group trials (NI-MC301/-302/-304). Subjects applied berdazimer gel, 10.3% once daily to all treatable MC lesions for up to 12 weeks. The three Phase 3 trials enrolled a total of 1596 subjects ≥6 months of age with between 3 to 70 MC lesions at baseline.

All trials evaluated the primary efficacy endpoint of the proportion of subjects with complete clearance of all treatable MC lesions at Week 12 and a key secondary efficacy endpoint of the complete clearance of all treatable MC lesions at Week 8.

The primary efficacy endpoint results from Study NI-MC304 were statistically significant ($p<0.0001$; treatment difference of 12.8%, 95% CI (7.1%, 18.6%)), consistent across subgroups and sensitivity analyses, and supported by the findings on the key secondary endpoint at Week 8. Thus, efficacy has been demonstrated in Study NI-MC304.

In Study NI-MC302, although the results for the primary endpoint analysis at Week 12 just missed the significance threshold ($p=0.0510$), the point estimates and treatment effect

estimate were similar to those observed in Study NI-MC304 (treatment difference of 9.2%, 95% CI (-0.04%, 18.4%)) and the secondary endpoint (complete clearance at Week 8) was supportive of the Week 12 result. The prespecified method of handling missing data in Study NI-MC302 was conservative, and many sensitivity analyses that used reasonable alternative methods of handling missing data had nominally significant findings. In addition, exploratory endpoints that evaluated change or percent change in lesion counts, rather than a dichotomized response endpoint, support an efficacy finding for Study NI-MC302. The complete evaluation of the efficacy results, including primary endpoint results, sensitivity and supplementary analyses, and secondary and exploratory endpoint results, were persuasive and confirm that efficacy had been demonstrated in Study NI-MC302.

While the third trial (Study NI-MC301) did not demonstrate efficacy on the primary endpoint, an imbalance in the amount of missing data on the two treatment arms along with a conservative method of handling missing data may have contributed to the attenuated treatment effect. Although the observed treatment effect in Study NI-MC301 was smaller than in the other two trials, the study did have a small trend in favor of the active treatment, and the results do not detract from an overall demonstration of efficacy in the development program.

To define the safety profile of berdazimer gel, 10.3%, the Applicant conducted a comprehensive assessment of the safety of the drug product in the target population. There were no deaths and no drug-related SAEs. The size of the safety database, subject exposure, and safety assessments were adequate to characterize the safety profile of berdazimer gel, 10.3%.

The Applicant submitted safety data from 1596 subjects who participated in the Phase 3, vehicle-controlled trials to support the safety of berdazimer gel, 10.3%, for topical treatment of MC. In the ISS safety pool, the most frequently reported adverse events were the following application site reactions: pain (18.7% v. 4.9%), erythema (11.7% v. 1.3%), pruritus (5.7% v. 1.0%), exfoliation (5.0% v. 0), dermatitis (4.9% v. 0.7%), swelling (3.5% v. 0.6%), erosion (1.6% v. 0.1%), discoloration (1.5% v. 0.1%), vesicles (1.5% v. 0.1%), irritation (1.2% v. 0), and infection (1.1% v. 0.4%); additional AEs included pyrexia (2.2% v. 1.0%), upper respiratory tract infection (1.2% v. 0.7%), nasopharyngitis (1.0% v. 0.9%), streptococcal pharyngitis (1.0% v. 0.9%), and vomiting (1.3% v. 0.1%).

The Applicant provided adequate efficacy and safety data to support the conclusion that the benefit-risk analysis is favorable for approval of NDA 217424. This reviewer recommends approval of berdazimer gel, 10.3%, applied topically once a day, for the treatment of molluscum contagiosum in patients ≥1 year of age.

9. Advisory Committee Meeting and Other External Consultations

The Agency did not hold an Advisory Committee Meeting for this application, because there were no efficacy, safety, or novel/complex regulatory issues that required input from an Advisory Committee.

10. Pediatrics

Because berdazimer gel, 10.3% is a new active ingredient, it triggers the requirement under the PREA (21 USC 355c) for an assessment of its safety and effectiveness for the topical treatment of MC in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In an Amended Agreed iPSP letter of 12/30/2021, the Agency agreed with the Applicant's plan to request a waiver for pediatric subjects between ages of 0 to <6 months of age (because necessary studies are impossible or highly impracticable), no request for deferral of pediatric studies, and inclusion of pediatric subjects between ages of 6 months to <18 years of age in the Phase 3 clinical trials.

The Applicant's PREA Waiver request/Deferral request/Pediatric Plan and Assessment Template was presented and discussed at the Pediatric Review Committee (PeRC) meeting on 8/22/2023. The PeRC agreed with the Division's recommendation to grant a partial waiver to subjects under 6 months of age, and pediatric assessment for subjects ≥6 months of age. The PeRC also agreed with the Division's recommendation for not issuing a PREA PMR for this product.

The PREA Waiver request/Deferral request/Pediatric Plan and Assessment Template was revised to reflect the review teams' recommended (b) (4) and discussed at the Pediatric Review Committee (PeRC) meeting on 12/5/2023. The PeRC agreed with the Division's assessment that a dedicated study in patients with MC between 6 months to less than one year of age may be impossible or highly impracticable, and a partial waiver be granted for patients less than one year of age.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI; also known as patient information), container labels and carton labeling for ZELSUVMI (berdazimer) gel, 10.3%. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, PPI, and the carton/container. These comments are reflected in final labeling.

Office of Prescription Drug Promotion (OPDP)) reviewed the Patient Package Insert (PPI) and Instructions for Use (IFU) and provided comments to convey to the Applicant (Review in DARRTS on 8/28/2023).

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) reviewed the revised container labels and carton labeling for ZELSUVMI to determine if they were acceptable from a medication error perspective and found the revisions acceptable and had no additional recommendations (Review in DARRTS on 11/29/2023) .

The Division of Antiviral Products (CDER/OND/OAP/DAV) evaluated (b) (4) non-clinical studies of berdazimer, in response to a consult request by DDD. (b) (4)

Other Prescription Drug Labeling

The final labeling, agreed with the Applicant, reflects all recommendations from the review teams.

12. Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time.

13. Postmarketing Requirements and Commitment

The review team recommends that no PMRs be required for this product based on their review of the data submitted to this NDA.

14. Division Director (Clinical) Comments

I concur with the review team recommendation for approval of berdazimer gel, 10.3%, a new molecular entity (NME) for the treatment of molluscum contagiosum (MC) in patients 1 year of age and older based on the review team determination that the benefit risk analysis is in favor of such approval.

The Applicant conducted three multicenter, randomized, double-blind, vehicle controlled, phase 3 trials (NI-MC301, NI-MC302, and NI-MC304) to evaluate the efficacy and safety of SB206 (berdazimer gel, 10.3%) in subjects with MC. The first two phase 3 trials (NI-MC301 and NI-MC302) were conducted concurrently and followed the same trial design with a randomization in a 2:1 ratio to either SB206 or vehicle. The third phase 3 trial (NI-MC304) generally followed the same study protocol as the first two except that the randomization ratio was 1:1 and stratification factors of the third trial were different.

For all three studies, the primary efficacy endpoint was the proportion of subjects with complete clearance of all treatable MC at Week 12. Complete clearance was defined as having

a total number of lesion count of 0 at assessment. For the primary endpoint, the complete clearance rate at Week 12 in the SB206 arm was statistically significantly higher than that in the vehicle arm in Study NI-MC304 ($p < 0.0001$); the statistical significance just missed the cutoff in Study NI-MC302 ($p = 0.0510$) and was not achieved in Study NI-MC301 ($p = 0.3637$). The review team had noted that in Study NI-MC301, missing data was highly imbalanced between treatment groups: the vehicle arm had a much lower proportion of missing data (3.4%) than the SB206 arm (16.1%). Similar as Study NI-MC302, non-responder imputation in the primary analysis made the resulting treatment effect in favor of the vehicle arm. Hence, the highly imbalanced missing data and non-responder imputation were considered to largely contribute to the inadequate efficacy in Study NI-MC301. Exploratory analyses based on the continuous endpoint of change or percent change in MC lesion count were supportive of the primary endpoint of complete clearance.

In Studies NI-MC302 and NI-MC304, the results for change in lesion count from baseline to Week 12 using MMRM were nominally statistically significant ($p=0.0015$ and $p < 0.0001$, respectively), lending support to the findings on the primary endpoint. The results in Study NI-MC301 were not nominally significant ($p=0.3033$). The results for percent change in lesion count from baseline to Week 12 were similar with supportive findings in Studies NI-MC302 and NI-MC304 ($p=0.0090$ and $p < 0.0001$) and non-significant findings in Study NI-MC301 ($p=0.1514$). The key secondary efficacy endpoint to be included into the labeling is the proportion of subjects with complete clearance of all treatable MC at Week 8.For the key secondary endpoint, efficacy of the SB206 arm compared to the vehicle arm was demonstrated in Study NI-MC304 ($p = 0.0012$) and the p-value was nominally significant in Study NI-MC302 ($p = 0.0114$); the statistical significance was not achieved in Study NI-MC301 ($p=0.1801$).

Thus, the findings of Studies NI-MC302 and NI-MC304 demonstrated substantial evidence of effectiveness. Although the observed treatment effect in Study NI-MC301 was smaller than in the other two trials, the study did have a small treatment effect trending in favor of the SB206 arm.

To support the efficacy of berdazimer gel, 10.3%, for topical treatment of MC, the Applicant submitted safety data from 1596 subjects who participated in the phase 3, vehicle-controlled trials. The most frequently reported adverse events were the following application site reactions: pain (18.7% v. 4.9%), erythema (11.7% v. 1.3%), pruritus (5.7% v. 1.0%), exfoliation (5.0% v. 0), dermatitis (4.9% v. 0.7%), swelling (3.5% v. 0.6%), erosion (1.6% v. 0.1%), discoloration (1.5% v. 0.1%), vesicles (1.5% v. 0.1%), irritation (1.2% v. 0), and infection (1.1% v. 0.4%); additional AEs included pyrexia (2.2% v. 1.0%), upper respiratory tract infection (1.2% v. 0.7%), nasopharyngitis (1.0% v. 0.9%), streptococcal pharyngitis (1.0% v. 0.9%), and vomiting (1.3% v. 0.1%).

Therefore, the Applicant provided adequate efficacy and safety data to support the conclusion that the benefit-risk analysis is favorable for approval of NDA 217424.

15. Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve NDA 217424, ZELSUVMI (berdazimer) topical gel, new molecular entity nitric oxide-releasing agent for the indication of topical treatment of molluscum contagiosum (MC) in adults and pediatric patients 1 year of age and older. Molluscum contagiosum is a highly transmissible cutaneous infection caused by the molluscum contagiosum poxvirus. While MC is self-limited, treatments are needed to result in early clearance of the lesions to alleviate discomfort, reduce autoinoculation, limit transmission of the virus to close contacts, reduce cosmetic concerns, and prevent secondary infections. Berdazimer topical gel was developed to address this need.

The Applicant conducted three phase 3 clinical trials (301, 302, and 304), designed to be adequate and well-controlled (AWC) investigations with adequate data for assessment of efficacy and safety. Trials 301 (N=352) and 302 (N=355) were identical – 2:1 randomized (R), double-blind (DB), and placebo-controlled (PC), while Trial 304 was larger (N=891) and a 1:1 R, DB, PC study. The primary efficacy endpoint for all studies was the proportion of subjects with complete clearance of all treatable MC lesions at Week 12, summarized in Table 40.

Table 40. Primary Efficacy Endpoint at Week 12

	Trial 301		Trial 302		Trial 304	
Endpoint	Berdazimer (N=236)	Vehicle (N=116)	Berdazimer (N=237)	Vehicle (N=118)	Berdazimer (N=444)	Vehicle (N=447)
Complete Clearance Rate	25.8%	21.6%	30.0%	20.3%	32.4%	19.7%
Treatment Difference (95% Confidence Interval)	4.3% (-5.0%, 13.6%)		9.2% (-0.04%, 18.4%)		12.8% (7.1%, 18.6%)	

Source: Adopted from Table 25.

Trial 304 demonstrated a statistically significant treatment effect. Trial 302 marginally did not meet the statistical significance based on the conservative responder (binary) analyses, despite the point estimates of the treatment response being very consistent with those in trial 304. However, trial 302 was sufficiently persuasive when considering the sensitivity analyses using continuous endpoints based on the lesion count. The use of responder versus continuous analyses was an important consideration in the interpretation of the data from the berdazimer clinical program. While the complete resolution of lesions may be intuitively easier to interpret, the responder analysis is not as powerful as continuous analysis and can be confounded by missing data and how the missing data is handled. For example, patients with resolution may not complete the study, or patients without improvement, similarly, may not complete the

study, and prior information on endpoint status (i.e., even up to a visit prior to the final visit) is not included in the final visit responder analysis. The supplementary analyses were performed for change from baseline in lesion count over time and the nominal p-value was < 0.05 for trial 302 over time, and at the final visit.

Based on the above considerations, both trials 302 and 304, were AWC investigations that provided sufficiently persuasive evidence of a treatment effect to support the conclusion of substantial evidence of effectiveness of berdazimer topical gel (10.3% strength) for the topical treatment of MC in the target population.

In trial 301, the proportions of subjects with complete clearance in the placebo group was consistent with that in studies 302 and 304. Imbalanced missing data between the active treatment and placebo groups in trial 301 and the pre-specified non-responder imputation were considered to potentially explain the inadequate efficacy of trial 301. However, while trial 301 had formally negative trial result, the data did not contradict the findings of drug effectiveness observed in trials 302 and 304.

In summary, the review team concluded that the effectiveness of berdazimer topical gel (10.3% strength) for the topical treatment of MC in the target population was demonstrated in two adequate and well-controlled trials, 302 and 304. I concur with the conclusion.

The safety profile of berdazimer gel, 10.3% has been adequately characterized by the available premarket safety database in the intended population. The most notable safety concerns, application site reactions, including, allergic contact dermatitis, are noted in the Warnings and Precautions in the product labeling. A theoretical risk of methemoglobinemia (methemoglobin is a biomarker for systemic exposure of nitric oxide) was investigated in a Phase 1 maximal use study and the Phase 2, dose ranging trial in patients 2 to 62 years of age. No clinical safety concerns were identified from the two studies. Based on the overall similar safety profiles observed in 28 subjects treated with berdazimer gel between 1 and <2 years of age and subjects 2 years of age and older, the clinical and clinical pharmacology review teams concluded that a dedicated PK/safety study to include methemoglobin measurements in the age group between 1 and <2 years of age would not be necessary. I agree with this conclusion and recommendation.

In summary, the benefit-risk of berdazimer topical gel is favorable in the intended population. The regulatory action for NDA 217424 is Approval with labeling agreed upon with the Applicant.

No post-marketing requirements or commitments are warranted for this NDA.

16. Appendices

16.1. References

16.1.1. Literature

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, https://www.ncbi.nlm.nih.gov/pubmed/3715678.

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Hebert, AA, N Bhatia, and JQ Del Rosso, 2023, Molluscum Contagiosum: Epidemiology, Considerations, Treatment Options, and Therapeutic Gaps, J Clin Aesthet Dermatol, 16(8 Suppl 1):S4-S11, https://www.ncbi.nlm.nih.gov/pubmed/37636018.

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Konya, J and CH Thompson, 1999, Molluscum contagiosum virus: antibody responses in persons with clinical lesions and seroepidemiology in a representative Australian population, J Infect Dis, 179(3):701-704, https://www.ncbi.nlm.nih.gov/pubmed/9952381.

16.1.2. Guidance for Industry

FDA Guidance for Industry Control of Nitrosamine Impurities in Human Drugs (September 2020), Food and Drug Administration (FDA), https://www.fda.gov/media/141720/download.

16.1.3. Validation Report

(b) (4) 2015a, Validation Report (b) (4) 0174-1406.01: Validation of an LC-MS/MS Assay for Determination of hMAP3 in K2EDTA Human Plasma, LNHC, Inc. (Novan), \\CDSESUB1\EVSPROD\nda217424\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0174-1406 (b) (4) 0174-1406-validation-report.pdf.

(b) (4) 2015b, Validation Report (b) (4) 0174-1406.02: Validation of an LC-MS/MS Assay for Determination of hMAP3 in K2EDTA Human Plasma LNHC, Inc. (Novan), \\CDSESUB1\EVSPROD\nda217424\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0174-1406 (b) (4) -0174-1406-02.pdf.

(b) (4) 2018, Validation Report (b) (4) 0174-1406.03: Validation of an LC-MS/MS Assay for Determination of hMAP3 in K2EDTA Human Plasma, LNHC, Inc. (Novan), \\CDSESUB1\EVSPROD\nda217424\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0174-1406\(b) (4) 0174-1406-03.pdf.

(b) (4) 2019, Validation Report (b) (4) 0174-1406.04: Validation of an LC-MS/MS Assay for Determination of hMAP3 in K2EDTA Human Plasma, LNHC, Inc. (Novan), \\CDSESUB1\EVSPROD\nda217424\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\0174-1406(b) (4) 0174-1406-04.pdf.

16.1.4. Other

LNHC, Inc. (Novan) 2023, NDA 217424, Zelsuvmi (berdazimer sodium gel) Submission: Data Sources Used in the Review of NDA 217424, Zelsuvmi (berdazimer sodium gel), Food and Drug Administration (FDA), \\CDSESUB1\evsprod\NDA217424\0001\m5\datasets\iss\analysis\adam\datasets.

16.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for berdazimer gel for treatment of MC. Prior to trial 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 Trials NI-MC301/-302/-304, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8 of this review for the trial designs.

The Applicant adequately disclosed financial interests involving (0) clinical investigators participating in the MC clinical trials. The Applicant enclosed financial interest disclosure forms for 3 investigators in their Phase 3 acne trials (NI-AC301/-302/-303), which were listed as supportive studies by the Applicant. However, because these studies did not provide the primary data to establish effectiveness and safety of this product for the indication of MC, they are not considered as covered clinical studies for MC.

Covered Clinical Study: (NI-MC301)

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 35		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	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 X	No (Request explanation from Applicant)

Covered Clinical Study: (NI-MC302)

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 34		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	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 X	No (Request explanation from Applicant)

Covered Clinical Study: (NI-MC304)

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 56		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	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 X	No (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

16.3.1. Nonclinical Labeling

Recommended changes to the applicant's proposed wording for the nonclinical and related sections of 8.1, 12.1, 13.1, and 13.2 of the label are provided below.

It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted. No multiples will be included in this labeling since subnanomolar levels of the active were seen under maximal clinical use conditions.

(b) (4)

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

16.4. Carcinogenicity

16.4.1. SB204 Gel: 104-Week Dermal Carcinogenicity Study in Mice

Table 41. Study No. 15-NC-004

Parameter	Description
Study report location:	SDN 1
Study initiation date:	September 16, 2015
Conducting laboratory and location:	(b) (4)
GLP compliance:	Y
Drug, lot #, and % purity:	Hydrogel (pH4), batch #: 1899900, 10304068,10304071,10304074, 2564400) NVN1000 gel 1%, batch #: 10241134,10278024, 10304059, 10328062; purity: 90.8%, 93.3%, 90.0%, 95.2% NVN1000 gel 4%, batch #: 10241137,10278027, 10304062, 10328065; purity: 88.9%, 96.1%, 93.6%, 95.4% NVN1000 gel 8%, batch #: 10241140,10278030, 10304065, 2563200; purity: 93.4%, 96.5%, 91.2%, 105.2%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	MTD (esophageal lesions at higher doses)

Source: NDA submission

- Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
- ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings

No SB204 gel treatment related tumor findings were noted in this study.

Table 42. Methods for Study No. 15-NC-004

Methods	Details
Doses:	0 (untreated control), 0 (vehicle control), 0.5, 2, and 4% SB204 gel (16, 64 and 128 mg/kg/day NVN1000)
Frequency of dosing:	Once daily
Number/Sex/Group:	60 animals/sex/group for the main study; 5/ animals/sex/group for untreated control and vehicle control in the TK study, 15 animals/sex/group for 0.5, 2 and 4% SB204 gel groups in the TK study
Dose volume:	4 ml/kg
Formulation/Vehicle:	An admixture of vehicle gel and pH 4 hydrogel gel
Route of administration:	TOPICAL
Species:	MOUSE
Strain:	CD1(ICR)
Age:	Approximately 5 weeks of age
Comment on Study Design and Conduct:	N/A
Dosing Comments (Dose Adjustments or Early Termination):	Early termination criteria were discussed and relayed to the Applicant on 8/7/2017. However, early termination was not needed based on the actual number of surviving animals during the study.
Dosing Solution Analysis:	The end of study stability analysis was conducted. All test articles remained stable throughout the duration of the study.

Source: NDA submission

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury, and the availability of food and water at least twice daily until Week 53. Beginning on Day 365, a third daily cageside observation was added.

Animals were terminated at Week 104. No SB204 gel-related effects on mortality were noted. Survival rates for males administered 0 (untreated control), 0 (vehicle control), 0.5, 2 and 4% SB204 gel were 50% (30/60), 42% (25/60), 52% (31/60), 50% (30/60), and 50% (30/60), respectively. Survival rates for females administered 0 (untreated control), 0 (vehicle control), 0.5, 2 and 4% SB204 gel were 48% (29/60), 53% (32/60), 38% (23/60), 32% (19/60), and 38% (23/60), respectively. Based on the analysis conducted by the Agency statistical reviewer, Dr. Feng Zhou, no statistically significant positive dose response relationship in mortality in males and females was shown when compared with vehicle control group. In addition, no statistically significant differences in mortality were observed between the vehicle control group and untreated control group.

Clinical Signs

A detailed clinical examination of each animal was performed weekly during the study. The observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects,

autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior, and the palpation of masses.

No SB204 gel-related effects on clinical signs were noted and no SB204 gel-related increases in masses were noted.

Dermal irritation of each main study animal was assessed weekly during the study. The sites were evaluated for gross signs of irritation (i.e., erythema and edema) and any other signs of local or systemic effect according to the Draize scale.

No SB204 gel-related effects on dermal irritation were noted in this study.

Body Weights

Body weights for all animals were measured and recorded at receipt, prior to randomization, on Day -1, and once weekly for the first 14 weeks, every two weeks until Week 28, and every 4 weeks thereafter during the study.

No SB204 gel-related effects on body weight were noted in this study.

Feed Consumption

Feed consumption was measured and recorded once weekly for the first 14 weeks, every two weeks until Week 28, and every 4 weeks thereafter during the study.

No SB204 gel-related effects on feed consumption were noted in this study.

Gross Pathology

The animals were examined for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision and any subcutaneous masses were identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities were examined for abnormalities.

Increased incidence of various findings was noted in the non-glandular stomach of males and females at doses ≥2% SB204 gel. These findings included mild tan focus/foci, mild to moderate irregular surface, presence of mass, presence of nodule and severe swollen/thickened in the non-glandular stomach. This treatment related finding was likely due to the animals licking the topically applied gel during self-grooming which does not apply to human use conditions.

Histopathology

- Peer Review Conducted: Yes
  - Historical Control Provided for Tumor Incidence: Yes

The following tissues was collected from all groups and all animals dying spontaneously or euthanized *in extremis* and preserved: adrenal glands, aorta, bone marrow smear, bone with bone marrow (femur), bone with bone marrow (sternum), brain, clitoral gland, epididymides,

esophagus, eyes with optic nerve, gallbladder, gut-associated lymphoid tissue, Harderian glands, heart, joint (tibiofemoral), kidneys, lacrimal glands (exorbital), large intestine (cecum), large intestine (colon), large intestine (rectum), larynx, liver, lung with bronchi, lymph node (mandibular), lymph node (mesenteric), mammary gland (process females only), nose (4 sections), nerve (sciatic), ovary, oviduct, pancreas, pharynx, pituitary, preputial gland, potential target organs, prostate gland, salivary gland (mandibular), salivary gland (parotid), seminal vesicles with coagulating glands, skeletal muscle (biceps femoris), skin (treated), skin (untreated), small intestine (jejunum), small intestine (duodenum), small intestine (ileum), spinal cord (cervical), spinal cord (lumbar), spinal cord (thoracic), spleen, stomach (glandular), stomach (nonglandular), testes, thymus, thyroid (with parathyroid), tissue masses with regional lymph node, tongue, trachea, urinary bladder, uterus with cervix, vagina, zymbal's gland (auditory sebaceous gland). Microscopic examination of fixed sections was performed on all tissues except for the bone marrow smear.

Neoplastic

No statistically significant differences in SB204 gel related tumor incidence were observed in mice of either sex in this study, according to the statistical criteria used by the Executive Carcinogenicity Assessment Committee (ECAC). The ECAC statistical criteria used to determine treatment related common tumors is that both the trend p-value should be less than 0.005 ($p<0.005$) and the pairwise p-value should be less than 0.01 ($p<0.01$). Based on the statistical criteria used by the ECAC, there were no treatment related tumors in this dermal carcinogenicity study. Also, there was not any statistically significant difference in tumor incidence for vehicle control compared to untreated control groups based on pairwise comparison.

The Agency statistical reviewer, Dr. Feng Zhou, independently performed the survival and tumor data analysis. The tumor types with p-values less than 0.05 for dose response relationship (trend comparison) and/or pairwise comparisons of vehicle control and treated groups were examined (see Table 43).

Non-glandular stomach squamous cell carcinoma in males is listed with a trend p-value of 0.0081; however, there are no statistically significant pairwise comparisons for this tumor type. Non-glandular stomach squamous cell papilloma is listed with a p-value of 0.0054; however, there are no statistically significant pairwise comparisons for this tumor type. Therefore, neither of these tumor types is not considered a treatment related tumor.

Non-glandular stomach squamous cell carcinoma in females is listed with a trend p-value of 0.0033 and the high dose pairwise comparison p-value of 0.0458. Since the high dose pairwise comparison p-value is not less than 0.01, then this tumor type is not considered a treatment related tumor.

Uterus with cervix leiomyoma in females is listed with a trend p-value of 0.0157; however, there are no statistically significant pairwise comparisons for this tumor type. Therefore, this tumor type is not considered a treatment related tumor.

There are some lymphomas in separate organs/tissues (femur bone marrow, sternum bone marrow and inguinal lymph node) in females listed as possible statistically significant tumor types in mice. However, the whole body lymphoma statistical analysis in females does not show either trend or pair-wise statistical significance. Therefore, this tumor type is not considered a treatment related tumor.

Table 43. Possible Statistically Significant Tumor Types in Mice: Tumor Types With Statistically Significant (at 0.05 Significant Level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ Name	Tumor Name	0 mg/kg/day V Control P - Trend	16 mg/kg/day Low (L) P - VC vs. L	64 mg/kg/day Mid (M) P - VC vs. M	128 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Naïve C (NC) P - VC vs. NC
Male	Stomach, Non-glandular	Carcinoma, Squamous Cell, Malignant	0/60 (45) 0.0081 *	0/60 (46) NC	2/60 (47) 0.2582	4/60 (47) 0.0638	0/60 (45) NC
		Papilloma, Squamous Cell, Benign	0/60 (45) 0.0054 *	0/60 (46) NC	1/60 (47) 0.5109	4/60 (46) 0.0611	1/60 (45) 0.5000
Female	Stomach, Non-glandular	Carcinoma, Squamous Cell, Malignant	0/60 (47) 0.0033 *	0/60 (42) NC	0/60 (40) NC	4/60 (42) 0.0458 **	0/60 (45) NC
	Uterus With Cervix	Leiomyoma, Benign	0/60 (47) 0.0157 *	0/60 (42) NC	1/60 (40) 0.4598	3/60 (41) 0.0971	0/60 (45) NC
	Bone Marrow, Femur	Lymphoma, Malignant	0/60 (47) 0.0181 *	1/60 (43) 0.4778	3/60 (42) 0.1011	4/60 (43) 0.0483 **	1/60 (45) 0.4891
	Bone Marrow, Sternum	Lymphoma, Malignant	0/60 (47) 0.0181 *	1/60 (43) 0.4778	3/60 (42) 0.1011	4/60 (43) 0.0483 **	1/60 (45) 0.4891
	Lymph Node, Inguinal	Lymphoma, Malignant	0/60 (47) 0.1757	4/60 (45) 0.0533	4/60 (42) 0.0458 **	3/60 (42) 0.1011	2/60 (45) 0.2365
	Whole body	Lymphoma, malignant	7/60 (50) 0.0724	13/60 (48) 0.0873	9/60 (43) 0.2714	14/60 (45) 0.0390	12/60 (48) 0.1310

Source: NDA submission.
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Non-Neoplastic

In males, SB204 gel-related non neoplastic findings included treated skin and non-glandular stomach in animals at doses ≥0.5% SB204 gel and the esophagus and pharynx in animals at doses ≥2% SB204 gel. Minimal to moderate hyperplasia in the squamous epithelium and minimal to mild subacute/chronic inflammation in the non-glandular stomach were noted at doses ≥0.5% SB204 gel. Minimal to mild hyperplasia in the squamous epithelium and minimal to mild subacute/chronic inflammation in pharynx and esophagus were noted at doses ≥2% SB204 gel.

In the treated skin, minimal to severe hyperplasia in the squamous epithelium was noted at doses ≥0.5% SB204 gel and minimal to moderate subacute/chronic inflammation was noted in all groups including untreated and vehicle control groups.

The severity of all the findings mentioned above generally showed a dose-dependent manner.

In females, SB204 gel-related non neoplastic findings included treated skin, non-glandular stomach, esophagus and pharynx in animals at doses ≥2% SB204 gel.

Females treated with doses ≥2% SB204 gel exhibited the following findings: minimal to mild hyperplasia in squamous epithelium in the non-glandular stomach; minimal to mild hyperplasia in squamous epithelium and subacute/chronic inflammation in pharynx; and minimal to mild hyperplasia in squamous epithelium and minimal to moderate subacute/chronic inflammation in the esophagus.

In the treated skin, minimal to mild hyperplasia in squamous epithelium was noted in the animals at doses ≥2% SB204 gel.

The above findings noted in the animals at 0.5% SB204 gel generally showed comparable incidence and severity compared to that of untreated and vehicle control groups. The severity of all the findings mentioned above at doses ≥2% SB204 gel generally showed a dose-dependent manner.

Toxicokinetics

Blood (plasma) collection on Day 181 from three control animals/sex/group at approximately 4 hours post dose, and from four cohorts of three animals/sex/treated group at approximately 0, 1, 4, and 8 hours post dose.

hMAP3 plasma concentrations were below the bioanalytical limit of quantitation (BLQ <5.00 ng/mL) in all plasma samples obtained from control animals on Day 181. Systemic exposure (C_{max} and $AUC_{0\text{-}8h}$) increased as doses increased from 0.5% to 4% SB204 gel but in a less than dose-proportional manner. Systemic exposure (C_{max} and $AUC_{0\text{-}8h}$) of hMAP3 in females were greater by 2-fold than that of males at 4% SB204 gel.

Table 44. hMAP3 TK Parameters

Table I. hMAP3 TK Parameters on Day 181					
Analyte	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}8hr}$ (hr*ng/mL)
hMAP3	16	Male	64.8	1	294
		Female	59.4	4	341
	64	Male	139	1	761
		Female	182	1	1030
	128	Male	202	1	1160
		Female	398	4	2140

Source: NDA submission.

Nitrate plasma concentrations were above the bioanalytical limit of quantitation (BLQ <500 ng/mL) in all plasma samples obtained from control animals on Day 181; however, this was not unanticipated as nitrate is endogenous. The systemic exposure (C_{max} and $AUC_{0\text{-}8h}$) of nitrate increased in a dose-dependent manner on Day 181. There were no apparent differences (less than 2-fold difference) in the systemic exposure of nitrate between male and female mice.

Table 45. Nitrate TK Parameters

Table J. Nitrate TK Parameters on Day 181					
Analyte	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}8hr}$ (hr*ng/mL)
Nitrate	Naïve Control	Male	2480	4	NA
		Female	2520	4	NA
	Vehicle Control	Male	1240	4	NA
		Female	1670	4	NA
	16	Male	1960	1	11500
		Female	2120	4	14800
	64	Male	6040	1	28300
		Female	6620	1	30500
	128	Male	17200	1	48100
		Female	20200	1	69100
NA-- $AUC_{0\text{-}8hr}$ excluded due to less than three consecutive quantifiable concentrations					

Source: NDA submission.

16.5. OCP Appendices (Technical Documents Supporting OCP Recommendations)

The clinical pharmacology program for the development of SB206 gel comprises of a maximal use PK study (MUsT) in subjects with MC applied QD (NI-MC101), a single-dose study in

subjects with MC (NI-MC201), ECG study (NI-AC104), a repeat-dose study in healthy Japanese adults (SKN15A01). Summary of individual studies are provided below. Per the Applicant, SB206 12% (nominal berdazimer sodium) is the same admixture formulation as SB206 10.3% (berdazimer). Nominal equivalent salt and base strengths for each product is provided below in Table 46.

Table 46. Berdazimer and Berdazimer Sodium Equivalents

Formulation	%w/w of berdazimer sodium in the Berdazimer Gel component	Nominal Strength*	%w/w of berdazimer sodium*	% w/w berdazimer equivalent*
SB206 Gel	24%	12%	10.9%	10.3%
SB204 Gel	8%	4%	3.6%	3.4%
SB204 Gel	24%	12%	10.8%	10.2%

Source: Reviewer's guide, Table 1.
* After mixing 1:1 with hydrogel.

16.5.1. Study NI-MC101: Phase 1 Safety, Tolerability, and PK Study in Subjects With MC (Maximal Use Trial; MuST)

Study NI-MC101 was a Phase 1 open label study to assess the safety, tolerability, and PK of SB206 12% QD for the topical treatment of MC under maximal use conditions. This study was conducted in 34 subjects with more than 20 MC lesions at baseline (mean lesion count=34) and 29 subjects (85.3%) completed the study. Eligible subjects applied SB206 12% QD for 15 days to the field treatment area totaling 484 cm^2 including as many MC lesions as possible. The fixed treatment area was equivalent to 2.3% body surface area (BSA) to 9.3% BSA (mean 5.98% BSA). Blood was collected for determination of hMAP3 and nitrate on Days 1 and 15 for PK sampling for each age group (<6 years and ≥6 years). The PK profile of hMAP3 and nitrate after repeated topical application of SB206 12% was assessed when the values were above the limit of detection. After completing the PK phase, subjects were allowed to continue in the treatment extension phase for a total of 12 weeks of treatment.

The mean age of subjects was 5.26 years (median = 5.00 years), with a range of 2 to 12 years. Gender was balanced with 17 (50.0%) females and 17 (50.0%) males. Subject demographics are shown in Table 47. The study was conducted in subjects with the upper range of severity of MC to be under maximal use conditions. An area of 484 cm^2 (e.g., 22 cm x 22 cm) for field treatment was determined based on coverage of approximately 100 nonconfluent MC lesions. The average MC lesion count in the phase 2 and 3 studies was around 20 (98 cm^2 when including the surrounding area of each MC lesion), indicating that the field treatment area of 484 cm^2 utilized in this study is representative of an exaggerated MC condition. A total of 3 mL of gel was used to cover the field treatment area(s) of 484 cm^2. Subjects were to continue to apply the treatment to the designated field treatment area(s) throughout the PK Phase even if the lesions became clear. Any lesions outside of the field treatment area were not to be treated until the PK Phase ended.

Table 47. Summary of Subject Demographics

	SB206 12% (N=34)
Age (years) [1]	
n	34
Mean	5.26
S.D.	2.466
Median	5.00
Min, Max	2, 12
< 6 years of age	21 (61.8%)
>= 6 years of age	13 (38.2%)
Gender	
Female	17 (50.0%)
Male	17 (50.0%)
Ethnicity	
Hispanic/Latino	5 (14.7%)
Non-Hispanic/Latino	29 (85.3%)
Race	
American Indian/Alaskan Native	0 (0.0%)
Asian	1 (2.9%)
Black/African American	0 (0.0%)
Native Hawaiian/Pacific Islander	0 (0.0%)
White	33 (97.1%)
Other	0 (0.0%)
Height (m) [2]	
n	34
Mean	1.16
S.D.	0.185
Median	1.14
Min, Max	0.85, 1.74
Weight (kg) [2]	
n	34
Mean	24.74
S.D.	15.759
Median	20.90
Min, Max	11.4, 95.2
BMI (kg/m^2) [2]	
n	34
Mean	16.94
S.D.	3.288
Median	15.89
Min, Max	12.8, 31.4
BSA (m^2) [2]	
n	34
Mean	0.88
S.D.	0.316
Median	0.81
Min, Max	0.52, 2.15

Percent (%) of BSA Treated [2]	
n	34
Mean	5.96
S.D.	1.477
Median	5.98
Min, Max	2.3, 9.3
Percent (%) of BSA Treated [2] among subjects < 6 years of age	
n	21
Mean	6.78
S.D.	1.017
Median	6.45
Min, Max	5.6, 9.3
Percent (%) of BSA Treated [2] among subjects >= 6 years of age	
n	13
Mean	4.64
S.D.	1.099
Median	5.09
Min, Max	2.3, 5.6
Total Number of Lesions [2]	
n	34
Mean	50.15
S.D.	43.072
Median	35.00
Min, Max	21, 212
Methemoglobin (%) [2]	
n	34
Mean	0.46
S.D.	0.526
Median	0.20
Min, Max	0.0, 1.7

Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – study-report-figures-and-tables, Table 14.1.3.1

A summary of hMAP3 concentrations by day is described in Table 48. No subjects had quantifiable concentrations of hMAP3 at any timepoint on Day 1, while 2 subjects (Subject (b) (6) (5 years of age) with 48 MC lesions at Baseline and 3.69% BSA treated) had a single quantifiable concentration (5.12 ng/mL) close to the LLOQ on Day 15. Subject (b) (6) (11 years of age) with 31 MC lesions at baseline and 6.05% of BSA treated had 4 quantifiable concentrations on Day 15 (Cmax of 33.9 ng/mL) had quantifiable concentrations on Day 15 (LLOQ= 5 ng/mL)). PK parameters for these subjects are reported in Table 49.

Table 48. Summary of hMAP3 Plasma Concentration-Time Data by Day

Day	Statistic	Nominal Time (h)			
		0	1	3	6
Day 1	N	35	34	13	12
	N>LLOQ	0	0	0	0
	Mean	0	0	0	0
	Min	0	0	0	0
	Median	0	0	0	0
	Max	0	0	0	0
Day 15	N	30	31	27	13
	N>LLOQ	1	1	2	1
	Mean	0.347	0.671	1.45	1.73
	Min	0	0	0	0
	Median	0	0	0	0
	Max	10.4	20.8	33.9	22.5

N = Sample size; Mean = Arithmetic mean; Min = Minimum; Max = Maximum
Values expressed in ng/mL
Greater than 30% of concentration values at nominal time (h) 0, 1, 3, and 6 were below the lower limit of quantitation (LLOQ) and imputed as 0.
Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Table 7

Table 49. hMAP3 Pharmacokinetic Parameters - Day 15

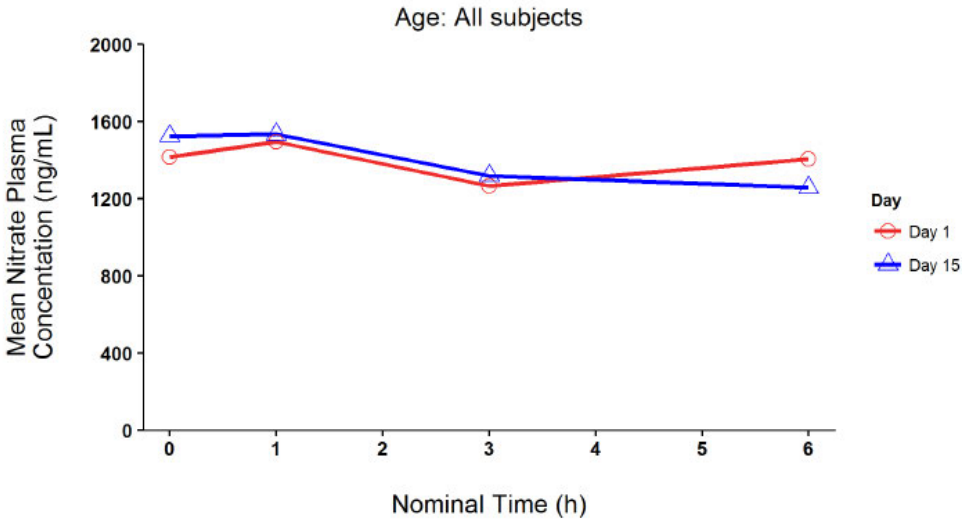
Day	Subject	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-3} (h*ng/mL)	AUC_{0-6} (h*ng/mL)
Day 15	(b) (6)	5.12	2.00	NA	NA
		33.9	2.08	75.5	NR

AUC_{0-3} and AUC_{0-6} are not reported for subjects who did not have quantifiable concentrations through 3 or 6 hours post-application, respectively.
NA = Not applicable; NR = Not reported. For the noncompartmental analysis, actual times were used. The nominal timepoint of 6 hours for this subject had a corresponding actual time 5.183 hours.
Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Table 9

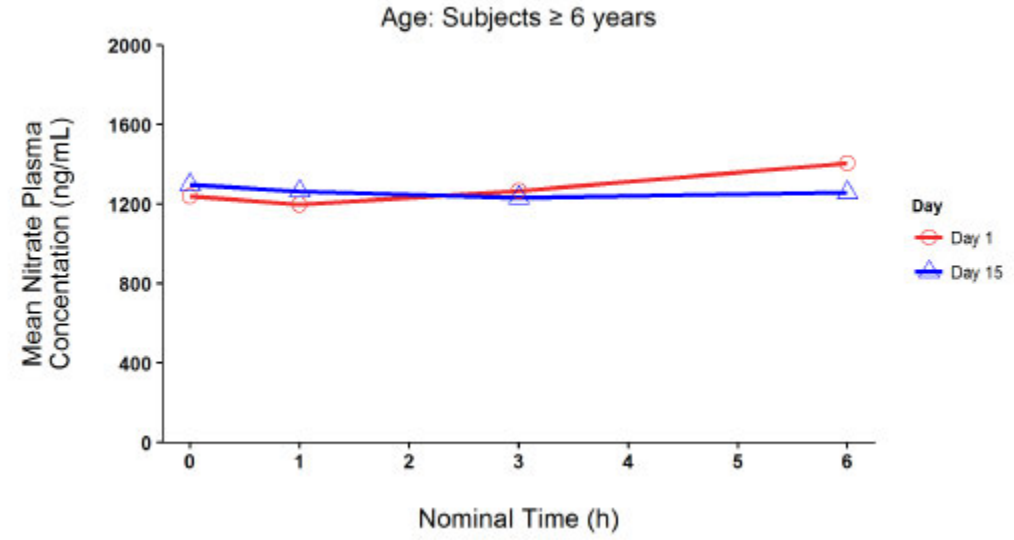
Mean nitrate plasma concentration-time data (not baseline-corrected) with day is shown in Figure 9. Summary of Nitrate Pharmacokinetic Parameters by Age and Day is provided in Table 50. Across all subjects, exposure was similar on Day 1 and Day 15. Individual Tmax values ranged across the entire sampling time course. There were no apparent differences in nitrate PK across the treatment between Day 1 and Day 15 as well as the time course of the PK days. The applicant collected nitrate levels in plasma at baseline, pre-dose that represented the endogenous, background nitrate profile. However, the nitrate values collected post-dose were not baseline corrected. As the total nitrate levels remained relatively unchanged with respect to baseline and between Day 1 and Day 15 (sampling interval), the use of non-baseline-corrected nitrate levels is acceptable and it informs systemic safety.

Overall, plasma nitrate levels were higher in subjects <6 years of age on Day 1 and Day 15 than the older subjects (≥ 6 years of age). Mean Cmax for subjects ≥6 years of age were 1540 ng/mL at Day 1 and 1420 ng/mL at Day 15, while for subjects <6 years of age, mean Cmax was 1740 ng/mL at Day 1 and 1820 at Day 15. AUC for subjects <6 years of age were not calculated. Plasma concentrations remained relatively flat between both age groups 0 and 1 h after treatment (3 h time point was not calculated in subjects <6 years of age on Day 1). There were no apparent differences in nitrate PK across the treatment between Day 1 and Day 15 as well as the time course of the PK days.

Figure 9. Mean Nitrate Plasma Concentration-Time Plot by Age with Day Overlaid



For Day 1, n=35, n=34, n=13, and n=12 for nominal times 0, 1, 3, and 6 h, respectively.
For Day 15, n=30, n=31, n=27, and n=13 for nominal times 0, 1, 3, and 6 h, respectively.



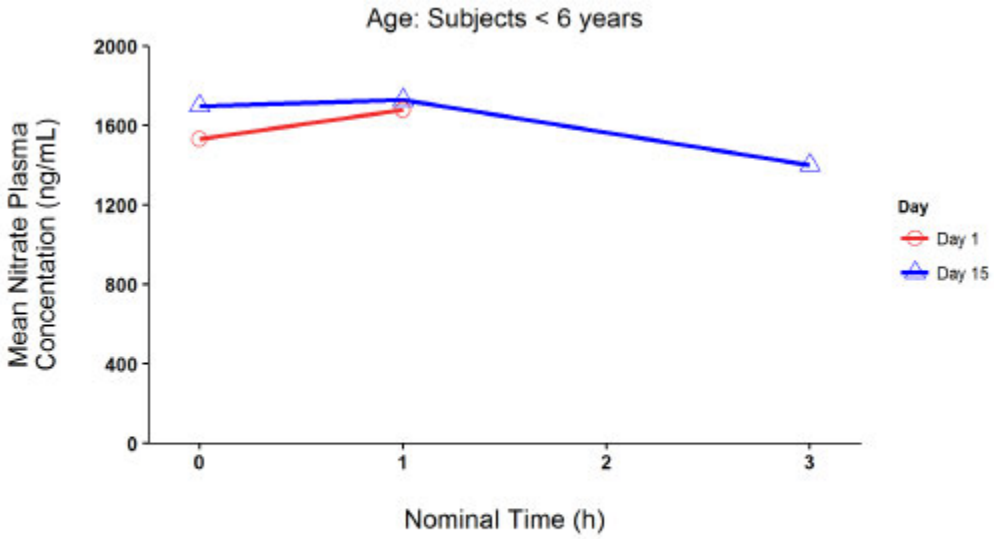


Figure 3 of 3
For Day 1, n=21 for both nominal times 0 and 1 h.
For Day 15, n=17, n=18, and n=14 for nominal times 0, 1, and 3 h, respectively.

Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Figure 1

Table 50. Summary of Nitrate Pharmacokinetic Parameters by Age and Day

Age	Day	Statistic	Cmax (ng/mL)	Tmax (h)	AUC0-3 (h*ng/mL)	AUC0-6 (h*ng/mL)
All subjects	Day 1	N	35	35	13	7
		Mean	1660	NC	3680	6270
		SD	540	NC	988	1160
		CV%	32.5	NC	26.9	18.5
		Geometric Mean	1580	NC	3570	6190
		Geometric CV%	32.2	NC	25.4	17.8
		Min	845	0.00	2700	5070
		Median	1590	1.00	3460	5960
		Max	3020	6.52	5640	8400
All subjects	Day 15	N	32	32	17	8
		Mean	1660	NC	4160	7460
		SD	929	NC	1140	1370
		CV%	56.1	NC	27.5	18.3
		Geometric Mean	1520	NC	4040	7350
		Geometric CV%	37.9	NC	24.7	18.1
		Min	924	0.00	2990	5790
		Median	1330	1.00	3750	7060
		Max	6070	6.03	7510	9670
Subjects ≥ 6 years	Day 1	N	14	14	13	7
		Mean	1540	NC	3680	6270
		SD	513	NC	988	1160
		CV%	33.2	NC	26.9	18.5
		Geometric Mean	1470	NC	3570	6190
		Geometric CV%	32.1	NC	25.4	17.8
		Min	983	0.00	2700	5070
		Median	1490	0.98	3460	5960
		Max	2760	6.52	5640	8400

Table 1 of 2

N = Sample size; Mean = Arithmetic mean; SD = Standard deviation; CV% = Arithmetic percent coefficient of variation; Geometric CV% = Geometric percent coefficient of variation; Min = Minimum; Max = Maximum; NC = Not calculated

AUC_{0-3} and AUC_{0-6} were not calculable for subjects who did not have quantifiable concentrations through 3 or 6 hours post-application, respectively.

Age	Day	Statistic	Cmax (ng/mL)	Tmax (h)	AUC0-3 (h*ng/mL)	AUC0-6 (h*ng/mL)
Subjects ≥ 6 years	Day 15	N	13	13	13	8
		Mean	1420	NC	3770	7460
		SD	252	NC	663	1370
		CV%	17.7	NC	17.6	18.3
		Geometric Mean	1400	NC	3720	7350
		Geometric CV%	17.4	NC	16.8	18.1
		Min	1130	0.00	2990	5790
		Median	1300	1.42	3550	7060
		Max	1850	6.03	4990	9670
Subjects < 6 years	Day 1	N	21	21	NC	NC
		Mean	1740	NC	NC	NC
		SD	555	NC	NC	NC
		CV%	31.9	NC	NC	NC
		Geometric Mean	1660	NC	NC	NC
		Geometric CV%	32.2	NC	NC	NC
		Min	845	0.00	NC	NC
		Median	1670	1.00	NC	NC
		Max	3020	1.25	NC	NC
Subjects < 6 years	Day 15	N	19	19	4	NC
		Mean	1820	NC	5450	NC
		SD	1170	NC	1530	NC
		CV%	64.7	NC	28.0	NC
		Geometric Mean	1610	NC	5290	NC
		Geometric CV%	47.4	NC	28.3	NC
		Min	924	0.00	3810	NC
		Median	1440	0.93	5240	NC
		Max	6070	2.25	7510	NC

Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Table 11

Adverse events are detailed by patient in Table 51.

Table 51. Study NI-MC101: Overview of Treatment-Emergent Adverse Events (TEAEs) – Safety Population

	SB206 12% QD (N = 34)
Number of TEAEs Reported	37
Subjects with at least 1 TEAE; n (%)	16 (47.1)
Mild	5 (14.7)
Moderate	8 (23.5)
Severe	3 (8.8)
Subjects with at least 1 TEAE Related to Study drug	15 (44.1)
Subjects with at least 1 Serious TEAE	0
Subjects with at least 1 TEAE leading to Discontinuation from treatment	0
Subjects with at least 1 TEAE with an outcome of Death	0

Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Table 12

Overall, 37 TEAEs were reported in 16 (47.1%) subjects. The most frequently reported TEAEs were application site pain and application site erythema. One subject was reported to have a mild TEAE of prolonged electrocardiogram QT interval that was considered unlikely related to study drug application. A summary of TEAEs by relationship to study drug is found in Table 52. A total of 15 (44.1%) subjects reported TEAEs as related to study drug. The most frequently reported TEAEs considered related to study drug were application site pain and application site erythema. There were no SAEs reported during this study. There were no TEAEs leading to study drug discontinuation reported during this study.

Table 52. Overview of Treatment-Emergent Adverse Events (TEAEs) – Safety Population

	SB206 12% QD (N = 34)
Number of TEAEs Reported	37
Subjects with at least 1 TEAE; n (%)	16 (47.1)
Mild	5 (14.7)
Moderate	8 (23.5)
Severe	3 (8.8)
Subjects with at least 1 TEAE Related to Study drug	15 (44.1)
Subjects with at least 1 Serious TEAE	0
Subjects with at least 1 TEAE leading to Discontinuation from treatment	0
Subjects with at least 1 TEAE with an outcome of Death	0

Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Table 13

Methemoglobin was to be monitored at every in-clinic visit. Methemoglobin was reported as a percentage of the total hemoglobin and was summarized descriptively by visit. Subjects with methemoglobin values of > 3.0% at Baseline were not eligible to participate in the study. Clinically significant changes in methemoglobin levels were to be collected as AEs. Subjects with persistent > 5% methemoglobin (confirmed by a second reading within 0.5% of the initial reading within 30 minutes) at any post-Baseline assessment were to be discontinued from the study. Table 53 reports the methemoglobin in safety population. For the two subjects with quantifiable plasma hMAP3 levels during the study, methemoglobin levels remained within the allowed ranges. Methemoglobin results were within the allowed ranges throughout the study; there were no reported TEAEs related to methemoglobin results.

Table 53. Methemoglobin (%) – Safety Population

	SB206 12% QD (N = 34)
Baseline (N = 34)	
Mean (SD)	0.46 (0.526)
Median	0.20
Minimum, maximum	0.0, 1.7
Week 2 – Pre-dose (N = 34)	
Mean (SD)	0.62 (0.620)
Median	0.40
Minimum, maximum	0.0, 2.0
Week 4 – Pre-dose (N = 29)	
Mean (SD)	0.62 (0.551)
Median	0.60
Minimum, maximum	0.0, 1.9
Week 8 – Pre-dose (N = 29)	
Mean (SD)	0.65 (0.623)
Median	0.40
Minimum, maximum	0.0, 2.0
Week 12 (N = 30)	
Mean (SD)	0.67 (0.722)
Median	0.45
Minimum, maximum	0.0, 3.2

Source: Module 5.3.3.2 Clinical Study Report NI-MC101 – Phase 1 Safety, Tolerability, and PK Study, Table 18.
Abbreviations: SD, standard deviation

(b) (4)

[redacted]

The MetHb values are shown in Table 54 for the 2-year-olds. Subject (b) (6) *discontinued at Week 4 (withdrawal by subject/caregiver). The subject had an*

AE of application site pain (severe/related) beginning at Day 1 and continuing until Week 4. The other two subjects completed both the PK phase and the extension phase of the study."

Table 54. Methemoglobin (MetHb) Values (%) of Three 2-Year-Old Subjects in NI-MC101

Subject ID	Age*	Baseline MetHb (%)	Min (%)	Max (%)	Time of max reading
(b) (6)	2 years, 9 months	1.4	0.3	1.8	Day 1 - 1 hr post-dose
	2 years, 7 months	0.0	0.0	2.1	Day 1 - 1 hr post-dose
	2 years, 3 months	0.0	0.0	2.0	Pre-dose--Week 8

Source: NI-MC101 Listings 16.2.4.1 and 16.2.8.5.1
*Listing 16.2.4.1 included subject ages in whole numbers only. Ages as shown here were calculated using the website www.timeanddate.com/date/duration using the subject's birthdate and the date of ICF signature.

The Applicant also provided comparative methemoglobin data in age groups 2-5 years and 6 years and older, which showed no difference in the measurements in the 2 groups.

The maximal use study was an open label study with SB206 12 % (same product as SB206 10.6 %) in 34 subjects with MC. A total of 29 patients completed the study (85.3%) and 31 patients completed the PK phase. Four subjects were withdrawn by the subject/caregiver, while 1 was lost to follow up. One discontinued due to an adverse event (application site hypersensitivity).

Mean lesion count in the study was 34 (1.7-times the average lesion count in phase 3) and field treatment area was around 484 cm^2 (~5-fold higher than 98 cm^2 treatment area in phase 3). Study duration was minimum of 2 weeks (PK Phase) and up to 12 weeks (Extension Phase). The number of molluscum lesions treated in the maximal use PK study were markedly higher than the pivotal studies and within the upper range of the disease severity.

The maximal use PK study results showed that only 2 subjects had quantifiable plasma concentrations of hMAP3 at Day 15. Remaining 33 subjects showed hMAP3 plasma concentrations below LLOQ of 5 ng/mL at all time points post dose. This suggested low systemic exposure following QD administration of berdazimer. Per the Applicant, Systemic exposure in 1 subject (Subject (b) (6)) was potentially due to ongoing local site reactions, possible disruption of the skin barrier functions, and increased skin penetration of the topically applied substances; this subject also experienced a mild TEAE of prolonged electrocardiogram QT interval that was considered unlikely to be related to study drug application. Mean nitrate plasma concentrations remained same on Day 1 and 15.

Methemoglobin is a biomarker for systemic exposure of nitric oxide (NO) as NO and nitrite are known to readily convert hemoglobin to methemoglobin. Methemoglobin levels were between 0 to3.2 % throughout the duration of the study in all the individuals. For the two subjects with quantifiable plasma hMAP3 levels during the study, methemoglobin levels remained within 5% (Subject (b) (6) and Subject (b) (6) highest level was 2.1 % and 2.2 %).

In this study patients below 2 years old were not enrolled despite the Applicant's efforts. Therefore, PK and methemoglobin data in less than 2-year-old population is not available. (b) (4) the lack of safety data with respect to methemoglobin was considered in this assessment. The indication was (b) (4) supported by the phase 3 data and the benefit-risk assessment is deferred to Clinical.

16.5.2. Study NI-MC201: Phase 2 MAD Study of SB206 in Subjects With MC

This was a Phase 2 multicenter, randomized, double-blind, vehicle-controlled ascending dose study conducted in 256 non-immunocompromised subjects with MC (range= 2 – 62 years old). Subjects were randomized 3:1 (active:vehicle) to ascending, sequential dose cohorts of SB206: 4% BID, 8% BID, and 12% BID. The highest tolerated dose (SB206 12%) was also run in a cohort once daily (QD). Subjects were treated BID until the highest tolerated concentration was identified (SB206 4%, 8%, and 12%) or QD for up to 12 weeks to all lesions identified at Baseline and new lesions that arose during treatment. Primary end point was proportion of subjects achieving complete clearance of all MC at Week 12. Plasma hMAP3 was measured in SB206 12% QD and BID cohorts only.

For the primary efficacy endpoint, the proportion of subjects achieving complete clearance at Week 12, the odds ratios between active treatments and vehicle, 95% CIs for the odds ratios, and P values for the differences in treatment at Week 12 are presented in Table 55 in the modified intent-to-treat (mITT). The mITT population consisted of all subjects who were randomized and completed the study treatment. At Week 12, the odds ratio (95% CI) between active treatments and vehicle treatment was statistically significant for individual treatments 8% BID (2.77 [1.12, 6.85], p = 0.027) and 12% QD (2.75 [1.14, 6.63], p = 0.024). Among the individual active treatment groups, the proportion of subjects achieving complete clearance was highest in the 12% QD group (18 subjects [41.9%]). For the ITT population, the odds ratio (95% CI) at Week 12 between active treatments and vehicle treatment was statistically significant only for the 12% QD group (2.57 [1.09, 6.03], p = 0.030).

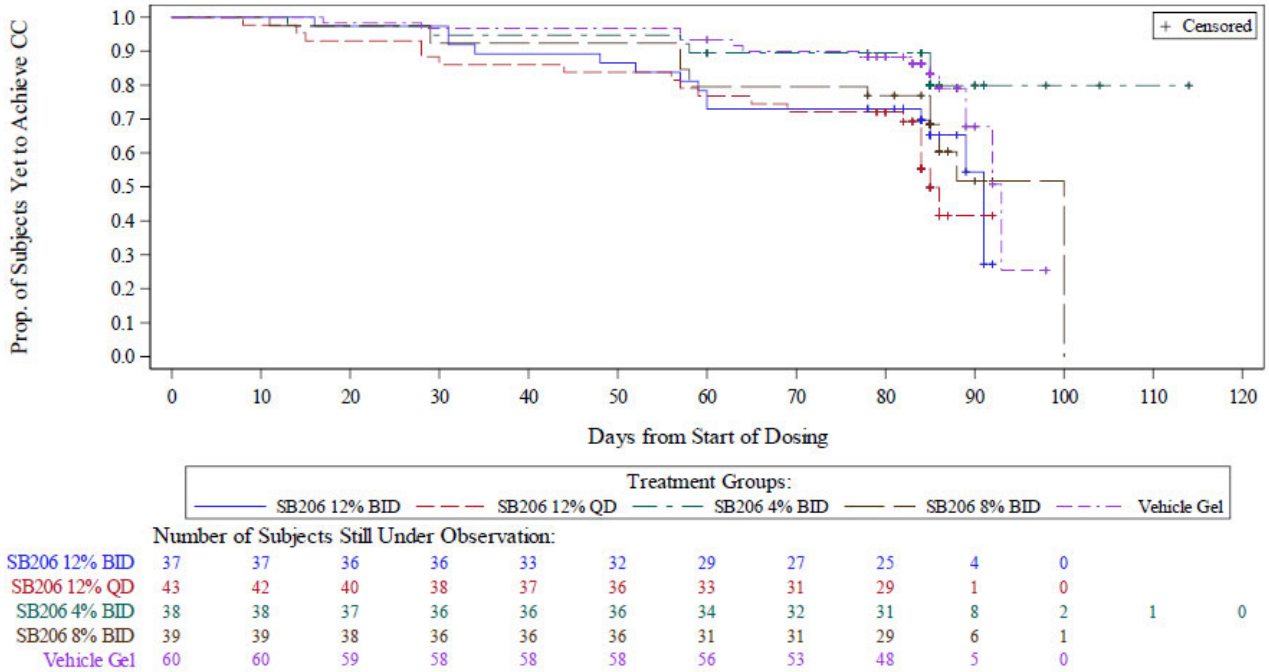
Table 55. Complete Clearance Lesion Count Response at Week 12 by Treatment Group: Summary of Fitted Point Estimates From Logistic Regression (mITT Population)

Statistic	Vehicle Gel (N = 60)	SB206 4% BID (N = 38)	SB206 8% BID (N = 39)	SB206 12% BID (N = 37)	SB206 12% QD (N = 43)	SB206 All SB206 (N = 157)
n[a]	59	34	39	36	43	152
Responders[b]	12 (20.0%)	5 (13.2%)	16 (41.0%)	13 (35.1%)	18 (41.9%)	52 (33.1%)
Odds ratio (SB206 vs vehicle)		0.70	2.77	2.05	2.75	1.97
95% CI for odds ratio		(0.23, 2.14)	(1.12, 6.85)	(0.81, 5.20)	(1.14, 6.63)	(0.96, 4.04)
P value[c]		0.532	0.027	0.129	0.024	0.063
Difference in proportion (SB206 vs vehicle)		-0.049	0.206	0.136	0.204	0.128
95% CI for proportion difference		(-0.199, 0.100)	(0.022, 0.389)	(-0.046, 0.319)	(0.027, 0.381)	(0.003, 0.253)
P value[c]		0.518	0.028	0.144	0.024	0.044

Source: Section 14.2, Table 14.2.1.3
Abbreviations: BID = twice daily; CI = confidence interval; max = maximum; min = minimum; N = number of subjects; QD = once daily
Note: Subjects are summarized by randomized treatment. Firth's penalized maximum likelihood estimation was used.
a Number of subjects with a lesion count measurement at Week 12.
b Number and percentage of subjects with complete clearance at Week 12. Complete clearance is defined as a subject having a lesion count of 0 at a visit. Percentages for each group are based on the number of subjects in the mITT population. Subjects with a missing response are counted as non-responders.
c Estimates for odds ratio, 95% CI for odds ratio, and *P* value are from a logistic regression model, with factors for treatment, number of lesions at baseline (3–18; 19–70), and atopic dermatitis history (with AD history; without AD history) as factors. Baseline is defined as the last measurement taken on or before the date of first application of study drug. The odds ratio is the estimate of the odds of having complete clearance for subjects treated with SB206 relative to that for subjects treated with vehicle.
Source: Clinical Study Report NI-MC201, Table 11-1

Time to first complete clearance of all MC was analyzed for the mITT population using Kaplan-Meier methods in Figure 10. In the mITT population, differences in Kaplan-Meier curves from those in the vehicle treatment group were statistically significant only for active treatments 12% BID (P = 0.047) and 12% QD (P = 0.003). In the ITT population differences in Kaplan-Meier curves from those in the vehicle treatment group were statistically significant only for active treatment 12% QD (P = 0.003).

Figure 10. Kaplan-Meier Plot of Time to First Complete Clearance (Days) From Start of Dosing (mITT Population)



Source: Clinical Study Report NI-MC201; Figure 11-1

At Week 12, the proportion of subjects achieving 75% reduction from baseline was higher in the pooled SB206 treatment group (72 subjects [45.9%]) than in the vehicle treatment group (18 subjects [30.0%]). Among the individual active treatment groups, the proportion was higher in the 8% BID group (20 subjects [51.3%]), 12% BID group (20 subjects [54.1%]), and 12% QD group (22 subjects [51.2%]) than in the vehicle treatment group.

Blood samples were collected and analyzed for plasma hMAP3 concentrations to confirm the level of systemic exposure to SB206 at Week 12 or end of treatment. The plasma hMAP3 concentrations in all such PK blood samples were below the LLOQ.

The incidence of TEAEs was higher for subjects receiving active treatment (82 subjects [43.6%]) than for those receiving vehicle gel (19 subjects [28.8%]). Among active treatment groups, the incidence ranged from 40.4% (19 subjects) in the 12% QD group to 50.0% (24 subjects) in the 8% BID group. No deaths or SAEs were reported. A total of 7 subjects were discontinued from treatment with the study drug due to an AE, all in active treatment groups (3 subjects in the 4% BID group; 2 in the 8% BID group; and 2 in the 12% BID group). Treatment discontinuation was due to application site reactions in 6 of these subjects and to worsening MC in the other. In the pooled SB206 treatment group, the most common TEAEs were application site erythema (20 subjects [10.6%]); application site pain (12 subjects [6.4%]); application site exfoliation, application site pruritus, and pyrexia (8 subjects [4.3%] each); pharyngitis streptococcal (6 subjects [3.2%]); and application site dryness and vomiting (5 subjects [2.7%] each). There appeared to be no clear relationship between increasing active treatment dose and TEAE incidence. Summary of TEAEs is shown in Table 56.

Table 56. Summary of Treatment-Emergent Adverse Events (Safety Population)

		SB206				
	Vehicle Gel (N = 66)	4% BID (N = 46)	8% BID (N = 48)	12% BID (N = 47)	12% QD (N = 47)	All SB206 (N = 188)
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least one TEAE	19 (28.8)	19 (41.3)	24 (50.0)	20 (42.6)	19 (40.4)	82 (43.6)
Subjects with a related TEAE[a]	0	5 (10.9)	11 (22.9)	8 (17.0)	8 (17.0)	32 (17.0)
Subjects with an AE leading to treatment discontinuation	0	3 (6.5)	2 (4.2)	2 (4.3)	0	7 (3.7)
Subjects with leading to death	0	0	0	0	0	0
Subjects with at least one SAE	0	0	0	0	0	0

Source: Section 14.3.1, Table 14.3.1.1
Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects experiencing an event; N = number of subjects; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Note: The denominator for percentage corresponds to the N in each column. N is the number of subjects in the Safety population. Subjects are summarized by treatment received. Number of subjects experiencing an event (n) and percentage of subjects experiencing an event (%) are summarized. AEs were coded using MedDRA version 20.1. TEAEs are events that occurred or worsened on or after the first application of study drug.
a AEs with a relationship of definite, probable, or possible, were considered related.
Source: Clinical Study Report NI-MC201; Table 12-1

No remarkable changes between Baseline (Screening) and Week 12/ET were observed for methemoglobin parameters. The average changes in methemoglobin were small at every post-baseline visit. The maximum value was 3.2% in one subject in the 12% BID dose group at Week 4.

16.5.3. Study NI-AC104: ECG Study

This study was a double-blind, double-dummy, randomized, 4-period crossover study to define the ECG Effects of SB204 using a clinical and supratherapeutic dose compared with placebo and moxifloxacin (a positive control) in subjects with acne vulgaris. The primary objective was to evaluate the safety and tolerability of a 12% single dose of SB204 applied to the face, upper chest, upper back, and shoulders (approximately 17% BSA) and to define the electrocardiogram (ECG) effects of SB204 administered at the therapeutic dose and the supratherapeutic dose as determined in Part 1 applied to the face, upper chest, upper back, and shoulders in adult male and female subjects with moderate to severe acne vulgaris. In addition, the safety of SB204 and PK for hMAP3 were evaluated.

Study NI-AC104 was reviewed by Interdisciplinary Review Team for Cardiac Safety Studies under IND 137015 and the detailed review can be found in DARRTS.[3] The review concluded that supratherapeutic dose of berdazimer gel did not significantly increase the QTcF interval and the study data did not suggest that berdazimer is associated with significant QTc prolonging effect.

[3] DARRTS, IND 137015, CONSULT REV-QTIRT-01 (QT-IRT Review), date 04/07/2022

It was also concluded that results of the TQT study that was conducted with SB204 (berdazimer sodium 4%) are applicable to the SB206 (berdazimer 10.3%) formulation.

16.5.4. Study SKN15A01: Repeat-Dose Study With SB206 12% Gel in Healthy Japanese Adults

Study SKN15A01 was a phase 1 single-center, randomized, double-blind, vehicle-controlled, 2-period crossover study in healthy Japanese adult subjects with SB206 12% gel (mixed gel of NVN1000 24% gel and hydrogel with a volume ratio of 1:1; application of SB206 12% gel at 3 mL/500 cm2/dose twice daily). This study was planned as a 2-period crossover study with repeated application of SB206 12% gel and vehicle gel to assess the safety and pharmacokinetics of SB206 12% gel. However, of the 8 subjects treated with the study drugs, 2 subjects had erythema, pruritus, and burning/stinging assessed as score 3 (severe) at an unscheduled local skin tolerability assessment conducted before study drug application on Day 5, due to which they were withdrawn from the study. Based on the notification of suspension of the entire study from the Applicant, the investigator terminated the study in remaining 6 subjects at the end of Period 1.

Contact dermatitis was reported in 2 subjects treated with SB206 12% gel, as an adverse event leading to withdrawal from the study before study drug application on Day 5. The entire study was suspended following the 2 subjects' withdrawal, which finally led to discontinuation of the entire study. Summary of number of subjects who discontinued is provided in Table 57.

Table 57. Disposition of Subjects Who Were Enrolled in the Study

Number of subjects who completed the study		
Group A n (%)	Group B n (%)	Total n (%)
0	0	0

	Number of subjects who discontinued the study				
	Group A		Group B		Total
	Period I (SB206 12% gel) n (%)	Period II (Vehicle gel) n (%)	Period I (Vehicle gel) n (%)	Period II (SB206 12% gel) n (%)	n (%)
	4 (50.0)	0	4 (50.0)	0	8 (100.0)
Reason:					
Adverse event	0	0	0	0	0
Local skin tolerability	2	0	0	0	2
Withdrawal by subject	0	0	0	0	0
Inclusion/Exclusion violation	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Number of subjects met the target number	0	0	0	0	0
Physician decision	2	0	4	0	6

Source: Clinical study report for SKN15A01; Table 11-4

All 8 randomized subjects (4 in Group A and 4 in Group B) were treated with the study drug. These 8 subjects were included in the pharmacokinetics- full analysis set (PK-FAS), pharmacokinetics- per protocol set (PK-PPS), and safety analysis set (SAF). The descriptive statistics for pharmacokinetic parameters of the plasma nitrate and their baseline correction values in the PK-PPS are shown by study drug in Table 58.

Table 58. Pharmacokinetic Parameters of Plasma Nitrate (PK-PPS)4

Time Point Study Drug	C_{max} (ng/mL)	C_{min} (ng/mL)	t_{max} (h)	t_{min} (h)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	RA_{max}	RA_{AUC}
Day 1 (Day 7)									
SB206 12% gel									
n	4	4	4	4	4	4	4		
Mean	5425	2008	11.833	5.000	33819	NC	NC		
SD	789	342	0.0000	3.8297	3270	NC	NC		
Min	4770	1660	11.83	0.00	30365	NC	NC		
Median	5190	1950	11.833	6.000	33870	NC	NC		
Max	6550	2470	11.83	8.00	37172	NC	NC		
CV%	14.6	17.0	0.0	76.6	9.7	NC	NC		
Geometric Mean	5384	1986			33700	NC	NC		
Geometric SD	1.15	1.18			1.10	NC	NC		
Geometric CV%	14.0	16.8			9.7	NC	NC		
Vehicle gel									
n	4	4	4	4	4	4	4		
Mean	5573	2178	11.833	6.000	34477	NC	NC		
SD	464	358	0.0000	4.0000	3753	NC	NC		
Min	5020	1660	11.83	0.00	29401	NC	NC		
Median	5560	2295	11.833	8.000	35044	NC	NC		
Max	6150	2460	11.83	8.00	38419	NC	NC		
CV%	8.3	16.4	0.0	66.7	10.9	NC	NC		
Geometric Mean	5558	2153			34318	NC	NC		
Geometric SD	1.09	1.19			1.12	NC	NC		
Geometric CV%	8.3	17.9			11.3	NC	NC		
Day 5 (Day 11)									
SB206 12% gel									
n	2	2	2	2	2	2	2	2	2
Mean	4255	1930	7.000	4.000	31191	NC	NC	0.712	0.854
SD	NC	NC	NC	NC	NC	NC	NC	NC	NC
Min	3730	1760	2.00	0.00	29464	NC	NC	0.69	0.79
Median	4255	1930	7.000	4.000	31191	NC	NC	0.712	0.854
Max	4780	2100	12.00	8.00	32919	NC	NC	0.73	0.91
CV%	NC	NC	NC	NC	NC	NC	NC	NC	NC
Geometric Mean	4222	1922			31143	NC	NC		
Geometric SD	NC	NC			NC	NC	NC		
Geometric CV%	NC	NC			NC	NC	NC		
Vehicle gel									
n	4	4	4	4	4	4	4	4	4
Mean	3425	2108	12.000	4.500	30892	NC	NC	0.617	0.901
SD	468	228	0.0000	4.1231	3144	NC	NC	0.0879	0.1003
Min	2820	1840	12.00	0.00	27546	NC	NC	0.50	0.77
Median	3500	2130	12.000	5.000	30553	NC	NC	0.630	0.914
Max	3880	2330	12.00	8.00	34916	NC	NC	0.71	1.01
CV%	13.7	10.8	0.0	91.6	10.2	NC	NC	14.3	11.1
Geometric Mean	3400	2098			30774	NC	NC		
Geometric SD	1.15	1.12			1.11	NC	NC		
Geometric CV%	14.2	11.0			10.1	NC	NC		

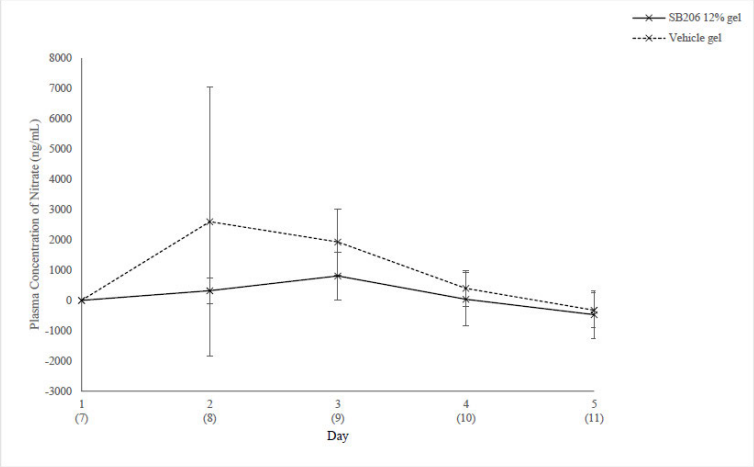
Abbreviation: SD=Standard deviation; Min=Minimum; Max=Maximum; CV=Coefficient of variation; NC=Not calculated; -=Missing value.

Source: Clinical study report for SKN15A01; Table 11-4

Baseline corrected plasma nitrate concentration values on Day 1 to Day 5 in the PK-PPS are shown by study drug in Figure 11.

[4] Nitrate levels were baseline corrected using baseline values from Day 1-Day 5 pre-dose.

Figure 11. Plasma Nitrate Concentration Baseline Correction Value-Time Profiles (Trough) (Mean ± SD) (PK-PPS) (Linear Scale)



Source: Clinical study report for SKN15A01; Figure 11-2

Baseline corrected plasma nitrate concentrations were lower in SB206 12% gel application compared to vehicle gel application at any time points of immediately prior to application (trough values) and 12 hours after study drug application on Day 1 and Day 5. The plasma nitrate concentration appeared to be higher in the vehicle gel application group than SB206 12% gel group. However, considering the variation in nitrate levels, that may be due to diurnal variation in plasma nitrate concentrations and/or the influence of dietary intake of nitric acid, this observation was not considered as significant. PK parameters could not be calculated for hMAP3 as the concentrations were below the lower LOQ (<5 ng/mL) at all the blood sampling points in all subjects. As a result of this study, local skin tolerability of SB206 12% gel was not obtained, under the application conditions of this study. The Applicant has attributed the irritation observed in this study to the size of the treatment area, which was limited to a single designated site (upper back), and the twice daily application.

16.5.5. Summary of Bioanalytical Methods

Bioanalytical methods using LC-MS/MS were developed and validated for the measurement of hMAP3 and nitrate concentrations in plasma.

The HMAP3 assay was developed by screening extraction, derivatization, and chromatographic separation schemes by (b) (4) Study Number: 0174-1406). Derivatization was required due to the high polarity and low molecular weight of hMAP3. This method was developed to cover the range of 5.00 to 500 ng/mL of hMAP3 using hBAP3 as the respective internal standard. The method was validated for precision, accuracy, selectivity, derivatization kinetics, and carryover.

All clinical samples were analyzed within the established stability period of the analytes. The performance and validation parameters of the analytical methods are summarized in Table 59 and Table 60.

Table 59. Summary of Bioanalytical Method for hMAP3 in Plasma

hMAP3 in Plasma	Method		
Bioanalytical method review summary	Method validation was adequate		
Report title	Bioanalytical Validation Report for the Determination of hMAP3 in Human Plasma (K2EDTA) by LC-MS/MS		
Matrix	K2EDTA Human plasma		
LC-MS/MS Instrumentation	Waters Acquity UPLC system, consisting of Sample Organizer, Sample Manager, Binary Solvent Manager, and Column Heater, and Thermo Scientific's TSQ Module. Thermo Scientific TSQ Vantage tandem mass spectrometer.		
Data Collection and Analysis Software	Thermo Scientific's Watson Laboratory Information System (LIMS) (v.7.4 SP4)		
Extraction method	Liquid-liquid extraction and derivatization		
Detection method	UPLC-MS/MS		
Sample aliquot volume	10 µL		
Regression model and weighting	Quadratic 1/x2 weighting		
Calibration Range	5.00 (LLOQ) to 500 (ULOQ) ng/mL		
Calibration standard concentrations	5, 10, 50, 75, 150, 250, 400, 500 ng/mL		
Validation Parameters	**Method Validation Summary**		**Acceptability**
	Accuracy (% bias)	**Precision (%CV)**	
Intra-assay validation	-7.6 – 3.2 %	≤ 5.6 %	Yes
Inter-assay validation	-2.7-0 %	≤ 5.5%	Yes
Dilution factors	Not reported		Yes
Performance of QCs during accuracy and precision runs			
Intra-assay validation	0-4 %	3.1-5.4 %	
Mean Analyte and IS Recovery	hMAP3 (%CV)	57.7-79.7 (2.2-3.0) %	Yes
	IS (%CV)	56.0-74.1 (1.3-2.6) %	Yes
Selectivity			
Matrix to Analyte & IS	No significant interfering peaks (>20.0% of the average LLOQ response) at the retention time of hMAP3 IS was ≤5.0% of the mean response 6/6 lots met the criteria		Yes
Matrix effect	For HQC and LQC, the precision of the internal standard normalized matrix factor was less than 15.0% The IS response tracked and mimicked the analyte		Yes
Carryover	No carryover result, expressed as a percentage of the LLOQ mean response, was greater than 10.5%		Yes
Stability			
Ambient Temperature Matrix Stability	6 replicates each of 15 ng/mL and 375 ng/mL 74.9 hours at room temperature The mean accuracy criterion was within ±15.0% and the %CV was ≤15.0%		
Freeze-thaw stability	4 freeze/thaw cycles at -20°C and -80°C		
Long-term storage	739 days at both -20°C and -80°C		

hMAP3 in Plasma	Method	
Extract stability	integrity of the analyte in the final extract for some storage period before first injection 91 Hours at 2 to 8°C	
Reinjection reproducibility	86 Hours at 2 to 8°C	
Stability in Whole Blood	0.53, 1.03, 1.54 and 2.05 Hours on Wet Ice in Whole Blood	
Method Performance in Study NI-MC101		
Assay passing rate	88.2% (sample analysis runs only)	
Cumulative accuracy (% bias)	-2.7-0 %	Yes
Cumulative precision (%bias)	≤ 5.5 %	Yes
Selectivity	No interferences in 6 lots of matrix, including 1 lipemic and 1 hemolyzed	Yes
Recovery	57.7-79.7% for hMAP3 and 56.0-74.1% for IS	Yes
Matrix Effects (IS normalized matrix factor)	Low level: 0.939, 1.8% CV High level: 0.937, 2.6% CV	Yes
Incurred sample reproducibility	100% of the paired results agree to within ±20.0% difference	Yes
Study sample analysis / stability		
Length of time samples were stored prior to analysis	64 days since collection	Yes

Source: (b) (4)
- Report 01:
- Report 02:
- Report 03:
- Report 04:

Abbreviations: CV, coefficient of variation; HQC, high quality control; IS, Internal standard; LLOQ, lower limit of quantitation; LOQ, low quality control; RE, relative error

Table 60. Summary of Bioanalytical Method for Nitrate in Plasma

Nitrate in Plasma	Method		
Bioanalytical method review summary	Method validation was adequate		
Report title	Bioanalytical Validation Report for the Determination of nitrate anion in Human Plasma (K2EDTA) by LC-MS/MS		
Method	Isotopically labeled nitrate anion ($15NO3^-$) is used as a surrogate analyte due to endogenous concentrations of nitrate in plasma. $15N18O3^-$ used as an internal standard.		
Matrix	K2EDTA Human plasma		
LC-MS/MS Instrumentation	Waters Acquity liquid chromatograph and Thermo Scientific's TSQ Module. Thermo Scientific TSQ Vantage tandem mass spectrometer		
Data Collection and Analysis Software	Thermo Scientific's Watson Laboratory Information System (LIMS) (v.7.4 SP4)		
Extraction method	Liquid-liquid extraction and derivatization		
Detection method	PLC-MS/MS		
Sample aliquot volume	20 µL		
Regression model and weighting	Linear 1/x2 weighting		
Calibration Range	300 (LLOQ) to 15,000 (ULOQ) ng/mL		
Calibration standard concentrations	300, 600, 1000, 2000, 4000, 8000, 12000, 15000 ng/mL		
Validation Parameters	**Method Validation Summary**		**Acceptability**
	Accuracy (% bias)	**Precision (%CV)**	
Intra-assay validation Inter-assay validation	-17 –5.6 % -1.7-2 %	≤ 15.9 % ≤ 5.8%	Yes Yes
Dilution factors	Not reported		Yes
Performance of QCs during accuracy and precision runs			
Intra-assay validation	0-4 %	3.1-5.4 %	
Mean Analyte and IS Recovery	hMAP3 (%CV)	57.7-79.7 (2.2-3.0) %	Yes
	IS (%CV)	56.0-74.1 (1.3-2.6) %	Yes
Selectivity			
Matrix to Analyte & IS	No significant interfering peaks (>20.0% of the average LLOQ response) at the retention time of hMAP3 IS was ≤5.0% of the mean response 6/6 lots met the criteria		Yes
Matrix effect	For HQC and LQC, the precision of the internal standard normalized matrix factor was less than 15.0% The IS response tracked and mimicked the analyte		Yes
Carryover	No carryover result, expressed as a percentage of the LLOQ mean response, was greater than 10.5%		Yes

Nitrate in Plasma	Method	
Stability		
Ambient Temperature Matrix Stability	6 replicates each of 15 ng/mL and 375 ng/mL 74.9 hours at room temperature The mean accuracy criterion was within ±15.0% and the %CV was ≤15.0%	
Freeze-thaw stability	4 freeze/thaw cycles at -20°C and -80°C	
Long-term storage	739 days at both -20°C and -80°C	
Extract stability	integrity of the analyte in the final extract for some storage period before first injection 91 Hours at 2 to 8°C	
Reinjection reproducibility	86 Hours at 2 to 8°C	
Stability in Whole Blood	0.53, 1.03, 1.54 and 2.05 Hours on Wet Ice in Whole Blood	
Method Performance in Study NI-MC101		
Assay passing rate	88.2% (sample analysis runs only)	
Cumulative accuracy (% bias)	-2.7-0 %	Yes
Cumulative precision (%bias)	≤ 5.5 %	Yes
Selectivity	No interferences in 6 lots of matrix, including 1 lipemic and 1 hemolyzed	Yes
Recovery	57.7-79.7% for hMAP3 and 56.0-74.1% for IS	Yes
Matrix Effects (IS normalized matrix factor)	Low level: 0.939, 1.8% CV High level: 0.937, 2.6% CV	Yes
Incurred sample reproducibility	100% of the paired results agree to within ±20.0% difference	Yes
Study sample analysis / stability		
Length of time samples were stored prior to analysis	64 days since collection	Yes

Source:
- Report 01: (b) (4)
- Report 02:
- Report 03:
- Report 04:

Abbreviations: CV, coefficient of variation; HQC, high quality control; IS, Internal standard; LLOQ, lower limit of quantitation; LOQ, low quality control; RE, relative error

Methemoglobin Method Validation

The Applicant did not provide assay validation for methemoglobin. In response to IR for assay validation for methemoglobin, the applicant stated the clinical studies including methemoglobin measurement utilized the Masimo RAD-57 pulse co-oximeter, an FDA cleared 510(k) device, following the manufacturer's instructions for use [510(k) K120657].

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/

DAVID L KETTL
01/04/2024 08:34:42 PM

NIKOLAY P NIKOLOV
01/04/2024 08:59:12 PM