A Phase 3 Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study Comparing the Efficacy and Safety of SB206 and Vehicle Gel Once Daily in the Treatment of Molluscum Contagiosum

A Phase 3 Molluscum Contagiosum Efficacy and Safety Study

Investigational Product	SB206
Protocol Number	NI-MC304
Version Number	3.0
Version Date	30 Sep 2020
Amendment	2
IND Number	137015
Sponsor	Novan, Inc. 4105 Hopson Road, Suite 146 Morrisville, NC 27560

CONFIDENTIALITY STATEMENT

The information contained in this protocol and all other information relevant to SB206 are the confidential and proprietary information of Novan, and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Novan.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by ICH E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Phase 3 Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study Comparing the Efficacy and Safety of SB206 and Vehicle Gel Once Daily in the Treatment of Molluscum Contagiosum
Protocol Number	NI-MC304
Version Number	3.0
Version Date	30 Sep 2020
Amendment	2

The design of this study as outlined by this protocol has been reviewed and approved by the sponsor's responsible personnel as indicated in the signature table below.

Medical Representative			
Name:	**Title:**	**Signature:**	**Date:**
Tomoko Maeda-Chubachi	Vice President, Medical		30 Sep 2020
Regulatory Representative			
Name:	**Title:**	**Signature:**	**Date:**
Emily de León	Senior Director of Regulatory Operations		30Sep2020
Biostatistics Representative			
Name:	**Title:**	**Signature:**	**Date:**
David Hebert	Senior Director, Head of Biometrics		30SEP2020

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study NI-MC304 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each subject's participation and all data required by the protocol

Name	**Title**	**Institution**

Signature	**Date**

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 3.0) relative to the prior approved version (Version 2.0) are summarized in the table below.

Section Number	**Section Title**	**Summary of Change**	**Rationale for Change**
10.2.1	Sample Size Rationale	Increased to approximately 850 patients and updated supporting rationale	Increased ability to detect treatment difference
Multiple sections	Changed throughout protocol for consistency	Permit remote or in-clinic visit to be performed at Visit 4/Week 4, and in-clinic visit to be performed at V5/Week 8	Ensuring data quality and operational ease for subjects/caregivers

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Atopic Dermatitis
AE	Adverse Event
BID	Twice Daily
BOTE	Beginning-of-the-end
BSA	Body Surface Area
CFR	Code of Federal Regulations
CM	Concomitant Medication
CRO	Clinical Research Organization
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
e-consent	Electronic Consent
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
hMAP3	Hydrolyzed N-Methylaminopropyl-trimethoxysilane
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone Releasing System
IWRS	Interactive Web Response System

LLOQ	Lower Limit of Quantitation
LSR	Local skin reaction (post exposure to study drug)
MC	Molluscum Contagiosum
MedDRA	Medical Dictionary of Regulatory Affairs
NO	Nitric Oxide
NOVAN	Novan, Inc.
OTC	Over the counter
PK	Pharmacokinetic
PP	Per-Protocol Population
QD	Once daily
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
UPT	Urine Pregnancy Test

1 SYNOPSIS

Title	A Phase 3 Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study Comparing the Efficacy and Safety of SB206 and Vehicle Gel Once Daily in the Treatment of Molluscum Contagiosum
Short Title	A Phase 3 Molluscum Contagiosum Efficacy and Safety Study
Acronym	B-SIMPLE4
Phase	3
Study Design	This is a phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in up to approximately 850 subjects 6 months of age and older with molluscum contagiosum (MC). After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized 1:1 (active:vehicle). Subjects receiving current treatment for MC at the time of the Screening Visit will enter a wash out period of up to 14 days prior to randomization. In the event no wash out period is required, Screening and Baseline visit activities may be combined into a single visit. At randomization, subjects will be stratified by investigator type (dermatologist vs. other), the subject's BOTE score at Baseline (no inflammation (BOTE = 0) vs. mild/moderate/severe inflammation (BOTE ≥ 1) and number of randomized subjects per household (1 subject per household vs. 2 subjects per household). Subjects will be stratified to 5 strata first by subjects per household. Subjects from 1 subject households will be stratified by investigator type and baseline BOTE score. Subjects from 2 subject households will not be further stratified with respect to investigator type and baseline BOTE score because the overall sample size that is expected for the stratum for households with two subjects is not large enough to support further stratification. The sponsor, investigator, site staff and study subjects will remain blinded to the study treatment during this study. All treatments are dosed topically, once daily (QD). Each dose will consist of berdazimer gel or vehicle gel that will be mixed with hydrogel on a supplied dosing guide, and then immediately applied by the subject to the affected designated area(s).

	Subjects or their caregivers will apply treatment once daily to all lesions identified at Baseline and new lesions that arise during treatment for a minimum of 4 weeks and shall continue unless otherwise instructed by the investigator up to 12 weeks. If the investigator determines all lesions are cleared at a visit, the investigator may instruct the subject to stop treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24/ET2. Study drug will be dispensed through Week 12/ET1 in case of lesion recurrence between study visits. At each visit subsequent to stopping treatment due to clearance, the investigator will determine if new lesions have occurred since the last visit, and if so, the subject or caregiver will be instructed by the investigator to re-initiate treatment. If the subject or caregiver see new lesions or re-occurrence of lesions in between visits, they should treat these lesions until the next visit. No study drug is planned to be provided after the Week 12 visit. The subject or caregiver will apply study drug to the individual lesions. Periocular lesions will be treated if the lesions are at least 2 cm from the edge of the eye. Subjects will visit the clinic in person at Screening/Baseline, Week 2, Week 4 (unless visit is performed remotely), Week 8, Week 12, and Week 24. At Baseline, the investigator will perform in person lesion counts. Then, the subjects/caregivers will be instructed on how to participate in remote visits and practice the technology. Once the initial in person lesion count has been completed by the assessor, an additional count by the same investigator will be made utilizing the remote technology platform to serve as a training for future remote visit. Subjects will be contacted via phone on Day 2 to collect subject information on early dose reactions. The Week 4 Visit may be performed remotely or as an in-clinic visit. At Weeks 16 and 20, subjects will be contacted via phone to capture information regarding MC recurrence and adverse events (AEs); at Week 24, the subject will be seen at the site for a final study visit to assess scarring, keloids, and MC recurrence. Subjects who discontinue the study prior to the Week 12 visit due to AEs or other reasons will be asked to complete the Week 12 visit assessments; this will

	be recorded as an Early Termination (ET1) visit. Subjects who discontinue from the study after Week 12 but prior to Week 24 will be asked to come to the site to complete Week 24 assessments; this visit will be recorded as an ET2 visit. Safety assessments include Beginning of the End (BOTE) Inflammation Scores, Local Skin Reactions (LSRs), adverse event collection, including presence of scars/keloids, and urine pregnancy tests (UPTs). Safety assessments except UPTs will be completed at all visits through Week 12; UPTs will be completed at Screening, Baseline, and Week 12. After Week 12, safety information for ongoing and new AEs will be collected, along with information regarding household MC occurrence. Additional procedures include subject/caregiver completion of a the Global Severity Assessment and the Global Impression of Change Assessment by the investigator and the subject/caregiver at Week 12 and 24. These procedures are designed to provide insight into the subject/caregiver's experience with MC and current MC disease state. A select number of sites will also consent subjects/caregivers to participate in a study exit interview, to be arranged by a third party after completion of Week 12. The interview will include questions to further detail the subject/caregiver perspective of their MC and treatment experience.
Target Population	Males and females, 6 months of age and older, with a minimum of 3 and a maximum of 70 MC lesions at Baseline
Number of Subjects	Approximately 850 Subjects will be assigned 1:1 to active:vehicle.
Length of Participation	On treatment: Approximately 12 weeks Safety follow-up period: Approximately 12 weeks In study (including screening and safety follow-up): Up to approximately 26 weeks

Intervention	SB206 10.3% or Vehicle Gel once daily Inflammatory reactions around the MC have been associated with imminent resolution of MC (sometimes referred to as "beginning-of-the-end" ["BOTE"] sign). In most cases, clinical features can differentiate between BOTE and LSR. BOTE may be associated with itch, but not pain. BOTE is usually asymptomatic, self-limited, localized to individual MC lesions, and does not require discontinuation of study treatment or additional treatment. LSR is generally more diffuse, associated with significant itch or tenderness, may necessitate discontinuation of study treatment, and may need treatment for symptomatic relief (e.g. a topical corticosteroid or topical anesthetic). For very severe LSR, systemic corticosteroids may be considered. Investigators will assess the treatment area at each scheduled visit and use their medical judgement to differentiate between BOTE and LSRs. The subject's baseline skin inflammatory condition will be assessed as part of the physical examination to be completed prior to randomization. BOTE Inflammation Score and LSR scores will be recorded at each visit. LSRs will be rated on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. When LSRs are clinically significant, the investigator should report the condition as AE(s). Clinically significant LSRs that are reported as adverse events and/or subject reported intolerability (i.e. itching, pain) may result in an investigator directed temporary treatment hold (drug holiday), and topical corticosteroids may be used to treat LSRs for up to 2 weeks. Per the investigator's instructions, the subject may re-initiate study drug treatment prior to the next scheduled visit. Upon re-initiation (challenge) of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. In the event of suspected allergic contact dermatitis, photographs may be taken of the affected area(s) and transmitted to the contract research organization (CRO) medical monitor for review and confirmation of allergic contact dermatitis prior to initiating patch testing. Consent must be in place for patch testing to occur. The investigator should also discuss the necessity of patch testing with the subject/caregiver. The investigator will then

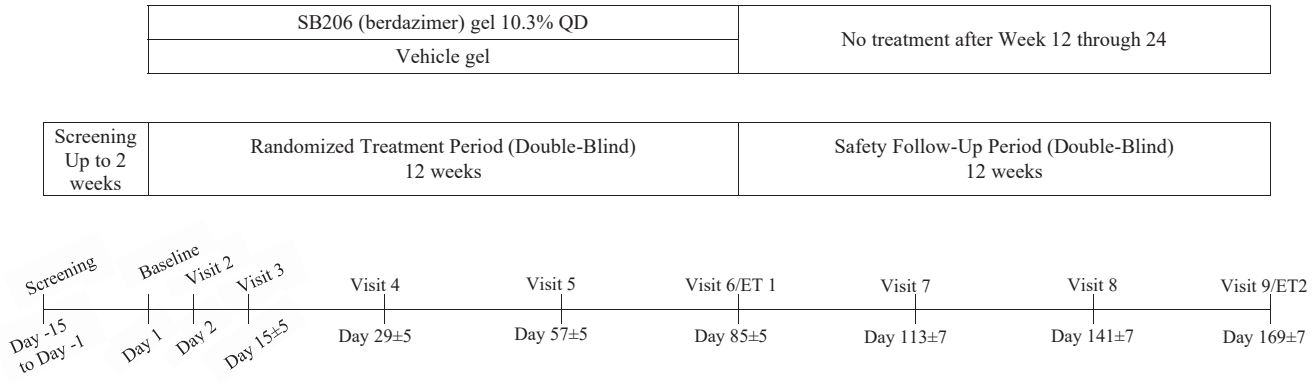
	discontinue the subject from study drug treatment and treat the area(s) with corticosteroids for up to 2 weeks. If the subject provides consent/assent, the investigator will consult the CRO medical monitor prior to implementing the process for patch testing. Adverse events will be assessed and collected after the initiation of study drug treatment through the end of the subject's last visit. Treatment related adverse events will be followed up until resolution or up to one year after last treatment, whichever is sooner. The investigator will map locations of the molluscum lesions at Baseline in clinic and through the remote visit platform. The investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. Additional lesions identified through Week 12 will be mapped at each visit. Using the map as a guidance, the investigator will assess the treated areas for scar/keloid formation. Scar formation will be assessed starting at the Week 4 visit through Week 12 and again at Week 24. Scars will be considered an adverse event for the purposes of this study. In addition, treatment related keloid/hypertrophic scars will also be recorded as adverse events. If a subject's treatment is discontinued by the investigator or the subject because of an AE, that AE should be indicated as the reason for treatment discontinuation. All subjects will be encouraged to remain in the study throughout the 24-week study duration, even if treatment is discontinued prematurely.
Primary Endpoint	This study is being conducted to evaluate the efficacy and safety of SB206 10.3% QD for the treatment of MC. The primary endpoint will evaluate the proportion of subjects with complete clearance of all treatable MC at Week 12.
Secondary Endpoints	• Proportion of subjects achieving a lesion count of 0 or 1 of all treatable MC at Week 12 • Proportion of subjects achieving at least a 90% reduction from Baseline in the number of all treatable MC at Week 12 • Proportion of subjects with complete clearance of all treatable MC at Week 8 • Percent change from Baseline in the number of all treatable MC at Week 4

Safety Endpoints	• Incidence of treatment-emergent adverse events • Change from Baseline in LSR scores • Change from Baseline in abbreviated physical examinations • Concomitant medications reported • Proportion of subject(s) with reported scar(s)
Other Endpoint	• Change from Baseline in BOTE scores
Exploratory Endpoints	• Percent change from Baseline in number of treatable MC at Weeks 2, 8, and 12 • Proportion of subjects achieving a lesion count of 0 or 1 of all treatable MC at Weeks 2, 4, and 8 • Proportion of subjects achieving at least a 90% reduction from Baseline in the number of all treatable MC at Weeks 2, 4 and 8 • Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at Weeks 2, 4, 8 and 12 • Absolute change from Baseline in number of treatable MC at Weeks 2, 4, 8 and 12 • Proportion of subjects with complete clearance of all treatable MC at Weeks 2 and 4 • Time to complete clearance of all treatable MC • Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed • Subject-reported spread to household members as measured by any new occurrence of MC in household members of subjects at Weeks 2, 4, 8, 12 • Investigator Global Severity Assessment at Baseline, Week 12 and 24 • Subject Global Severity Assessment at Baseline, Week 12 and 24 • Investigator Global Impression of Change at Week 12 and 24 • Subject Global Impression of Change at Week 12 and 24
Number of Sites	Approximately 55 sites in the United States
Study Duration	Estimated start date: 01 Sep 2020 Projected stop date: 31 Mar 2021 Estimated duration: 3.5 months of enrollment

1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Timeline Diagram



*Subjects that do not require a washout may have Screening and Baseline procedures conducting on the same day. Screening/Baseline visits will be done in-clinic if completed on the same day.

*Week 12 procedures should be completed for subjects who early terminate (ET) from the study prior to Week 12; Week 24 procedures should be completed for subjects who ET after Week 12 but prior to Week 24.

1.2 Schedule of Assessments

The schedule of assessments (SOA) is presented in Table 1.

Table 1 Schedule of Assessments

	Screening	**Treatment**					
	Screening[1] (Day -15 to Day 1)	Visit 1[1] Baseline (Day 1)	Visit 2 TC (Day 2)	Visit 3[2] Week 2 (Day 15 ±3)	Visit 4[2] Week 4 (Day 29 ±5)	Visit 5[2] Week 8 (Day 57 ±5)	Visit 6[2] Week 12/ ET1 (Day 85 ±5)
Informed Consent (Assent)	X						
Demographics	X						
Medical and Medication History	X						
Molluscum Lesion Count	X	X[3]		X	X	X	X
Physical Exam[4]		X					X
Urine Pregnancy Test[5]	X[6]	X					X
BOTE Inflammation Score[7]		X (pre-dose)		X	X	X	X
Local Skin Reactions (LSR)[8]		X (post-dose)		X	X	X	X
Scarring/Keloid Assessment					X	X	X
Review of Inclusion/Exclusion Criteria	X	X					
Drug Dispensed		X			X	X	
Collect Study Drug					X	X	X
Provide instructions on and test remote visit technology		X					
Provide Subject Diary		X					
Review Subject Application Instructions		X		X	X	X	
In Clinic Study Drug Application[9]		X		X	X	X	X
Review/reinforce Study Drug Compliance				X	X	X	X
Record Adverse Event (AE) and Concomitant Medication (CM) Changes		X	X	X	X	X	X
Household status of MC[10]	X	X		X	X	X	X
Investigator Global Severity Assessment & Subject Global Severity Assessment		X					X
Investigator Global Impression of Change & Subject Global Impression of Change							X
Consent for Study Exit Interview[11]		X					

	Safety Follow-up		
	Visit 7 Week 16 TC (Day 113 ± 7 days)	Visit 8 Week 20 TC (Day 141 ± 7 days)	Visit 9 Week 24/ET2 (Day 169 ± 7 days)
Scarring/Keloid Assessment			X
Record Adverse Event (AE) and Concomitant Medications[10]	X	X	X
Household status of MC[10]	X	X	X
Investigator Global Severity Assessment & Subject Global Severity Assessment			X
Investigator Global Impression of Change & Subject Global Impression of Change			X

[1] Screening and Baseline may occur on the same day. If this occurs, lesion count and review of inclusion/exclusion criteria will only occur once.

[2] All visit dates are in reference to Baseline (e.g. Week 2 occurs 14 days after Baseline Visit). The Week 4 visit may be performed remotely or in clinic. Baseline, Week 2, Week 8, Week 12, and 24 visits will be performed in clinic. Day 2, Week 16, and Week 20 will be performed via phone. If a subject terminates early, an in-clinic visit is preferred, but a remote visit may be performed with sponsor approval.

[3] Lesion counts will be performed twice during the Baseline visit; the first assessment will be performed by the investigator in person, and the second assessment will be performed by the investigator through image evaluation.

[5] The physical exam will include a directed examination of the skin (presence or absence of individual features of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

[6] Females who have reached 9 years of age, unless they are post-menopausal (at least 12 months of continuous amenorrhea without an alternative medical cause), or surgically sterilized (documented hysterectomy, documented bilateral salpingectomy, or documented bilateral oophorectomy). Tubal ligation does not meet the definition of surgically sterile.

[7] UPT will be performed at Screening if the visit takes place in the clinic.

[8] BOTE Inflammation Score will be assessed pre-dose at Baseline. The Baseline LSR assessment should be done at least 30 minutes after study drug is applied on Day 1. After Baseline, BOTE Inflammation score and LSRs can be evaluated at any time pre- or post-dose during the visit, regardless of whether lesions are present and whether study drug is applied.

[9] Study drug application will occur in clinic at Baseline, Week 2, Week 4, Week 8, and Week 12. On days when a remote visit will occur, subjects/caregivers will not apply the study drug until the study visit so that the mixing/application of study drug can be observed by site staff during the remote visit.

[10] At Screening, subjects should be asked if any household members currently have MC. In addition to recording AE and CM changes, subjects should be asked if there are any new occurrences of MC in household members of subjects at each visit, except Day 2.

[11] Follow up interviews will be performed with selected consented subjects that complete Week 12. Consent can be obtained starting at Baseline, and the follow up interview will be performed with the subject/caregiver at a later date.

NOTE: The Week 4 visit can be performed in clinic or remote. Baseline, Week 2, Week 8, Week 12, and Week 24 should be performed in clinic wherever possible. Day 2, Week 16, Week 20 should be performed as telephone contacts. Unscheduled visits are permitted as needed for medical reasons. In-clinic unscheduled visits should be reserved for evaluation of adverse events, lesion clearance, and study drug dispensation as needed. Remote unscheduled visits may be utilized as well as/if applicable.

2 INTRODUCTION

2.1 Background

Molluscum contagiosum (MC) is a common skin disorder that affects mainly healthy children (Dohil et al., 2006). MC has the greatest incidence in individuals aged 1–14 years (Schofield et al., 2011); prevalence in children is between 5% and 11% (FDA, 2020).

MC virus is an important human skin pathogen and can cause disfigurement and suffering in children. In adults, MC is less common and often sexually transmitted. Extensive and persistent skin infection with the virus can indicate underlying immunodeficiency. MC virus is distinct from other poxviruses because of its host and tissue adaptations. It infects only the skin and, rarely, the mucous membranes. The virus has developed efficient mechanisms to grow in differentiating cells of the human epidermis and is well adapted to human hosts (Chen et al., 2013).

Patients with atopic dermatitis (AD) have an impaired skin barrier in addition to immunological changes which could explain the rising prevalence and high number of lesions in this population. Topical corticosteroids and calcineurin inhibitors (both local immunosuppressants commonly applied to the skin in patients with atopic dermatitis) have been implicated as contributing factors in some patients (Olsen et al., 2014).

MC is transmitted between human hosts by the infectious matter discharged from the lesions. According to a prospective community cohort study (Olsen et al., 2015), the mean time to resolution was 13.3 months (SD 8.2). Eighty (30%) of 269 cases had not resolved by 18 months; 36 (13%) had not resolved by 24 months. Transmission to other children in the household occurred in 102 (41%) of 250 cases in the literature.

Novan, Inc. (Novan) conducted Study NI-MC201, a phase 2, multi-center, double-blind, vehicle-controlled ascending dose, 12-week study to assess the tolerability, safety, and efficacy of SB206 in subjects with molluscum contagiosum. In this study, the safety and efficacy of SB206 was evaluated in 256 subjects, males and females, 2 years of age or older, with 3 to 70 MC lesions. Different concentrations and dosing frequency of SB206 were tested for up to 12 weeks and the number of the subjects of each dose group were: 47 (4% BID), 48 (8% BID), 47 (12% BID), 48 (12% QD) and 66 (Vehicle). In the intent-to-treat (ITT) analysis, 37.5% of subjects achieved complete clearance when treated with SB206 12% QD, compared to 18.2% of subjects achieving complete clearance with vehicle BID/QD combined (p=0.024).

Based on the clear treatment effect demonstrated in NI-M201, Novan conducted two phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group studies of SB206 in subjects 6 months of age and older with molluscum contagiosum, NI-MC301 and NI-MC302. In NI-MC301, 352 subjects were randomized across 33 sites in the United States and had an average of 18.1 molluscum lesions at baseline and an average of age 7.1 years. The study discontinuation rate was 15.3%. In NI-MC302, 355 subjects were randomized across 33 sites in

the United States and had an average of 18.3 molluscum lesions at baseline and an average age of 6.5 years. The study discontinuation rate was 17.2%.

The primary endpoint for these studies was the proportion of subjects in the ITT population with complete clearance of all treatable molluscum lesions at Week 12. Subjects with missing Week 12 lesion count data were counted as non-responders. In NI-MC301, 25.8% achieved complete clearance at Week 12 with SB206 and 21.6% achieved complete clearance at Week 12 with Vehicle; 30.0% of subjects on SB206 and 20.3% of subjects on Vehicle in NI-MC302 achieved complete clearance at Week 12. Although the primary analysis alone did not achieve statistical significance at the 0.05 level in either study, there is a positive trend within and across both studies. An integrated analysis of the primary endpoint for the combined studies was performed. This post hoc analysis shows a continued trend of effectiveness by achieving statistical significance with a complete clearance of 27.9% for SB206 and 20.9% for vehicle (p= 0.0387). Based on these results, an additional phase 3 study, NI-MC304, is being conducted with SB206.

Topical formulations of berdazimer sodium at concentrations ranging from 1-16% have been studied. Over 1900 healthy volunteers or subjects with MC, acne, genital warts, atopic dermatitis, psoriasis, or tinea pedis have been exposed to Vehicle and over 3,400 exposed to berdazimer sodium as of January 31, 2020. In clinical studies completed to date, topical application of berdazimer sodium has generally been well-tolerated with no safety concerns identified. Note that description of the concentration of SB products used nominal numbers based on percent berdazimer sodium historically. Novan has updated the naming convention to use percent berdazimer. Therefore, SB206 12% (nominal berdazimer sodium) is the same admixture formulation as SB206 10.3% (berdazimer). In this protocol, the nominal berdazimer sodium numbers remain in historical studies.

2.1.1 Target Indication and Population

SB206 is being developed to treat molluscum contagiosum in children and adults.

2.1.2 Description of SB206

SB206 is a topical gel, formed by mixing berdazimer gel and hydrogel. Berdazimer gel is a nitric oxide-releasing macromolecule containing covalently bound N-diazeniumdiolate nitric oxide donors; nitric oxide release from the macromolecule is initiated by mixing the berdazimer gel with hydrogel. A summary of nonclinical and clinical data is provided below; additional details are provided in the Investigator's Brochure.

2.1.2.1 Administration Regimen

Subjects will apply treatment once daily for up to 12 weeks to all active lesions identified at Baseline and new lesions that arise during treatment. If the investigator determines all lesions are cleared at a visit, the treatment may stop. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24 and study drug will be dispensed in case of lesion recurrence between study visits. Prior to Week 12, if lesions recur or new lesions appear

after the subject has cleared, treatment should be resumed. No further treatment will occur after Week 12.

An increase in the number of MC lesions (with or without inflammatory reaction) during the early treatment period is often observed. It is important to instruct the subject/caregiver to treat the new lesions as well as the existing lesions.

Each dose will consist of berdazimer gel or vehicle gel with hydrogel thoroughly mixed together by the subject or caregiver on a supplied dosing guide and applied to the individual lesions. Periocular lesions will be treated if the lesions are at least 2 cm from the edge of the eye. If a subject has more than 20 MC, a second dose of berdazimer gel or vehicle gel with hydrogel can be prepared to ensure appropriate coverage of all lesions.

2.1.2.2 Justification for Dosing Strategy

Based on totality of the data presented in Section 2.1, SB206 12% QD (now SB206 10.3% QD) was selected for this phase 3 study.

2.1.3 Supportive Nonclinical Data

Novan has completed over 150 non-clinical studies during the development of multiple berdazimer sodium products (SB204, SB206, SB208, SB414) to assess pharmacology, PK, ADME, and toxicology. For additional nonclinical information refer to the Investigator's Brochure (IB).

2.1.4 Supportive Clinical Data

Over 5300 subjects have been treated, including over 3400 subjects who have been treated with topical berdazimer sodium (SB204, SB206, SB208, SB414) and over 1900 subjects have been treated with vehicle. The conditions investigated include acne, external genital warts and perianal warts, tinea pedis, psoriasis, atopic dermatitis and molluscum contagiosum. Topical administration of berdazimer sodium has had an overall favorable safety and tolerability profile. Application site pain has been the most common treatment related adverse event in completed studies. There has been no evidence of meaningful trends in safety parameters. There have been no clinically significant changes in physical examination in subjects treated with topical berdazimer sodium; however, there have been a few sporadic clinically significant changes identified in laboratory assessments and vital signs.

2.1.4.1 Clinical Pharmacology and Pharmacokinetics

The systemic bioavailability of SB206 after dermal administration has been investigated in one maximal use study, NI-MC101 in patients, at least six months of age, with a minimum of 20 MC lesions at baseline. For 15 days, subjects received once daily field treatment, which totaled an area of 484 cm^2, which approximates to 100 MC lesions. The PK profile was assessed after repeated topical application of SB206 under the maximal use condition. No detectable systemic

exposure on Day 1 to hydrolyzed N-methylaminopropyl-trimethoxysilane (hMAP3), a silicon containing component of the parent compound was noted. Further PK analysis of Day 15 samples indicated two subjects demonstrated negligible systemic concentration of hMAP3: one showed one measurable time point with 5.12 ng/mL at 3 hours post dose among 3 time points (pre-dose, 1, and 3 hours post dose), and the other showed 4 measurable time points with the maximum concentration of 33.9 ng/mL at 3 hours post dose among 4 time points (pre-dose, 1, 3, and 6 hours post-dose). Plasma nitrate concentrations were within normal variability. The maximum recorded post-Baseline value for methemoglobin of the study was 2.8%, and methemoglobin values from the 2 subjects who showed systemic exposure did not exceed 2.2 %.

In the NI-MC201 study, plasma hMAP3 concentrations in all PK blood samples at Week 12 or end or treatment were below the lower limit of quantitation (LLOQ).

In addition, two other supportive studies with the berdazimer drug product SB204 have been conducted in adults and adolescent subjects with moderate to severe acne vulgaris, and no quantifiable systemic exposure was observed. In adult subjects with moderate to severe acne vulgaris (NI-AC101) administration of SB204 8% (berdazimer sodium gel 16% co-administered with hydrogel) or Vehicle Gel daily for 5 days to the face, chest, back, upper shoulders twice daily (BID) (17% body surface area [BSA]) showed no detectable systemic exposure on Day 1 or Day 5 to hydrolyzed N-methylaminopropyl-trimethoxysilane (hMAP3), a silicon containing component of the parent compound. There was no noticeable difference in systemic nitrate levels on Day 1 or Day 5 in subjects treated with SB204 or Vehicle Gel and no evidence of accumulation. Likewise, in an open-label pharmacokinetic (PK) study (NI-AC103) in adolescents (ages 9-16 years) with moderate to severe acne vulgaris, SB204 4% was applied topically once daily (QD) for 21 days to 17% BSA and again no detectable systemic exposure to hMAP3 and no plasma nitrate concentrations outside of normal variability and negligible accumulation of nitrate after 21 days of dosing were noted.

Additionally, in a 4-way, randomized, double-blind, cross-over study examining electrocardiogram (ECG) effects following SB204 application (NI-AC104), there was no quantifiable systemic exposure to hMAP3 and no difference in plasma nitrate levels in 48 subjects with moderate to severe acne treated with SB204 (berdazimer sodium) 4%, SB204 (berdazimer sodium) 12% or Vehicle Gel applied to 17% BSA. No changes in ECG were observed with therapeutic or supratherapeutic doses of SB204.

In a 2-week atopic dermatitis (AD) study (NI-AD101), and a 4-week psoriasis study (NI-PS101), a limited number of subjects who received SB414 6% (berdazimer sodium ointment 12% co-administered with buffered hydrogel) demonstrated quantifiable systemic exposure to the study treatment at limited time points. Although both SB206 and SB414 have the same active pharmaceutical ingredient, the formulations are different: SB206 is a gel and SB414 is a cream. The cream formulation of SB414 resulted in low and not quantifiable systemic exposure to hMAP3 observed in the NI-AD101 and NI-PS101 studies for all but 2 subjects at 12 hours post-

dose. Note that SB414 formulation is cream while SB204 formulation is gel, similar to SB206. For more information, refer to the Investigator's Brochure.

2.1.4.2 Clinical Safety

It should be noted some subjects have experienced transient asymptomatic erythema at the application site within 5 minutes of dosing, which typically lasted ≤15 minutes. This is due to nitric oxide's vasodilatory pharmacologic effect and is an expected event.

Summaries of the safety analyses of the phase 3 studies (NI-MC301 and 302) are ongoing, and the CSRs are under preparation. The treatment emergent adverse event (TEAE) profile of SB206 through the Week 24 was found to be favorable and was very similar between the two studies. Study drug discontinuations in the SB206 treatment arm were all due to application site reactions and no treatment-related serious adverse events were reported across both studies.

Table 2 Overall Summary of TEAEs (Safety Population) through Week 24

	NI-MC301		**NI-MC302**	
	Vehicle (n=116)	SB206 (n=235)	Vehicle (n=117)	SB206 (n=237)
Subjects who reported at least one TEAE	36 (31.0%)	115 (48.9%)	30 (25.6%)	120 (50.6%)
Serious TEAE	0	0	1 (0.9%)	1 (0.4%)
Treatment-related TEAE	19 (16.4%)	86 (36.6%)	8 (6.8%)	86 (36.3%)
TEAE leading to study drug discontinuation	1 (0.9%)	7 (3.0%)	1 (0.9%)	17 (7.2%)

The TEAEs reported in greater than 5% of subjects in the SB206 treated groups were application site pain and application site erythema, with the majority of these TEAEs being mild or moderate in severity.

Table 3 TEAEs in ≥ 2% of subjects in either SB206 treated group or Vehicle group (NI-MC301)

	Vehicle (n=116)			**SB206 (n=235)**		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Application site pain	8 (6.9%)	0	0	34 (14.5%)	16 (6.8%)	1 (0.4%)
Application site erythema	2 (1.7%)	1 (0.9%)	0	13 (5.5%)	15 (6.4%)	1 (0.4%)
Application site pruritus	0	0	0	8 (3.4%)	2 (0.9%)	1 (0.4%)
Pyrexia	3 (2.6%)	1 (0.9%)	0	7 (3.0%)	4 (1.7%)	0
Application site exfoliation	0	0	0	4 (1.7%)	5 (2.1%)	1 (0.4%)
Application site scar	9 (7.8%)	0	0	6 (2.6%)	0	0
Application site swelling	1 (0.9%)	0	0	5 (2.1%)	1 (0.4%)	0
Application site dermatitis	1 (0.9%)	0	0	1 (0.4%)	3 (1.3%)	1 (0.4%)
Application site discolouration	0	0	0	5 (2.1%)	0	0
Vomiting	1 (0.9%)	0	0	2 (0.9%)	5 (2.1%)	0
Upper respiratory tract infection	2 (1.7%)	0	0	3 (1.3%)	2 (0.9%)	0

Table 4 TEAEs in ≥ 2% of subjects in either SB206 treated group or Vehicle group (NI-MC302)

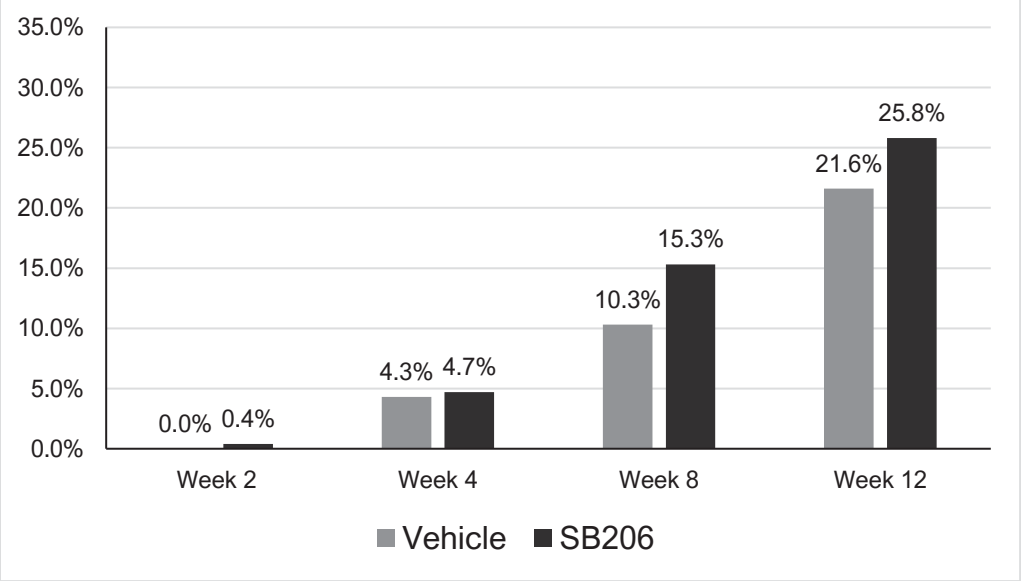
	Vehicle (n=117)			SB206 (n=237)		
	mild	moderate	severe	mild	moderate	severe
Application site pain	1 (0.9%)	1 (0.9%)	0	15 (6.3%)	22 (9.3%)	0
Application site erythema	0	0	0	10 (4.2%)	14 (5.9%)	2 (0.8%)
Application site dermatitis	1 (0.9%)	0	0	6 (2.5%)	5 (2.1%)	0
Application site scar	10 (8.5%)	0	0	10 (4.2%)	0	0
Application site exfoliation	0	0	0	3 (1.3%)	5 (2.1%)	1 (0.4%)
Application site pruritus	1 (0.9%)	1 (0.9%)	0	3 (1.3%)	5 (2.1%)	0
Application site swelling	0	0	0	1 (0.4%)	5 (2.1%)	1 (0.4%)
Pyrexia	2 (1.7%)	0	0	5 (2.1%)	2 (0.8%)	0
Application site vesicles	0	0	0	0	5 (2.1%)	0
Dermatitis contact	0	0	0	3 (1.3%)	3 (1.3%)	0

Additional details regarding safety are available in the Investigators Brochure (IB).

2.1.4.3 Clinical Efficacy

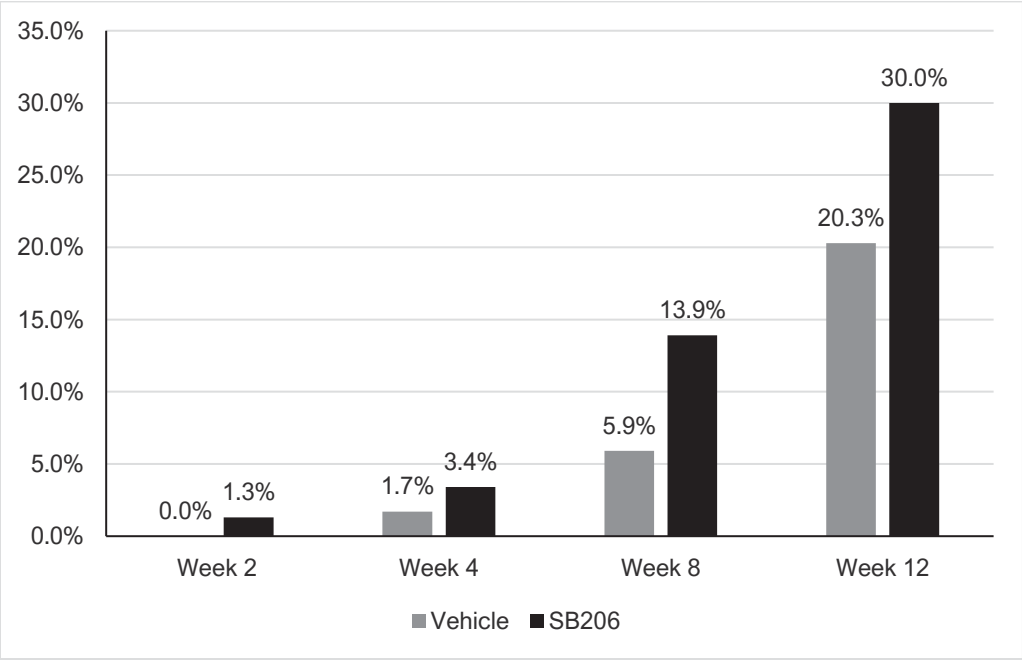
Recently two phase 3 studies have been completed and the clinical study reports are under preparation. The primary efficacy endpoint for the studies was complete clearance of all treatable MC lesions at Week 12 in the ITT population. The proportion of subjects with complete clearance at each visit is shown in Figure 2 and Figure 3.

Figure 2 NI-MC301: Percentage of Subjects with Complete Clearance



Note: Subjects with missing lesion count data at the Week of interest were counted as non-responders.

Figure 3 NI-MC302: Percentage of Subjects with Complete Clearance



Note: Subjects with missing lesion count data at the Week of interest were counted as non-responders.

The proportion of subjects with complete clearance of all treatable molluscum lesions at Week 12 in NI-MC301 was 25.8% for SB206 and 21.6% for vehicle (p=0.375) and 30.0% for SB206 and 20.3% for vehicle (p=0.062) in NI-MC302. For the secondary endpoint, the proportion of subjects with complete clearance of all treatable molluscum lesions at Week 8 in NI-MC301 was 15.3% for SB206 and 10.3% for vehicle (p=0.202) and 13.9% for SB206 and 5.9% for vehicle (p=0.028) in NI-MC302. The results of other endpoints are available in the IB. The Kaplan-Meier analysis in both studies also support the effectiveness of SB206 by showing the reduction of time to complete clearance.

Analysis of the integrated data from NI-MC301 and NI-MC302 resulted in statistically significance for complete clearance at Week 12 (p= 0.038). Analysis of data from NI-MC302 study demonstrated substantial effectiveness for reducing lesions to 1 or 0 (p=0.011) and reducing lesions by at least 90% (p=0.002). SB206 demonstrated statistical effectiveness in complete clearance for up to 28%, reduced lesions to 1 or 0 for up to 39% and approximately 37% of subjects achieved a 90% reduction in lesions in NI-MC302. In addition, subjects treated with SB206 showed a lower occurrence of scarring when compared to the vehicle arm. Molluscum, caused by a family of pox viruses, is known to occasionally heal with small pitting (scar formation).”

2.1.5 Benefit: Risk Assessment

Subjects may not expect to receive direct benefit from study drug treatment during study participation. This study is designed to provide information about the efficacy and safety of an investigational medication compared to placebo/vehicle.

There is a theoretical risk of methemoglobinemia resulting from dermal application of NO, i.e., through NO binding with systemic hemoglobin and thus methemoglobin levels have been closely monitored in Novan clinical trials. There have been no reports of methemoglobinemia or observed methemoglobin levels greater than 4.7% in subjects treated with topical berdazimer sodium in completed studies. Fluctuations in methemoglobin during treatment have been similar in subjects treated with berdazimer sodium or vehicle. Methemoglobin increases following treatment are rare. In subjects treated with berdazimer sodium, there have been a few sporadic clinically significant changes identified in laboratory assessments and vital signs. There have been no clinically significant changes in physical examination. No related SAEs have been reported for berdazimer sodium.

Based on the known mechanism of action of NO as a vasodilator, theoretical risks from systemic exposure after topical administration of berdazimer sodium include hypotension and headache. There have been no reports of hypotension and no clinically significant changes in vital signs (blood pressure, pulse) judged by the investigators to be related to the administration of berdazimer sodium in clinical studies performed to date. Reported rates of headache in the clinical development program to date are similar across berdazimer and vehicle-treated subjects.

Note that transient asymptomatic erythema at the application site within 5 minutes of dosing, which typically lasts ≤15 minutes, is an expected sign. This is due to nitric oxide's vasodilatory pharmacologic effect.

2.2 Study Rationale

There is a significant unmet medical need to treat MC, considering most patients with MC are healthy young children. Ablative treatment often causes fear to the children and interferes in physician-patient relationships. Repeated ablative treatments are difficult. Procedural treatments as well as self-limiting resolution may result in scarring. Using anesthesia involves safety risk and costs. Not treating increases the potential of further dissemination of the disease. Prevention of further dissemination of the disease is also important from a public health perspective. Topical application of SB206 may accelerate resolution of MC without causing pain and/or scarring, decrease the frequency of ablative treatment, and provide an effective, convenient treatment option for patients with MC.

3 OBJECTIVES AND ENDPOINTS

Tier	Objectives	Endpoint(s)
Primary Efficacy	To evaluate the efficacy of SB206 10.3% as compared to Vehicle in subjects with molluscum contagiosum	The proportion of subjects with complete clearance of all treatable MC at Week 12
Secondary Efficacy Endpoints	To evaluate the efficacy of SB206 10.3% as compared to Vehicle in subjects with molluscum contagiosum	• Proportion of subjects achieving a lesion count of 0 or 1 of all treatable MC at Week 12 • Proportion of subjects achieving at least a 90% reduction from Baseline in the number of all treatable MC at Week 12 • Proportion of subjects with complete clearance of all treatable MC at Week 8 • Percent change from Baseline in the number of all treatable MC at Week 4
Safety endpoints	To evaluate the safety of SB206 10.3% compared to Vehicle in subjects with molluscum contagiosum	• Incidence of treatment-emergent adverse events • Change from Baseline in LSR scores • Change from Baseline in abbreviated physical examinations • Concomitant medications reported • Proportion of subject(s) with reported scar(s)
Other Endpoint	To evaluate BOTE and SB206 10.3% compared to Vehicle in subjects with molluscum contagiosum	• Change from Baseline in BOTE scores
Exploratory endpoints	To evaluate various efficacy and other parameters of SB206 10.3% compared to Vehicle in subjects with molluscum contagiosum.	• Percent change from Baseline in number of treatable MC at each visit (Weeks 2, 8, 12) • Proportion of subjects achieving a lesion count of 0 or 1 of all treatable MC at Weeks 2, 4 and 8 • Proportion of subjects achieving at least a 90% reduction from Baseline in the number of all treatable MC at Weeks 2, 4 and 8 • Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at Weeks 2, 4, 8 and 12 • Absolute change from Baseline in number of treatable MC at Weeks 2, 4, 8 and 12 • Proportion of subjects with complete clearance of all treatable MC at Week 2 and Week 4 • Time to complete clearance of all treatable MC • Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed • Subject-reported spread to household members as measured by any new occurrence of MC in household members of subjects at each visit (Weeks 2, 4, 8, 12) • Investigator Global Severity Assessment at Baseline, Week 12 and 24 • Subject Global Severity Assessment at Baseline, Week 12 and 24 • Investigator Global Impression of Change at Week 12 and 24 • Subject Global Impression of Change at Week 12 and 24

4 STUDY PLAN

4.1 Study Design

In response to the recent COVID-19 pandemic, it is imperative to include additional protections to enhance the assurance of subject safety while protecting the integrity of the clinical trial data. In alignment with the FDA's recommendation to utilize electronic and remote methods, the NI-MC304 study was designed to include remote technology for the study visits between Week 2 and Week 12, our primary endpoint, in an effort to minimize the amount of time that subjects and caregivers are required to be present in clinic if necessary, while also minimizing the number of contacts for our site personnel (FDA, 2020). Subjects/caregivers and investigators will practice at least one (simulated) remote assessment at the Baseline visit to familiarize each party with the technology before the first remote use. The frequency of planned on-site monitoring visits will be reduced, and more frequent remote monitoring visits will be incorporated to support protection of all team members. Enhanced central monitoring, telephone contact with the sites to review study procedures, trial participant status, and study progress, or remote monitoring of individual enrolled trial participants, will be performed as outlined in the monitoring plan. Additional information will be captured on any protocol deviations that occur due to COVID-19. Finally, a clinical trial continuity plan has been established for situations to outline the current modifications in place and in case of further impact the existing study design and plans. The plan incorporates contingency measures for additional disruptions due to COVID-19 and other unforeseen circumstances, provides a process for documenting any participants impacted by the circumstance and what was impacted. The statistical analysis plan (SAP) includes analyses that will be performed to address the impact of the implemented contingency measures, and any necessary ad hoc analyses not incorporated into the SAP will be discussed in the clinical study report.

This is a phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in approximately 850 subjects with MC. After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized 1:1 (active:vehicle) using an interactive web response system (IWRS). Subjects receiving current treatment for MC at the time of the Screening Visit will enter a wash out period of up to 14 days prior to randomization. In the event no wash out period is required, Screening and Baseline visit activities may be combined into a single in-clinic visit. At randomization, subjects will be stratified by investigator type (dermatologist vs. other), the subject's BOTE score at Baseline (no inflammation (BOTE = 0) vs. mild/moderate/severe inflammation (BOTE ≥ 1) and number of randomized subjects per household (1 subject per household vs. 2 subjects per household). Subjects will be stratified to 5 strata first by subjects per household. Subjects from 1 subject households will be stratified by investigator type and baseline BOTE score. Subjects from 2 subject households will not be further stratified with respect to investigator type and baseline BOTE score because the overall sample size that is expected for the stratum for households with two subjects is not large enough to support further stratification.

A maximum of two subjects from the same household may be randomized to the study. They must be randomized on the same day and both must individually meet all inclusion/no exclusion criteria. For subjects in the same household, Screening can occur on different days; however, the Baseline visit must occur on the same day. Households randomizing two subjects will receive the same treatment assignment for both subjects.

Subjects or their caregivers will apply SB206 10.3% or Vehicle Gel once daily for a minimum of 4 weeks and shall continue unless otherwise instructed by the investigator up to 12 weeks to all lesions identified at Baseline and new treatable lesions that arise during the course of the study. Subjects or their caregivers will continue to treat the area until the next scheduled visit even if the lesion(s) clear. At each in-clinic and remote visit, the investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. Complete clearance should be confirmed by an in-clinic lesion count before treatment is discontinued. If the investigator determines all lesions are cleared at a visit, the investigator may instruct the subject to stop treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 12/ET and all procedures outside of study drug activities should be continued. If lesions recur or new lesions occur between visits after being stopped due to clearance, the subject or caregiver should re-initiate treatment to the recurring and new lesions. A new kit should be dispensed at Weeks 4 and 8 regardless of lesion count so that treatment can be restarted if lesions are observed between visits. An unscheduled visit is not required for the subject/caregiver to resume treatment. No study treatment is planned to be dispensed after the Week 12 visit.

Remote visits may be performed at Week 4 using remote technology. During the Baseline visit, the subject/caregiver will be instructed on the technology to be used for remote visits. After the initial molluscum lesion count is completed, it will be repeated by the same assessor and the subject/caregiver using the subject/caregiver's electronic device that will be utilized to capture photographs for remote visits. This will provide the subject/caregiver an opportunity to practice with the technology and will allow for the assessor to understand lesion appearance in person compared to through the technology platform.

Subjects will be contacted via phone on Day 2 to collect subject information on early dose reactions. At Weeks 16 and 20, subjects will be contacted via phone to capture information regarding MC recurrence and adverse events (AEs); at Week 24, the subject will be seen at the site for a final study visit to assess scarring, keloid, and MC recurrence.

Subjects who discontinue the study prior to the Week 12 visit will be asked to complete the Week 12 visit assessments in the clinic; this will be recorded as an Early Termination (ET1) visit. Subjects who discontinue from the study after Week 12 but prior to Week 24 will be asked to come to the site to complete Week 24 assessments; this visit will be recorded as an ET2 visit.

Safety assessments include BOTE Inflammation Scores, Local Skin Reaction (LSR) scores, adverse event collection, including scarring/keloid and urine pregnancy tests (UPTs). Safety

assessments will be completed at specified visits through Week 12. Adverse events and concomitant medications will be reviewed and updated as needed at each visit through Week 24.

Inflammatory reactions around MC lesions has been associated with imminent resolution of MC (sometimes referred to as "beginning-of-the-end" ["BOTE"] sign). The investigator (or designated evaluator) will assess the presence and overall degree of inflammatory reactions at MC lesions at Baseline (pre-dose) and Weeks 2-12 using the BOTE Inflammation Score (Section7.1.2.1). BOTE may be associated with itch, but not pain. BOTE is usually asymptomatic, self-limited, localized to individual MC lesions, and does not require discontinuation of study treatment or additional treatment. LSR is generally more diffuse, associated with significant itch or tenderness, may necessitate discontinuation of study treatment, and may need treatment for symptomatic relief (e.g. a topical corticosteroid or topical anesthetic). For very severe LSRs, systemic corticosteroids may be considered (Section 7.2.3 for additional details). Investigators will assess the treatment area at each scheduled visit and use their medical judgement to differentiate between BOTE and LSRs. BOTE Inflammation Score and LSR component scores will be recorded at each visit. When LSRs are clinically significant at the application site, the investigator should report the condition as AE(s).

Prior to the first application of study drug at Baseline, the investigator will assess the subject's skin as part of the physical examination, including the presence or absence of individual features of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. At Baseline (30 min. post-dose) and at Week 2 through Week 12 the evaluators will rate LSRs on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration using the LSR Assessment scale (Table 6).

Adverse events will be assessed and collected after the initiation of study drug treatment through the end of the subject's last visit. Treatment-related adverse events and all serious adverse events will be followed up until resolution or up to one year after last treatment, whichever occurs earlier.

Scar formation (scars/keloids/hypertrophic scars) will be assessed starting at the Week 4 visit through Week 24. The investigator will map locations of the molluscum lesions at Baseline. Additional lesions identified through Week 12 will be added to the map. Using the map as a guidance, the investigator will assess the treated areas for scar/keloid formation. All scars, including keloid/hypertrophic scars, that develop after the Baseline assessment should be captured as AEs and assessed for relatedness to study treatment.

If a subject's treatment is discontinued by the investigator or the subject because of an AE, that AE should be indicated as the reason for treatment discontinuation. All subjects will be encouraged to remain in the study and to complete all required study visits throughout the 24-week study duration.

A Data Safety Monitoring Board (DSMB) will review all available unblinded safety data (including completed patch testing results). Section 11.2 provides additional details regarding the DSMB.

4.2 Number of Participants and Study Sites

Approximately 850 male and female subjects ages 6 months of age and older with a minimum of 3 and a maximum of 70 molluscum lesions at Baseline will be enrolled at approximately 55 sites in the United States.

4.3 Treatment Arms and Duration

A double-blind randomization will be generated that randomly allocates subjects to one of 2 treatment arms (SB206 10.3% or Vehicle gel) in a 1:1 ratio, so that approximately 50% of subjects will be randomized to receive SB206 10.3% and 50% will be randomized to receive Vehicle gel. Subjects receiving current treatment for MC at the time of the Screening Visit will enter a wash out period of up to 14 days prior to randomization. In the event no wash out period is required, Screening and Baseline visit activities may be combined into a single visit.
The sponsor, investigator, site staff and study subjects will remain blinded to the study treatment during this study. Each dose will consist of berdazimer gel or vehicle gel that will be mixed by finger with hydrogel on a supplied dosing guide, and then immediately applied topically by the subject to the affected designated area(s). Treatment will be applied once daily to all lesions identified at Baseline and new lesions that arise during treatment for a minimum of 4 weeks and shall continue unless otherwise instructed by the investigator up to 12 weeks. If the investigator determines all lesions are cleared at an in-clinic visit, the investigator may stop treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24/ET, and study drug will be dispensed in case of lesion recurrence between study visits. If lesions recur or new lesions occur between visits after being stopped due to clearance, the subject or caregiver should reinitiate treatment to the recurring and new lesions. At each visit, sites should remind subjects/caregivers that if new lesions or recurring lesions are noticed between visits, treatment should be applied to those new or recurring lesions. The subject or caregiver will apply to the individual lesions. Periocular lesions will be treated if the lesions are at least 2 cm from the edge of the eye.

5 POPULATION

5.1 Eligibility Criteria and Definitions

Subjects officially enter the Screening Period following provision of informed consent either directly, via a legal guardian, or a combination of both. Consent signatures may be obtained in person or via electronic consent.

A Screen Failure is a consented subject who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Subjects may be rescreened once.

A randomized subject is one who has been deemed eligible and has been assigned to a treatment group. To be eligible to participate in this study, a subject must meet the eligibility criteria - all of the Inclusion Criteria, and none of the Exclusion Criteria.

5.2 Inclusion Criteria

To be considered eligible to participate in this study, the subject must satisfy all the following criteria:

1. Be 6 months of age or older, and in good general health;
2. Have a documented informed consent form signed by subject or a parent or legal guardian and an assent form as required;
3. Have between 3 and 70 treatable MC lesions at Baseline;
4. For women of childbearing potential (WOCBP): Must have a negative urine pregnancy test prior to randomization and must agree to use an effective method of birth control during the study;
   Note: WOCBP and effective methods of birth control are outlined in Section 9.4.
5. Have a device (phone, tablet, personal computer, etc.) that will support remote visits, including a camera;
6. Be willing and able to follow study instructions and likely to complete all study requirements, including remote study visits.

5.3 Exclusion Criteria

Subjects will not be eligible for entry into this study if they meet any of the following criteria:

1. Have strongly suggested sexually transmitted MC and do not agree to refrain from sexual activities throughout the study period;
2. Are immunosuppressed, have immunodeficiency disorder, or are on immunosuppressive treatment;
3. Have significant injury on and/or surrounding MC that may impact ability to treat and count lesions;
4. Have received treatment with topical calcineurin inhibitors or steroids on MC or within 2 cm of MC lesions within 14 days prior to Baseline;
5. Have received treatment for MC during the 14 days prior to Baseline with podophyllotoxin, imiquimod, cantharidin, sinecatechins, topical retinoids, oral or topical zinc, or other homeopathic or over the counter (OTC) products including, but not limited to, ZymaDerm and tea tree oil, cimetidine and other histamine H2 receptor antagonists (including Zantac), or any agent that in the opinion of the investigator may be relevant – (e.g. wart therapies);

6. Have received surgical procedures related to MC (e.g. cryotherapy, curettage) within 14 days prior to Baseline;
7. Have MC only in periocular area;
8. Female subjects who are pregnant, planning a pregnancy or breastfeeding;
9. Have known hypersensitivity to any ingredients of SB206 or Vehicle Gel including excipients;
10. Have participated in a previous study with a berdazimer containing product (i.e. SB204, SB206, SB208, SB414);
11. Have more than one other family member participating in this study (NI-MC304);
12. Have at least 1 family member currently participating in a study, other than this study, with a berdazimer containing product (i.e. SB204, SB206, SB208, SB414);
13. Have participated in any other trial of an interventional investigational drug or device within 14 days or concurrent participation in another interventional research study;
14. History or presence of clinically significant medical, psychiatric, or emotional condition that, in opinion of the investigator, would compromise the safety of the subject or the quality of the data.

5.4 Subject Screening

Written informed consent (including assent form where required) will be obtained before any study-related procedures are performed. The investigator may discuss the study and the possibility for entry with a potential subject/caregiver without first obtaining consent and/or assent. A hard-copy or electronic informed consent may be utilized. A subject wishing to participate must give documented informed consent/assent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation or withdrawal from current medication (if required prior to study entry). The investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this study has been given a full explanation of the procedures and expectations for study participation.

The site-specific informed consent forms (ICF)/assent forms must be forwarded to the CRO for approval prior to submission to an Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) as appropriate, in cases in which a local IRB is being used. Each subject will sign the ICF that has been approved by the same IRB responsible for protocol approval. Each ICF/assent form must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by Food and Drug Administration (FDA) regulations in 21 CFR as well as the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable federal and local regulatory requirements. The ICF/assent form(s) must also include a statement that Novan and the CRO (or their designees) and auditing regulatory agencies will have direct access to the subject's records and medical history.

Once the appropriate essential information has been provided to the subject/caregiver and fully explained by the investigator (or a qualified designee) and it is felt that the subject/caregiver

understands the implications and risks of participating in the study, the IRB approved ICF/assent document shall be signed and dated by both the subject/caregiver and the person obtaining consent (investigator or designee), and by any other parties required by the IRB or other regulatory authorities. The subject/caregiver will be given a copy of the signed ICF/assent document with the original kept on file by the investigator. All the above activities must be completed before any study related procedures are conducted.

5.5 Screen Failures

Study site personnel will use an interactive web response system (IWRS) system to assign a unique study number to each potential study participant, following informed consent. Subjects that ultimately do not meet eligibility criteria or who withdraw their consent prior to randomization will be considered a Screen Failure. The site will document the Screen Failure status in the IWRS and in their source documents/eCRF and will document their demographics and reason for screen failure.

5.6 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion/exclusion criteria is not allowed. Any deviation identified during the study will be documented and should be discussed with the CRO and/or sponsor.

6 STUDY CONDUCT

6.1 Study Procedures

Subjects are expected to be in this study for up to 27 weeks. There is a 2-week screening/washout period if needed and the treatment period is expected to be a minimum of 4 weeks and a maximum of 12 weeks. After the 12-week treatment period, subjects will enter a 12-week safety follow-up period. The Schedule of Assessments (Table 1) summarizes the study procedures/assessments to be performed/collected at each study visit. Some Baseline/Day 1 procedures (i.e. review of inclusion/exclusion criteria, brief physical examination including a directed assessment of skin condition prior to application of study drug, adverse event assessment, concomitant medication review, and UPT if applicable) must be completed prior to randomization. Subjects who meet all eligibility criteria who do not require washout from any current treatment may be screened and randomized the same day. At Baseline, subjects at selected sites will have an opportunity to consent to a study exit interview. Once randomized, the subject/caregiver will be trained on the mixing, application, and storage of the study drug. The first application should be done at the clinic as well as having in-clinic applications being performed at Week 2, Week 4 (if the visit is performed in the clinic), Week 8, and Week 12. Subjects/caregivers will be observed mixing and applying study drug during each study visit through the final scheduled dose of study drug during the Week 12 visit. Additionally, the Investigator and subject/caregiver will assess the impact of MC at Baseline, Week 12, and Week 24. The Investigator and subject/caregiver will also complete the global impression of change at

Week 12 and Week 24. From Week 12 to Week 24, additional safety assessments will be performed, including scar assessment and household MC occurrence.

6.2 Subject Engagement and Retention

It is important to support subjects and caregivers throughout their participation in this study and to provide a path for every subject to complete the study. To achieve this, Novan created an engagement and retention plan that includes the following, in addition to other supportive processes:

- Remote visits, to decrease subject/caregiver burden and exposure
- Daily dosing reminders and appointment reminders
- Brief (1-3 minute) educational videos, including training on normal lesion healing
- Study-related retention items, provided at each visit
- Certificate of participation
- Travel and childcare reimbursement as needed
- Site outreach to subject/caregiver after a missed visit
- Standardized follow up letter process if subject/caregiver are unresponsive to contacts (Section 6.8.5)

Additional details can be found in the Study Procedures Manual. This plan will continue to be revised as study circumstances evolve.

6.3 Study Visit Scheduling

At the end of each study visit the next visit should be scheduled/confirmed. Screening, Baseline, Week 2, Week 8, Week 12 and Week 24 visits are to be performed in the clinic, with the option to perform Week 4 in clinic or remotely. A reminder of the next scheduled visit date will be shared with the subject. Every effort should be made to adhere to the allowable study visit window period as described in the Schedule of Assessments (Table 1). All visit dates are in reference to Baseline Day 1. In the event that a subject visit is performed out of window or if a visit is skipped, every effort should be made to get the subject to return for the next visit or complete the early termination visit if the subject is discontinuing from the study. A text messaging service or application may be utilized during the trial to send reminders and other educational messages to subjects/caregivers throughout the course of the study.

6.4 Remote Visits

Week 4 can be performed as a remote visit or in clinic visit. All subjects/caregivers will be instructed on the technology to be utilized during the Baseline visit. Approximately 24-48 hours in advance of the remote visit, the subject or caregiver should utilize the historic lesion map to

take images of all lesion areas noted at the previous visit and any new lesion areas that developed since the previous visit. Photographs of the lesions should be taken prior to IP application for the day or at least 1 hour after application. The remote visit should be rescheduled within visit window if acceptable images have not been received by the site. Additional instructions on how to take and upload photographs is provided in the Study Reference Manual.

6.5 Unscheduled Visits

The investigator may deem it clinically necessary to conduct visits outside of the ones specified in the Schedule of Assessments, in order to investigate a possible adverse event, follow up on adverse events, etc. The date and reason for the Unscheduled visit should be recorded in the source documents, with the specific procedures performed determined by the investigator, and in consultation with the medical monitor as needed, depending on the reason for the visit. In-clinic unscheduled visits should be reserved for assessment or follow-up of AEs and dispensation of drug. Remote visits can be used when possible.

6.6 Order of Assessments

At the Baseline visit on Day 1, the physical examination and BOTE Inflammation Score should be done prior to randomization to study treatment. For WOCBP (see definition in Section 9.4), the UPT must be done prior to randomization. The initial Local Skin Reaction (LSR) assessment should be done at least 30 minutes after study drug is applied on Day 1. The BOTE and LSR assessments should be completed at each scheduled visit even if the subject is not going to be dosed or if the MC lesions have cleared. It may be most convenient to perform lesion counting, mapping, and scarring assessments immediately following the BOTE and LSR assessments. In order to ensure consistent counting of MC lesions, the same assessor should complete the lesion counts at all visits, but at a minimum, at Baseline and Week 12.

6.7 Study Procedures by Time Point

6.7.1 Screening (Day –15 to Day 1) (In-Clinic Visit)

The following procedures must be performed and recorded at the Screening visit:

1. Review study procedures and information regarding the study including the potential risk and benefits of SB206 with the subject/caregiver and obtain documented consent/assent.
2. Obtain demographic information.
3. Obtain subject's medical history (including start date of the subject's current episode of molluscum [i.e., when molluscum was first noticed by the subject/caregiver]), household MC status, medication history, and concomitant medication information.
4. Perform lesion mapping and lesion count.

5. If applicable and visit is conducted in clinic, obtain UPT and evaluate results. If pregnancy test is positive, the subject may not participate in the study.
6. Review inclusion/exclusion to confirm whether subject qualifies to participate in the study.

6.7.2 Visit 1/Baseline (Day 1) (In-Clinic Visit)

The following procedures must be performed and recorded at the Baseline visit. If Screening and Baseline visits occur the same day, procedures with an asterisk (*) should only be performed once and will be recorded as Baseline values.

1. Perform a brief physical examination, including the directed examination of the skin (presence or absence of individual features of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration).
2. Perform lesion mapping and lesion count.*
3. Perform BOTE Inflammation Score (pre-dose).
4. Complete Investigator Global Severity Assessment.
5. Complete Subject Global Severity Assessment.
6. Obtain UPT, as applicable. If pregnancy test is positive, the subject may not participate in the study.*
7. Update concomitant medication information.
8. Confirm eligibility and randomize subject.
9. Provide subject diary and dispense study drug.
10. Weigh and record study product tubes.
11. Instruct and practice remote visit technology with subject/caregiver, preferably on the device that will be used for the duration of the study. The investigator should review and perform a lesion count with the captured images.
12. Instruct subject on dispensing, mixing, and application of study product and diary completion.
13. Have subject/caregiver apply first dose in clinic from kit assigned at randomization.
14. Complete Local Skin Reaction assessment approximately 30 minutes post dose.
15. Collect and record AE information for any AEs reported.
16. Confirm household MC status (any new cases in household members since screening visit).*

Note: Follow up interviews will be performed with a subset of subjects that complete Week 12. Consent will be obtained between screening and the Week 12 visit. The follow up interview will be performed with the subject/caregiver at a later date after Week 12 is completed.

6.7.3 Visit 2/Day 2 (Telephone Contact)

The following procedure must be performed and recorded at the Day 2 telephone contact.

1. Contact subject to confirm how the subject is feeling and assess if any changes to AEs or concomitant medications.

6.7.4 Visit 3/Week 2 (Day 15 ± 3 days) (In-clinic Visit)

The following procedures must be performed and recorded at the Week 2 visit.

1. Perform BOTE Inflammation Score.
2. Complete Local Skin Reaction Assessment.
3. Perform lesion counting and mapping and update lesion map with location for any new lesions.
4. Review study drug compliance/diary completion.
5. Review dosing instructions and observe the subject/caregiver apply daily dose using the kit assigned at randomization.
6. Collect and record AE information for AEs reported.
7. Update concomitant medication information and confirm if any new occurrences of MC were reported in the subject's household.

6.7.5 Visit 4/Week 4 (Day 29 ± 5 days) (In-clinic or Remote Visit)

This visit can occur in clinic or be performed as a remote visit. If this visit is performed remotely, subjects/caregivers will upload images of all treatable lesions for the site to review in advance of the visit. If additional images are required, the site will notify the subject and provide any necessary feedback. The remote visit should be rescheduled within visit window if acceptable images have not been received by the site. Additional details on this process are found in the Study Reference Manual. If this visit is performed in clinic, no images are required, and the visit procedures are expected to be completed while the patient is in clinic. The following procedures must be performed and recorded at the Week 4 visit.

1. Perform BOTE Inflammation Score.
2. Perform Local Skin Reaction Assessment.
3. Perform lesion counts and update lesion map with location for any new lesions.
4. If previously cleared, assess for subject recurrence of MC.
5. Perform scarring/keloid assessment; if present, document location on lesion map and record as an AE.

6. Weigh returned study drug and review study compliance.*
7. Weigh, record, and dispense new supply of study product.*
8. Review dosing instructions and observe subject/caregiver apply daily dose.
9. Collect and record AE information for AEs reported.
10. Update concomitant medication information and confirm if any new occurrences of MC were reported in the subject's household.

    * Note: If Visit 4 is performed as a remote visit, the subject/caregiver can return the study drug kit and receive a new kit after completion of the remote visit and within the established visit window. If Visit 4 is performed in clinic, the subject/caregiver will return the study drug kit and will receive a new kit while in clinic.

6.7.6 Visit 5/Week 8 (Day 57 ± 5 days) (In-clinic Visit)

The following procedures must be performed and recorded at the Week 8 visit.

1. Perform BOTE Inflammation Score.
2. Perform Local Skin Reaction Assessment.
3. Perform lesion counts and update lesion map with location for any new lesions.
4. If previously cleared, assess for subject recurrence of MC.
5. Perform scarring/keloid assessment; if present, document location on lesion map and record as an AE.
6. Weigh returned study drug and review study compliance.
7. Weigh, record, and dispense new supply of study product.
8. Review dosing instructions and observe subject/caregiver apply daily dose.
9. Collect and record AE information for AEs reported.
10. Update concomitant medication information and confirm if any new occurrences of MC were reported in the subject's household.

6.7.7 Visit 6/Week 12/ET (Day 85 ±5 days) (In-clinic Visit)

The following procedures must be performed and recorded at the Week 12/ET visit.

1. Obtain pregnancy test and evaluate results, as applicable.
2. Perform BOTE Inflammation Score.
3. Perform Local Skin Reaction Assessment.
4. Perform lesion counts and update lesion map with location for any new lesions.
5. If previously cleared, assess for subject recurrence of MC.
6. Perform scarring/keloid assessment; if present, document location on lesion map and record as an AE.

7. Perform a brief physical examination.
8. Complete Investigator Global Severity Assessment and Investigator Global Impression of Change Assessment.
9. Complete Subject Global Severity Assessment and Subject Global Impression of Change Assessment.
10. Subject/caregiver administer final dose of study drug from previously dispensed kit only if lesions are present.
11. Weigh returned study drug and review study compliance.
12. Collect and record AE information for AEs reported.
13. Update concomitant medication information and confirm if any new occurrences of MC were reported in the subject's household.
14. Review interview procedures with the subject/caregiver and obtain documented ICF/assent.

    Note: Follow up interviews will be performed with a subset of subjects that complete Week 12. Consent will be obtained during the Week 12 visit, and the follow up interview will be performed with the subject/caregiver at a later date.

6.7.8 Visit 7/Week 16 and Visit 8/Week 20 (Day 113 ±7 days; Day 141 ±7 days) (Telephone Contact)

The following procedures must be performed and recorded at the Week 16 and Week 20 visits. It is expected that these visits should be done by telephone.

1. Collect and record information for new and ongoing AEs, including recurrence of MC.
2. Confirm household MC status (any new cases in household members since last visit).
3. Update concomitant medication information.

6.7.9 Visit 9/Week 24 (Day 169 ± 7 days) (In-clinic Visit)

The following procedures must be performed and recorded at the Week 24 visit.

1. Perform scarring/keloid assessment; if present, document location on lesion map and record as an AE.
2. Complete Investigator Global Severity Assessment and Investigator Global Impression of Change.
3. Complete Subject/Caregiver Global Severity Assessment and Subject Global Impression of Change.
4. Collect and record information for new and ongoing AEs, including subject recurrence of MC.
5. Confirm household MC status (any new cases in household members since last visit visit).
6. Update concomitant medication information.

6.8 Discontinuation or Withdrawal

6.8.1 Individual Subjects

If at any time during the study the investigator determines that it is not in the best interest of the subject to continue treatment, the subject's treatment will be discontinued. The investigator can discontinue the treatment for a subject at any time if medically necessary. If a subject's treatment is permanently discontinued by the investigator because of an AE, that AE should be indicated as the reason for treatment discontinuation. In this case, the subject is discontinued from the treatment, but still participates in the study and the subject is encouraged to follow the visit schedule and complete all assessments, particularly those at Week 12 and 24.

6.8.2 Treatment Modifications, Interruptions, and Discontinuation

If a subject experiences an LSR (AE) for the first time, the investigator must confirm if treatment is needed, if a treatment modification (hold treatment for certain areas) is needed, and/or if a treatment interruption (discontinue treatment in all areas) is needed. If the investigator confirms treatment is needed, the subject can continue study treatment on all areas, hold treatment in certain areas, or interrupt treatment completely, and add non-medicated treatment such as petroleum gel as a concomitant medication. This option can be exercised at any point during the study as needed.

If no concomitant treatment is added, the investigator may choose to withhold study treatment on either specific areas (modification) or all areas (interruption) until the investigator confirms it is appropriate to continue. It is recommended to modify or interrupt treatment for 2-3 days before re-starting the study treatment; the investigator should use their discretion for when to reinitiate treatment by discussing the status of the AE with the subject/caregiver to determine if the event is resolved or if continued modification/interruption of study treatment is necessary. The investigator will confirm when reintroduction of study treatment can occur. This option can be exercised at any point during the study as needed.

For more severe AEs, concomitant treatment such as corticosteroids can be added while withholding study treatment on specific areas (modification) or all areas (interruption) until the investigator confirms it is appropriate to continue with the study drug. Similar to the modifications and interruptions above, it is recommended to modify or interrupt treatment for 2-3 days before re-starting the study treatment; the investigator should discuss the status of the AE with the subject/caregiver to determine if the event is resolved or if continued modification/interruption of study treatment is necessary. The investigator will confirm when reintroduction of study treatment can occur. This option can also be exercised at any point during the study as needed.

After the resolution of the first LSR and reinitiation of treatment, if a more severe second LSR occurs, it is appropriate to suspect the cause is allergic contact dermatitis. Study treatment on all areas should be discontinued, and after resolution of the second LSR, patch testing is

recommended if the subject/caregiver consents. This step should be exercised only if the LSR is more severe than previous LSR(s). See Appendix 1 for additional information.

6.8.2.1 Temporary Treatment Discontinuation

The investigator may instruct the subject to temporarily hold treatment to a specified region or completely (i.e., due to an adverse event). This treatment modification and the reason for the temporary drug interruption should be documented in the subject's source documents. The lesions in the impacted area should continue to be counted in the lesion count during the period of treatment modification. See Section 6.8.2 for additional details.

6.8.2.2 Permanent Discontinuation of Treatment

The investigator may discontinue a subject's treatment if the subject/caregiver has failed to follow study procedures or to keep follow-up appointments. Appropriate documentation in the subject's study record and the study database regarding the reason for treatment discontinuation must be completed. See Section 6.8.2 for additional details.

Reasons for an investigator's withdrawal of a subject **from the treatment** may include, but are not limited to, the following:

- Safety (e.g., severe adverse reactions, pregnancy)
- When a concomitant medication or treatment likely to interfere with the results of the study is reported, or required, by the subject, the investigator will decide, in consultation with the CRO whether the subject is to be withdrawn.

Reason(s) for discontinuation from the treatment as listed in the study record will be entered into the study database as follows:

- Complete clearance confirmed by investigator prior to Week 12
- Adverse Event (including LSRs deemed to be significant by investigator)
- Withdrawal of Consent by Subject/Caregiver
- Lost to Follow-Up
- Other

6.8.3 Withdrawal from Study

A subject/caregiver may voluntarily withdraw from study participation at any time. If the subject/caregiver withdraws consent and discontinues from the study, the investigator will attempt to determine the reason for discontinuation and record the reason in the subject's study records and in the study database. In the event of discontinuation from the study prior to the

Week 12 visit, every effort should be made to have the subject return to the study site to complete the Week 12 evaluations (ET1 visit). If the subject/caregiver is unable or unwilling to return to clinic for the Week 12 visit, the investigator should discuss with the medical monitor the option to perform a remote Week 12 visit. All premature discontinuations and their causes must be carefully documented in the subject's study record and in the study database.

All Week 12 evaluations should be performed at the time of premature discontinuation as applicable if the subject discontinues prior to Week 12. If the subject discontinues after the Week 12 visit, the Week 24 evaluations should be performed. All data gathered on the subject prior to termination will be made available to the CRO. The investigative site should make all reasonable efforts to ensure the subject returns to complete the termination visit, even if the subject is not able to attend other study visits.

Study completion or reason(s) for discontinuation from the study as listed in the study record will be entered into the study database as follows:

- Withdrawal of Consent by Subject/Caregiver
- Lost to Follow-Up
- Adverse Event
- Other

Novan has the right to terminate or stop the study at any time. Should this be necessary, the investigator will ensure that proper study discontinuation procedures are completed.

6.8.4 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

6.8.5 Subjects Lost to Follow-up

All subjects who fail to return to the study site will be contacted by telephone to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject/caregiver is unreachable by telephone after a minimum of three documented attempts (one attempt on three different days using at least 2 different forms of communication), a certified letter will be sent requesting that the subject contact the investigator to confirm the final status of their molluscum lesions and to return any outstanding study drug. These actions will be reported on the subject's study record and a copy of the follow-up letter maintained in the investigator's file. The certified letter should include the following questions:

- Please choose one of the following:
    - I/my child want to continue participating in this study.

  - I/my child am no longer interested in participating in this study and withdraw my consent.
- At the time you chose to stop participating in study visits, was your/your child's molluscum contagiosum:
  - Resolved (no lesions left)
  - Resolving (number of lesions is decreasing)
  - Unchanged (number of lesions is similar to previous visit)
  - Worsening (number of lesions increased)

An investigator may withdraw a subject from the study when a subject is lost to follow-up.

6.9 Study Termination

Both Novan and the principal investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Novan or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study, Novan and the principal investigator will assure that adequate consideration is given to the protection of the subjects' interests.

7 DESCRIPTION OF STUDY ASSESSMENTS

The following study assessments will be done. Additional details can be found in in the Study Reference Manual and in the supportive online trainings.

7.1 Efficacy Assessments

7.1.1 Molluscum Contagiosum Lesion Counts

Molluscum contagiosum is a viral infection characterized by small, discrete, waxy, skin-colored, dome-shaped raised papules, an average of 3–5 mm in diameter. The papules may be umbilicated and contain a caseous plug. When the lesions are squeezed or traumatized, a creamy, grey-white material can be extruded. If the investigator cannot clearly differentiate the lesions as is the case for agminated (clustered) lesions this should be counted as one lesion. If the investigator can differentiate and count the umbilical tops separately, each lesion should be counted separately. The investigator should be consistent with the method of recording agminated lesions throughout the study.

For the purpose of this clinical trial, only treatable MC lesions are counted. Treatable lesions are any active (raised, palpable) MC lesions that are dome-shaped, pearly, and shiny white top centered papules that are at least 2 cm away from the ocular region. In clinic, investigators may choose to palpate the lesion to confirm if it is raised. Treatable region is any skin area containing a molluscum lesion, with the exception of the periocular region.

All study personnel who will perform lesion counts must pass the study training including lesion count training. Training on how to accurately count the number of MC lesions will be provided.

Mapping of lesions: At every visit from Baseline through Week 12, all lesions should be recorded on the body map and will clearly note the location of each lesion or agminated lesion. The lesion map is intended to assist study personnel in performing lesion counting and scar/keloid assessment. The body map will also be shared with the subjects/caregivers at Week 2 to assist with counting of lesions.

Definition of Clearance: For the purpose of this study, "clear" means resolution of the active (raised, palpable) treatable molluscum lesion(s). After a lesion has cleared, the residual surface changes such as a pitted scar (indentation), hyperpigmentation, or hypopigmentation may remain. Additional details will be provided in the lesion count training. Complete clearance can only be confirmed by an in-clinic lesion count.

The same evaluator should perform lesion counts at Screening, Baseline, and Weeks 2, 4, 8 and 12/ET. In the event that this is not possible due to unforeseen circumstances, a different evaluator may evaluate the subject. All evaluators must pass the study training including lesion count training. It is particularly important to ensure the same evaluator performs the Baseline and Week 12/ET for lesion counts for a subject,

7.1.2 Other Assessments

7.1.2.1 BOTE Inflammation Score

Inflammatory reactions around MC lesions has been associated with imminent resolution of MC (sometimes referred to as "beginning-of-the-end" ["BOTE"] signs). Investigators should educate subjects and caregivers on the characteristic stages of BOTE as it is recognized as the natural course of self-limiting clearance of MC. BOTE may be associated with itching, but not pain. BOTE is usually asymptomatic, self-limited, localized to individual MC lesions, and does not require discontinuation of study treatment or additional treatment.

Investigators will assess the treatment area at each scheduled visit and use their medical judgement to differentiate between BOTE and LSRs. The BOTE Inflammation Score will be recorded at each visit (Table 5).

Table 5 BOTE Inflammation Score

Score	Global Assessment	Description
0	No inflammation	No evidence of local inflammation
1	Mild	Minimal erythema and/or edema
2	Moderate	Definite erythema and/or edema with or without hemorrhagic crusting
3	Severe	Erythema and edema with definite hemorrhagic crusting
4	Very Severe	Strong reaction spreading beyond the treated area, bullous reaction, erosions

7.1.2.2 Investigator Global Severity Assessment

The Investigator Global Severity Assessment will be completed by the investigator to assess overall impression of severity of MC and completed at Baseline, Week 12, and Week 24. The investigator will be asked to answer the following question:

Please choose the response below that best describes the overall molluscum severity of the subject.

0. None
1. Mild
2. Moderate
3. Severe
4. Very severe

7.1.2.3 Subject Global Severity Assessment

The Subject Global Severity Assessment will be completed by the subject/caregiver to assess overall impression of severity of MC and completed at Baseline, Week 12, and Week 24. The subject or caregiver will be asked to answer the following question:

Please choose the response below that best describes the severity of your/your child's molluscum contagiosum today.

0. None
1. Mild
2. Moderate
3. Severe
4. Very severe

7.1.2.4 Investigator Global Impression of Change

The Investigator Global Impression of Change will be completed by the investigator to assess their overall impression of change from baseline in overall MC condition at Weeks 12 and 24. The investigator will be asked to answer the following question:

> Please choose the response below that best describes the overall change in the subject's molluscum contagiosum since he or she started taking the study medication.

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

7.1.2.5 Subject Global Impression of Change

The Subject Global Impression of Change will be completed by the subject/caregiver to assess their overall impression of change from baseline in overall MC condition at Weeks 12 and 24. The subject or caregiver will be asked to answer the following question:

> Please choose the response below that best describes the overall change in your/your child's molluscum contagiosum since you/your child started applying the study medication.

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

7.1.2.6 Study Exit Interview

Study exit interviews may be conducted with a selected subset of subjects that complete Week 12. Consent will be obtained starting at Baseline, and the professional interview will be performed with the subject/caregiver after completion of Week 12. The objective of the interview is to better understand the subject/caregiver perspective of their MC and treatment experience.

7.2 Safety Assessments

7.2.1 Physical Exam

A brief physical examination will be performed to evaluate objective anatomic findings. This physical examination will be performed at Baseline and at Week 12/ET. At Baseline, the physical examination will include a directed examination of the skin condition prior to any

application of study drug. This skin assessment will include the presence or absence of individual features of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. Any clinically significant changes in the physical exam from baseline will be recorded as AEs.

7.2.2 Pregnancy Testing

Urine pregnancy testing will be required for females 9 years of age and older unless they are post-menopausal or surgically sterile (see Section 9.4). UPTs will be collected at Screening (if in -clinic visit), Baseline, and Week 12/ET. In addition to having a negative UPT at Baseline, before the first application of study drug, females who are 9 years of age and older must be willing to use an acceptable form of birth control during the study. The following are considered acceptable methods of birth control for this study: hormonal contraceptives (combined estrogen and progestogen or progestogen only, including oral, injectable, transdermal or injectable formulations); intrauterine device (IUD); intrauterine hormone releasing system (IUS); bilateral tubal occlusion or ligation if performed ≥ 3 months prior to Baseline; same sex partner or partner who has had a vasectomy ≥ 3 months prior to Baseline; sexual abstinence with a documented acceptable method of birth control if the subject becomes sexually active; female or male condoms with or without spermicide; or a cervical cap, diaphragm, or sponge with spermicide. Women with tubal occlusion or ligations or whose partner had a vasectomy will be required to complete UPTs at the required timepoints if their procedure was done < 3 months prior to Baseline. Tubal ligations or occlusion procedures should be recorded as part of the subject's medical history if applicable.

7.2.3 Local Skin Reaction Assessment

The investigator (or designated evaluator) will assess localized skin reactions (LSRs) at Baseline (at least 30 minutes post-dose), and at any time during the visit at Weeks 2, 4, 8 and 12. The individual components of LSRs are scored separately on a scale of 0-4, with higher numbers indicating more severe reactions. The individual components include erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

Compared to BOTE, LSRs are generally more diffuse, associated with significant itch or tenderness, may necessitate discontinuation of study treatment, and may need treatment for symptomatic relief (e.g. a topical corticosteroid or topical anesthetic). For very severe LSR, systemic corticosteroids may be considered.

Investigators will assess the treatment area at each scheduled visit and use their medical judgement to differentiate between BOTE and LSRs. When LSRs are clinically significant in the opinion of the investigator (i.e. they interfere with the subject's normal daily activities), s/he should report the condition as an AE(s) (e.g. application site erythema, application site edema).

Clinically significant LSRs that are reported as adverse events and/or subject reported intolerability (i.e. itching, pain) may result in an investigator directed temporary treatment hold

(drug holiday), and topical corticosteroids may be used to treat LSRs for up to 2 weeks. The subject may re-initiate study drug treatment prior to the next scheduled visit. Upon re-initiation (challenge) of study drug treatment, if a subject develops worsening LSRs (more severe than the first LSRs), allergic contact dermatitis may be suspected. In the event of suspected allergic contact dermatitis, photographs may be taken of the affected area(s) and transmitted to the CRO medical monitor for review and confirmation of allergic contact dermatitis prior to initiating patch testing. Consent must be in place for patch testing to occur. The investigator should also discuss the necessity of patch testing with the subject/caregiver. The investigator will then discontinue the subject from study drug treatment and treat the area(s) with corticosteroids for up to 2 weeks. If the subject provides consent/assent, the investigator will consult the CRO medical monitor to implement the process for patch testing. See Section 7.2.5 for information on patch testing.

Table 6 Local Skin Reaction Scale

	Erythema	**Flaking/ Scaling**	**Crusting**	**Swelling**	**Vesiculation/ Pustulation**	**Erosion/ Ulceration**
0	Not present	Not present	Not present	Not present	Not present	Not present
1	Slightly pink	Mild, limited	Isolated crusting	Minimal, limited	Fine vesicles	Superficial erosion
2	Pink or light red	Moderate	Crusting < 50%	Mild, palpable	Scant transudate or exudate	Moderate erosion
3	Red, restricted to treatment area	Coarse	Crusting > 50%	Moderate	Moderate transudate or exudate	Marked, extensive
4	Red extending outside treatment area	Scaling extending outside treatment area	Crusting extending outside treatment area	Marked swelling extending outside treatment area	Marked transudate or exudate	Black eschar or ulceration

7.2.4 Scarring/Keloid Assessment

Scar formation (scars/keloids/hypertrophic scars) will be assessed starting at the Week 4 visit through Week 12 and again at Week 24. Using the lesion map as a guide, the investigator will assess the treated areas for scar/keloid formation. All scars, including keloid/hypertrophic scars, that develop after the Baseline assessment should be captured as AEs and assessed for relatedness to study treatment.

7.2.5 Diagnosis of Allergic Contact Dermatitis and Patch Testing

After treatment is reintroduced post-LSR, if a subject experiences a stronger LSR (second LSR event) than the first LSR event, allergic contact dermatitis may be suspected. In order to confirm whether the reaction is allergic contact dermatitis, patch testing should be conducted. If the investigator determines that patch testing is appropriate, he/she should contact the CRO medical monitor to discuss next steps. Patch testing supplies will be provided once requested from the CRO medical monitor. Additional drug product for patch testing may be supplied through IWRS if the currently assigned subject's investigational product was assigned more than 60 days prior to the patch testing date(s) or if the subject had previously returned all their drug product.

Additionally, patch testing should be discussed with the subject/caregiver. If the subject/caregiver consents to patch testing and once the LSR has been completely resolved for a period of 2 weeks and up to 2 months, patch testing will commence. If allergic contact dermatitis is suspected, study drug should be permanently discontinued and an AE of allergic contact dermatitis should be recorded as the reason for discontinuation. Week 12/ET assessments should be completed at the time of discontinuation.

In the event of suspected allergic contact dermatitis developed, photographs may be taken of the affected area(s) and transmitted to the CRO medical monitor for review prior to initiating patch testing. See Appendix 1 for further information.

7.2.6 Adverse Events

Adverse events will be assessed and collected after the initiation of study drug treatment through the end of the subject's last visit. Treatment-related adverse events and serious adverse events will be followed up until resolution or up to one year after last treatment, whichever occurs earlier.

If a subject's treatment is discontinued by the investigator or the subject because of an AE, that AE should be indicated as the reason for treatment discontinuation. All subjects will be encouraged to remain in the study and to complete all required study visits throughout the 24-week study duration.

If a subject achieves complete clearance at Week 12 or before and experiences new lesions between Week 12 and Week 24, an AE of molluscum contagiosum should be documented to capture this recurrence since there is no lesion count after Week 12.

See Section 9 for additional information regarding adverse events.

8 STUDY DRUG TREATMENT

8.1 Description of Products

Study drug treatment will include once daily application of SB206 10.3% or Vehicle (placebo) gel. Each dose will consist of berdazimer gel or vehicle gel that will need to be mixed with

hydrogel on a supplied dosing guide, and then immediately applied by the subject or caregiver to the affected designated area(s).

All study drug treatments will be manufactured and provided by the sponsor. The study treatments and their attributes are described in Table 7.

Table 7 Study Drug

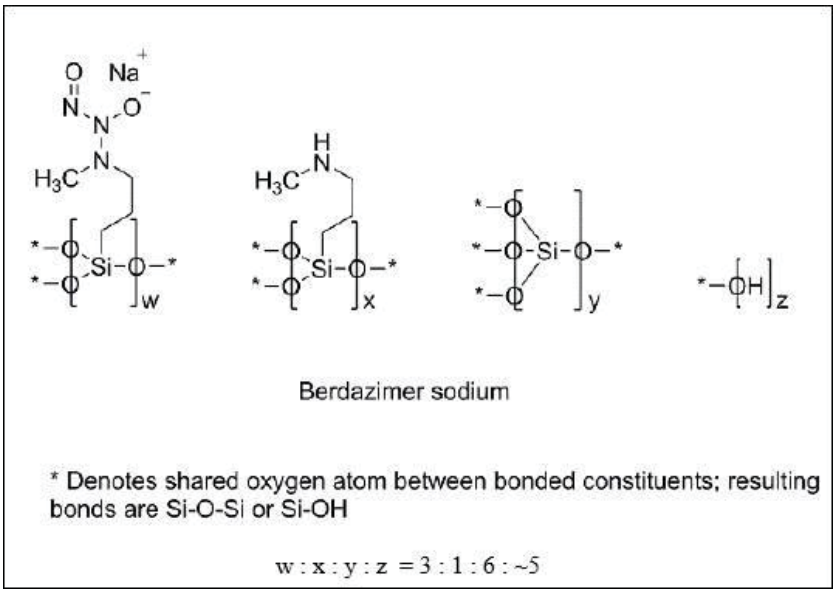
	SB206 10.3%	**Vehicle gel**
Study Drug Components	Berdazimer gel 22.7% and buffered hydrogel Mixed immediately prior to application	Vehicle gel and buffered hydrogel Mixed immediately prior to application
Name of Active Ingredient	Berdazimer Sodium	None
Packaging	One kit will include 3 x 14g aluminum tubes of berdazimer gel and 3 x 14g aluminum tubes of hydrogel	One kit will include 3 x 14g aluminum tubes of vehicle gel and 3 x 14g aluminum tubes of hydrogel
Storage Requirements	Refrigerated, horizontal 2-8°C until dispensed	Refrigerated, horizontal 2-8°C until dispensed
Appearance Post-Mixing	Opaque white gel	Opaque white gel
Dosing Schedule	QD	QD
Route of Administration	Topical Application	Topical Application

Note that description of the concentration of SB products used nominal numbers based on percent berdazimer sodium historically. Novan has updated the naming convention to use percent berdazimer. Therefore, SB206 12% (nominal berdazimer sodium) is the same admixture formulation as SB206 10.3% (berdazimer). In this protocol, the nominal berdazimer sodium numbers remain in historical studies.

8.1.1 Formulation, Storage, Preparation, and Handling

SB206 is a two-component drug product formulation intended for topical administration. The drug product is comprised of an active gel component containing the berdazimer sodium drug substance, and a buffered hydrogel (aqueous) component that when mixed releases nitric oxide. Berdazimer sodium is silsesquioxanes, 3-(2-hydroxy-1-methyl-2-nitrosohydrazinyl)propyl 3-(methylamino)propyl, polymers with silicic acid (H_4SiO_4) tetra-Et ester, hydroxy-terminated, sodium salts.

Figure 4 Structure of Berdazimer Sodium (active ingredient in SB206)



8.2 Dosing and Administration

During the double-blind treatment period, study drug will be assigned using an IWRS. Approximately 850 subjects, 6 months of age and older, with a minimum of 3 and a maximum of 70 lesions at Baseline will be randomized. A drug kit consisting of 6 tubes of assigned study drug sufficient for 4 weeks of dosing will be dispensed to the subject at the Baseline Day 1 visit. A second kit will be dispensed at Week 4, and a third kit will be dispensed at Week 8. Three of the tubes will contain berdazimer gel or vehicle gel and 3 of the tubes will contain buffered hydrogel. When the gel and hydrogel are mixed together, the components form a gel that will be applied to the lesions. If a subject's lesions have been confirmed by an investigator as completely cleared at Weeks 4 or 8, a new kit should still be dispensed so that the subject can resume once daily treatment in the event of recurrence or new lesions prior to the next scheduled visit.

The first study drug dose will occur on Baseline Day 1, with application by the subject or caregiver following training by the site. Subsequent applications of study drug occur at home or on-site at the clinic visits at Week 2, Week 4 (if the visit is performed in clinic), Week 8, and Week 12. Subjects will return their kit to each clinic visit for weight and retraining purposes; at Week 2 only, the kit will be re-dispensed to the subject.

The following is a summary of the subject's/caregiver's role in treatment of lesions:

- Continuous daily treatment of treatable lesions to Week 4 at a minimum
- Continued treatment of treatable lesions after Week 4 unless otherwise instructed by the Investigator
- Self-initiated treatment of new or recurrent lesions
- Documentation of daily dose application in subject diary

Withdrawal and discontinuation are covered in Section 6.8.

8.3 Treatment Allocation

Subjects will be randomly assigned in a 1:1 fashion to either SB206 10.3% or Vehicle gel.

8.4 Randomization Strategy and Procedure

The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. As subjects qualify to be randomized into the study, a randomization number will be assigned through a central IWRS. At randomization, subjects will be stratified by investigator type (dermatologist vs. other), the subject's BOTE score at Baseline (no inflammation (BOTE = 0) vs. mild/moderate/severe inflammation (BOTE ≥ 1) and number of randomized subjects per household (1 subject per household vs. 2 subjects per household). Subjects will be stratified to 5 strata first by subjects per household. Subjects from 1 subject households will be stratified by investigator type and baseline BOTE score. Subjects from 2 subject households will not be further stratified with respect to investigator type and baseline BOTE score because the overall sample size that is expected for the stratum for households with two subjects is not large enough to support further stratification. Approximately 850 subjects, 6 months of age and older, with a minimum of 3 and a maximum of 70 lesions at Baseline will be randomized.

8.5 Extent and Maintenance of Blinding

All subjects, investigators, and study personnel involved in the conduct of the study will be blinded to treatment assignment, with the exception of a specified unblinded statistician who will generate and have access to the randomization code. The unblinded study personnel will not otherwise participate in study procedures or data analysis prior to unblinding of the study data to all study related personnel.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study.

8.5.1 Unblinding Procedures

8.5.1.1 Planned Unblinding

Individual treatment unblinding is discouraged since knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding should be discussed in advance with the medical monitor if possible. Study personnel will utilize the IWRS for emergency unblinding. If the investigator is not able to discuss treatment unblinding in advance, then he or she must notify the CRO medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for

that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he or she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

Of note, all available unblinded safety data will be provided to the DSMB to review after approximately 200 subjects are randomized. Personnel who are not otherwise involved in the study will prepare the unblinded data and summary tables for this analysis.

8.5.1.2 Unplanned or Unintentional Unblinding

All instances of unplanned or unintentional unblinding will be documented.

8.6 Assessment and Verification of Compliance

Subjects will be provided a diary to record doses taken on a daily basis. The diary will contain a reminder for subjects to not administer their dose the day of each visit. Review of subject compliance with the diary completion and dosing will be conducted at each visit. Subject compliance will be based on calculation from the missed doses recorded from the subject diary and from additional information noted in the source (e.g. investigator instructed interrupted or modified doses).

8.7 Prior and Concomitant Therapies

At Screening, prior MC medications/therapies taken within 6 months of Screening will be recorded. Subjects receiving medicinal treatment or other therapy for MC as defined in the study Exclusion Criterion #4, 5, or 6 at the time of the Screening Visit may enter a washout period of up to 14 days prior to the Baseline visit. Subjects receiving or that have received an investigational drug/device within 14 days or 5 half-lives (whichever is longer) prior to Baseline as described in Exclusion Criterion #13 may enter a washout period of up to 14 days prior to the Baseline visit (Section 5.2).

Initiation of new medications and changes to ongoing medications will be reviewed and documented at each study visit from Screening through Week 24, as well as at Unscheduled Visits. Any medication/therapy used by the subject following first application of study product will be considered a concomitant medication (e.g., aspirin, acetaminophen, birth control pills, vitamins, etc.). Every attempt should be made to keep concomitant medication/therapy dosing constant during the study. Any change to concomitant medications/therapies should be noted on the subject's study record and in the study database. When applicable, an AE should be completed for any subject starting a concomitant medication/therapy after enrollment into the study.

Clinically significant LSRs (e.g., those that interfere with a subject's normal daily activities) that are reported as adverse events and/or subject reported intolerability (i.e. itching, pain) may result in an investigator directed temporary treatment hold (drug holiday), and topical corticosteroids may be used to treat LSRs for up to 2 weeks. The subject may re-initiate study drug treatment prior to the next scheduled visit. Upon re-initiation (challenge) of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. In the event of suspected allergic contact dermatitis, the investigator will discontinue the subject from study drug treatment and treat the area(s) with corticosteroids for up to 2 weeks. If the subject provides consent/assent, the investigator will consult the CRO medical monitor to implement the process for patch testing

8.7.1 Prohibited Therapies

Immunosuppressive treatment is prohibited during the study. Use of topical calcineurin inhibitors or steroids on MC or within 2 cm of MC lesions is prohibited within 14 days of baseline and during the study. Use of the following concomitant medications to treat MC 14 days prior to baseline and during the study is prohibited: podophyllotoxin, imiquimod, cantharidin, sinecatechins, topical retinoids, oral or topical zinc, other homeopathic or over-the-counter products including, but not limited to, ZymaDerm and tea tree oil, cimetidine and other histamine H2 receptor antagonists. Surgical procedures to treat MC (e.g. cryotherapy, curettage) are prohibited during the study. The CRO medical monitor should be contacted for any questions regarding prohibited therapies.

9 SAFETY MONITORING

Adverse events will be assessed and collected after the initiation of study drug treatment through the end of the subject's last visit. In order to avoid bias in eliciting AEs, subjects/caregivers should be asked the following non-leading question: "How have you felt since your last visit?" SAEs will be collected from the time of consent through the end of the subject's last visit. Adverse events that occur from time of consent up to the time of treatment administration should be recorded as medical history for all participants. Serious adverse events will be followed until resolution.

9.1 Definitions

- Adverse event – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related.
- Serious adverse event (SAE) – An event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (An event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at

immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- Causality or relatedness – Determination of whether there is a reasonable possibility that the product is causally related to the adverse event. Causality assessment includes, for example, evaluation of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, and biologic plausibility.
- Adverse reaction – An AR is any AE caused by a drug.
- Suspected adverse reaction (SAR) – An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.
- Unexpected – An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

9.2 Documenting Adverse Events

All AEs (serious and non-serious) reported by the subject must be recorded on the subject's study record and entered into the study database no later than 5 days of the site's first knowledge. The site must report all SAEs to the CRO within 24 hours after first knowledge of the event by the study site. The date of onset, date ended, accurate event term, seriousness, severity, outcome, causality (relationship to study drug), therapy required, and action taken regarding study drug and study participation will be reported for each AE.

Significant LSRs (as judged by the investigator), scarring, and hypertrophic/keloid scars will be captured as adverse events.

9.2.1 Assessment of Severity

The investigator is responsible for evaluating all AEs and determining the severity of the event. Severity will be categorized according to the following definitions:

- Mild: Event may be noticeable to subject; does not influence daily activities; usually does not require intervention
- Moderate: Event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- Severe: Event 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

9.2.2 Assessment of Causality

Several factors should be considered when assessing the relationship (causality) of an event to the study drug or administration of the study drug. The investigator should assess the relatedness to the study drug using a standard of a reasonable possibility of a causal relationship between the study drug and the AE, as per the examples in Table 8:

Table 8 Assessment of Causality

Related Events: Include those assessed as definitely, possibly, or probably related events	• Reasonable temporal sequence to drug administration • Event can be fully attributable to administration of the study drug • Known pharmacological action of the study drug • Specific tests available (positive allergy test, antibodies, metabolites) • As adverse drug reaction in the product information (Investigator's Brochure) • Reported in the literature as a possible side effect • Dechallenge (event abates on discontinuation of the study drug/without treatment) • Rechallenge positive (event reappears on re-exposure to study drug) • Not explained otherwise by the subject's clinical state or medical history or by other concomitant agents/therapies, etc.
Unrelated Events: Include those assessed as unlikely or unrelated events	• No reasonable temporal sequence to study drug administration • Event is explained by a number of other factors such as a subject's clinical state, medical history, or other concomitant agents/therapies • Etiology has been clarified and is in no way related to the study drug • No reason for suspecting a causal relationship to the study drug and • Investigators have established this beyond reasonable doubt

9.2.3 Reporting Serious Adverse Events

Any SAE, whether deemed drug-related or not, must be reported to the CRO as soon as possible after the investigator or coordinator has become aware of its occurrence. The investigator/

coordinator must notify the CRO within 24 hours of notification of the event. When appropriate, Novan will notify the appropriate regulatory body of drug related SAEs.

If a subject experiences an SAE or pregnancy, the investigator must:

1. Report the SAE or pregnancy immediately (within 24 hours) after the investigator becomes aware of the event.

2. Complete an SAE or pregnancy notification form and send the appropriate reporting form to the CRO within 24 hours of knowledge of the event.

3. Obtain and maintain all pertinent medical records, information and medical judgments of medical personnel who assisted in subject's treatment and follow-up and document as appropriate.

4. Provide a more detailed report to both the CRO and the IRB, if applicable, no later than seven days after the investigator discovers the event as further information becomes available, and when necessary update the information with follow-up information including outcomes. This report should include a statement as to whether the event was or was not related to the use of study drug.

5. The investigator will notify the IRB of the SAE or pregnancy according to specific IRB requirements.

6. The investigator will collect information on SAEs until the subject's health has returned to baseline status, until all parameters have returned to normal, or remaining health issues have otherwise been explained.

7. The investigator is responsible for following pregnancies through the end of the pregnancy and for providing the assessment of the healthy live birth or for reporting any abnormal pregnancy outcome such as stillbirth, miscarriage, or deformity to the CRO/sponsor.

For clarity on how to record an adverse event that progresses into a serious adverse event, there should be two events recorded: the first event would be the beginning adverse event, and the second event would be the serious adverse event (i.e. only the time the AE qualified as serious). Resolution of the SAE should be recorded in the same manner, two end dates for SAE and AE, where the SAE and AE may or may not share the same end date.

9.3 Adverse Event Follow-up

AEs that are not resolved at the time of the last scheduled study visit (Week 24/ET2) must be recorded in the study database as ongoing/not recovered/not resolved/resolving. Treatment related adverse events and serious adverse events, including LSRs and scars/keloids, will be followed until resolution or up to 1 year after last treatment, whichever is sooner.

The investigator should follow all SAEs until the events are resolved, or the subject completes study participation at Week 24/ET2. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition.

9.4 Women of Childbearing Potential & Pregnancy

A female is considered of childbearing potential if she has reached 9 years of age or unless she is post-menopausal (no menses for 12 consecutive months), surgically sterilized (documented hysterectomy, documented bilateral salpingectomy, documented bilateral oophorectomy). Tubal ligation does not meet the definition of surgically sterile.

WOCBP must use an effective method of birth control during the study. The following are considered acceptable methods of birth control for this study: hormonal contraceptives (combined estrogen and progestogen or progestogen only, including oral, injectable, transdermal or injectable formulations); intrauterine device (IUD); intrauterine hormone releasing system (IUS); bilateral tubal occlusion or ligation if performed ≥ 3 months prior to Baseline; same sex partner or partner who has had a vasectomy; sexual abstinence .with a documented acceptable method of birth control if the subject becomes sexually active; female or male condoms with or without spermicide; or a cervical cap, diaphragm, or sponge with spermicide. Women with tubal occlusion or ligations or whose partner has had a vasectomy will be required to complete UPTs at the required timepoints if the procedure was done < 3 months prior to Baseline.

Before enrolling any subject in this clinical trial, the investigator must review guidelines about study participation including the topics below:

- Informed consent document
- Pregnancy prevention information
- Risks to unborn child(ren)
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to study enrollment, all subjects must be advised of the importance of avoiding pregnancy during participation in this clinical study and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent document stating that the above-mentioned risk factors and the consequences were discussed.

During the study, females who have reached the age of menarche should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late

menstrual cycle). Study drug shall be held immediately if a subject is suspected to be pregnant and study drug must be permanently discontinued if pregnancy is confirmed. The investigator must immediately notify the medical monitor/CRO of any female subject who becomes pregnant any time during study participation, record the information on the pregnancy notification form and email the form to the CRO. Subjects found to be pregnant prior to Week 12 will be discontinued from study drug treatment, continue with study visits through Week 24 and follow up with pregnancy outcome. The site should follow-up with the subject periodically during the pregnancy for ongoing health and safety information through the end of the pregnancy, as applicable. The investigator is responsible for following the pregnancy through the end of the pregnancy and for providing the assessment of the healthy live birth or for reporting any abnormal outcome such as stillbirth, miscarriage, or deformity to the CRO/sponsor (Note: Congenital anomalies are considered SAEs and require separate reporting per Section 9.2.3).

9.5 Overdose or Misuse

There is no specific antidote for SB206. In the event of an overdose, best supportive care should be utilized. Methylene blue may be used to treat subjects exhibiting methemoglobinemia. The medical monitor/CRO/sponsor must be notified of any subject exhibiting signs of methemoglobinemia.

10 ANALYSIS

10.1 Hypothesis

This study is intended to formally evaluate the efficacy of SB206 10.3% QD against Vehicle.

The primary efficacy comparison will test the following hypotheses:

H0: The proportion of subjects with complete clearance is equal between SB206 10.3% QD and Vehicle;

H1: The proportion of subjects with complete clearance is different between SB206 10.3% QD and Vehicle.

10.2 Population

10.2.1 Sample Size Rationale

Approximately 850 subjects, 6 months of age and older, with a minimum of 3 and a maximum of 70 MC lesions at Baseline will be randomized in a 1:1 (active:vehicle) scheme. The sample size assumptions for this study were informed by the integration of the completed phase 3 studies NI-MC301 and NI-MC302. Multiple replications of simulated random sampling of the integrated NI-MC301 and NI-MC302 data was performed to ensure the sample size assumptions align with the proposed design of NI-MC304. This includes the 1:1 ratio (active:vehicle) and the percentages observed in NI-MC301 and NI-MC302 for each stratum of each of the stratification

factors: investigator type, number of randomized subjects per household, and baseline BOTE score that are planned for NI-MC304.

The analysis of the proportion of subjects with complete response of all treatable MC at Week 12 within the Intent-to-Treat (ITT) Population of the multiple replications of simulated random sampled integrated data yields rates of 20% for vehicle and 29.5% for SB206 10.3% QD with the covariate-adjusted treatment difference was 9.5%. A sample size of 850 subjects (425 subjects in the SB206 10.3% QD group and 425 subjects in the vehicle group) will provide 90% power for a 2-sided alpha test of size 0.05 to detect an absolute difference of 9.5% when the vehicle response rate is 20%.

10.2.2 Analysis Subsets

The Intent-to-Treat (ITT) analysis population will include all randomized subjects who have a signed informed consent or assent as applicable. The ITT analysis population will be used as the main analysis population for efficacy (primary and secondary) and exploratory endpoints. Subjects will be analyzed according to the treatment group to which they were randomized.

The Per Protocol (PP) analysis population will include all ITT subjects with no significant protocol deviations potentially having an impact on the efficacy evaluations. Subjects will be analyzed according to the treatment group to which they were randomized. The PP analysis population will be used as a supportive analysis population for the primary and secondary efficacy endpoints.

The Safety analysis population will include all ITT subjects who received at least one dose of the study treatment. Subjects will be analyzed according to the study treatment actually received. The Safety analysis set will be used for the summary of demographic and other baseline characteristics, prior and concomitant medications, exposure and compliance with the study drug, and all safety endpoints.

10.2.3 General Considerations

Continuous variables will be summarized by treatment group and visit, when applicable, using the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by treatment group and visit, when applicable, using frequencies and percentages.

All statistical tests will be two-sided and will be performed with a significance level of 0.05, unless otherwise specified.

Additional details regarding the analysis of primary, secondary, exploratory, safety endpoints and all sensitivity analysis will be included in the SAP. The SAP will be finalized before unblinding and database lock.

10.3 Testing Procedures

10.3.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the proportion of subjects achieving complete clearance of all treatable molluscum lesions at Week 12 for the ITT population. Complete clearance of all MC at Week 12 is defined as having a lesion count of 0 at Week 12. The number and percentage of subjects with complete clearance at Week 12 will be summarized by treatment group.

The primary efficacy endpoint will be analyzed using a generalized estimating equation (GEE) for logistic regression with an exchangeable working correlation structure. The model will include treatment, investigator type (dermatologist vs other), Baseline BOTE score (no inflammation (BOTE = 0) vs. mild/moderate/severe inflammation (BOTE ≥ 1) and number of randomized subjects per household (1 subject per household vs. 2 subjects per household), age and Baseline lesion count as factors. The odds ratio between SB206 10.3% and vehicle gel, 95% CIs for the odds ratio, and P-value for the covariate-adjusted treatment comparison will be presented; together with predicted proportions along with their associated 95% confidence interval. Only subjects who achieve complete clearance at Week 12 will be counted as responders for the primary analysis. Subjects who discontinue the study before the Week 12 analysis visit for any reason will be considered not to have achieved complete clearance at Week 12, even if the subject discontinues after a lesion count of 0.

As a sensitivity analysis, the primary efficacy analysis will also be applied to the PP population. Additional sensitivity analyses may be performed including analyses that utilize alternative assumptions from those of this primary method to ensure that efficacy results are not driven by the method of handling missing data.

10.3.2 Analysis of Secondary Efficacy Endpoints

The familywise error rate with respect to the primary endpoint and secondary endpoints will be strongly controlled at the alpha=0.05 level using a hierarchical fixed sequence method testing strategy. If the primary endpoint is not statistically significant at the alpha=0.05 level, the secondary efficacy endpoints will be considered not significant. If the primary endpoint is statistically significant at the alpha=0.05 level, the secondary efficacy endpoints will be tested in the following hierarchical fixed sequence:

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

At each subsequent test of the secondary efficacy endpoints, if the secondary endpoint is not statistically significant at the alpha=0.05 level, the remaining secondary efficacy endpoints will

be considered not significant. If the secondary endpoint is statistically significant at the alpha=0.05 level, the next subsequent secondary efficacy endpoint will be tested following the sequence.

10.3.3 Population Analysis

10.3.3.1 Disposition

Subject disposition information will be summarized for all subjects by treatment group. Summaries will include: the number of subjects screened, the number of subjects in each analysis population, the number of subjects where study treatment stopped, primary reason for study treatment stopped, the number of subjects completing 12 weeks of the study, the number of subjects completed the study, and the primary reason for discontinuation.

10.3.3.2 Demographics and Baseline Characteristics

Demographic variables include age, sex, ethnicity, and race. Age will be calculated in years relative to the informed consent date.

Other baseline characteristics include lesion counts at baseline, baseline BOTE score, site type (dermatologist vs other), and age at and time since onset of symptoms of current molluscum episode. Demographic and baseline characteristics will be summarized for the Safety, ITT, and PP Populations.

10.3.4 Safety Analysis

No missing safety data will be imputed, and no inferential statistics will be done for any safety endpoints. Change from Baseline in abbreviated physical examinations and a summary of concomitant medications will be presented.

10.3.4.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 23.0 or later).

A treatment-emergent AE (TEAE) is defined as those AEs that occurred any time on or after the first in-clinical application of study drug through the last application of study drug and those existing AEs that worsened during this same period. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). For the summary by SOC and PT, each subject will be counted only once within a SOC or a PT. AEs with an outcome of death, SAEs, TEAEs leading to discontinuation from study treatment, and TEAEs leading to discontinuation from the study will be summarized similarly.

TEAEs will be further summarized by worst severity and highest relationship with study treatment, separately. For the summary by worst severity, each subject will be counted only once

within a SOC or PT according to the worst reported severity. Similarly, for the summary by highest relationship with study treatment, each subject will be counted only once within a SOC or PT according to the highest reported relationship with study treatment.

Separate listings will be provided for the AEs with an outcome of death, SAEs, TEAEs leading to discontinuation from study treatment, and TEAEs leading to discontinuation from study.

The proportion of subjects with scarring and the proportion of subjects with keloid or hypertrophic scarring will be summarized descriptively.

10.3.4.2 Local Skin Reactions

The LSR composite score will be calculated by summing up all the numerical responses (0-4) to each individual parameter for a composite score that ranges between 0 and 24. The change from Baseline of the LSR composite score will be summarized descriptively. A table summarizing each LSR parameter (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) score at each scheduled postbaseline assessment will be presented. Additionally, a shift table comparing the baseline score for each LSR parameter to each scheduled postbaseline assessment will be presented for the Safety Population.

10.3.5 Other Analyses

A shift table comparing the baseline BOTE score to each scheduled post-baseline assessment will be presented for the Safety Population. Additional BOTE vs lesion count/complete clearance analyses may be explored and further detailed in the SAP.

10.3.6 Exploratory Analysis

The exploratory endpoints based on the proportion of subjects achieving complete clearance (at Weeks 2, 4) or 75% (at Weeks 2, 4, 8, 12), 90% (at Weeks 2, 4, 8) reductions will be analyzed in the same manner as the primary endpoint.

Likewise, the proportion of subjects achieving a lesion count of 0 or 1 of all treatable MC at Weeks 2, 4 and 8 will be analyzed in the same manner as the primary endpoint.

The change and percent change from Baseline in the number of treatable MC will be analyzed using a repeated measures mixed model for the respective visits with the same covariates as the primary model together with visits and treatment by visit.

Time to first complete clearance of all MC will be analyzed using Kaplan-Meier methods. The number and percentage of subjects achieving complete clearance, number and percentage of censored subjects, and Kaplan-Meier estimates of first quartile, median, and third quartile will be summarized by treatment group.

The proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed will be summarized.

The subject-reported spread of MC to household members not in the study will be summarized descriptively including a breakdown of whether or not there was any spread and then a breakdown of the amount of spread within the household at each visit at the household level.

Investigator global severity assessment and investigator global impression of change will be summarized descriptively. Subject global severity assessment and subject global impression of change will be summarized descriptively.

Listings will be provided for the results from the study exit interview.

11 ETHICAL CONSIDERATIONS

11.1 Good Clinical Practice

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 (R2) Good Clinical Practice: Consolidated Guidance and the applicable regulatory requirements. The investigator must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and informed consent/assent form by an IRB) to the CRO before investigational product will be shipped to the study site. The investigator will review the final study results to confirm that to the best of his/her knowledge, it accurately describes the conduct and results of the study.

11.2 Data Safety Monitoring Board (DSMB)

When approximately 200 subjects are randomized, a Data Safety Monitoring Board (DSMB) will review all available unblinded safety data (including completed patch testing results). The DSMB will provide their recommendation for the study to proceed or not proceed.

11.3 Ethics Review

The protocol, informed consent/ assent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent/assent form must be obtained before any subject is screened. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent/assent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent using a previously approved consent form.

11.4 Informed Consent

In compliance with 21 C.F.R. § 50.25, informed consent is a process that is initiated prior to the subject agreeing to participate in the study and continues throughout the subject's study participation. This study may include both paper-based informed consent/assent forms, and electronic consent/assent forms. All consent/assent forms will be IRB-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in

terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study, alternative treatment options, and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent/assent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The informed consent/assent document should be signed prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent/assent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.5 Data Privacy

Pursuant to 21 CFR, all information, including images and remote visits via video and telephone, generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior documented consent is gained from Novan. However, authorized regulatory officials, IRB/IEC personnel, Novan and its authorized representatives are allowed full access to the records.

Subjects will only be identified at a minimum by unique subject numbers in the study database. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

11.6 Disclosure

The study will be posted to clinicaltrials.gov.

Novan is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of Novan is discussed in the investigator's Clinical Research Agreement.

12 OVERSIGHT

12.1 Quality Control and Assurance

12.1.1 Monitoring

All aspects of the study will be monitored by the CRO or Novan according to GCP and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (i.e., informed consent regulations, (21 CFR § 50.20, 1999), and Institutional Review Board regulations, (21 CFR § 56.103, 1981)). Access to all records, both during the trial and after trial completion, should be made available to the CRO and Novan at any time for review and audit to

ensure the integrity of the data. The investigator must notify the CRO immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun.

The investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines, applicable informed consent regulations (21 CFR § 50.20, 1999), and in compliance with the principles in the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data is not recorded per protocol, the reason(s) must be clearly documented on the study records.

Before study initiation, at a site initiation visit or at a meeting with the investigator(s), a CRO or Novan representative will review the protocol and study records with the investigator(s) and their staff. During the study, the study monitor will be in regular contact with the site and will perform remote visits and on-site visits in accordance with the monitoring plan. The objective of these communications is to review the completeness of subject records, the accuracy of entries into the study database, the adherence to the protocol and to GCP, the progress of enrollment, to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the investigational product is being stored, dispensed and accounted for according to specifications. The investigator and key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the study database entries. No information in these records about the identity of the subjects will leave the study site. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of AEs/SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the study records with the study database will be performed according to the study specific monitoring plan.

The investigator or designee must promptly enter the data into the study database after the subject's visit. The monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the study records will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the Investigator's Brochure, and any protocol amendments.

The investigator must provide the responsible IRB with a study summary shortly after study completion, as per IRB requirements.

This study may incorporate the use of remote monitoring and on-site monitoring visits based on many factors. Risk based monitoring may also be utilized to focus on oversight of subject safety and data integrity. Additional details regarding these visits can be found in the clinical monitoring plan.

12.1.2 Audits

In addition to the routine monitoring procedures, audits of clinical research activities in accordance with SOPs may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the investigator must inform the CRO immediately that this request has been made.

Study conduct may be assessed during the course of the study by a Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol and GCP. He/she will be permitted to inspect the study documents (study protocol, study records, study drug, original, study-relevant medical records). All subject data will be treated confidentially.

12.1.3 Protocol Modification/Deviations

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the sponsor. All protocol modifications should be submitted to the IRB in the form of an amendment, with approval obtained prior to implementation of changes unless the amendment is intended to reduce immediate subject risk. When the protocol modification substantially changes the protocol design or updates the potential study risks section of the Informed Consent Form, the Informed Consent Form will be amended/approved by the IRB, requiring all subjects already enrolled to provide informed consent, again.

This study will be conducted as described in this protocol, except for in emergency situations in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the CRO at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the study. All deviations, as well as subject participations decisions, will be documented by the investigator and the CRO.

If additional contingency measures that require deviation from the protocol are enacted, efforts will be made to minimize impacts on trial integrity, and to document the reasons for protocol deviations as outlined in the clinical trial continuity plan.

12.1.4 Records

12.1.4.1 Data Capture and Management

Subject data will be entered into a sponsor-approved electronic database compliant with 21 CRF Part 11, into electronic case report forms (eCRFs) and combined with data provided from other sources (e.g., laboratory) in validated datasets then transmitted electronically to the sponsor or designee. Management of clinical data will be performed in accordance with the applicable

sponsor-approved standards and data cleaning processes to ensure the integrity of the data. A data management plan for the study will be maintained by the CRO.

Adverse events and prior/concomitant medications and medical history terms will be coded using the most current versions of MedDRA and the World Health Drug Dictionary (WHODrug), respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Subject initials will not be collected or transmitted to the sponsor.

12.1.4.2 Source Documentation

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded on the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data will be entered into a 21 CFR Part 11-compliant data capture system provided by the CRO. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.1.4.3 Study Files and Records Retention

It is a Novan requirement that all investigators participating in clinical studies maintain detailed clinical data for one of the following periods, whichever is longest:

- Country-specific requirements; or
- A period of at least two years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region; or,
- A period of two years after Novan notifies the investigator that the data will not be submitted for review by any Regulatory Authority.

The investigator must not dispose of any records or essential documents relevant to this study without either (1) written permission from Novan, or (2) providing an opportunity for Novan to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Novan and relevant regulatory agencies. If the investigator withdraws from the study (e.g., relocation, retirement), all study-related records should be transferred to a mutually agreed-upon designee. Notice of such transfer will be provided to Novan in writing.

12.2 Study Termination or Study Site Closure

Both Novan and the principal investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Novan or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study, Novan and the principal investigator will assure that adequate consideration is given to the protection of the subjects' interests.

13 PUBLICATION POLICY

Novan is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

Novan's publication policy is discussed in the investigator's Clinical Study Agreement.

14 REFERENCES

Chen et al., 2013

Chen X, Anstey A, Bugert J. Molluscum contagiosum virus infection. Lancet Infect Dis. 2013 Oct;13(10):877-88.

Dohil et al., 2006

Dohil MA, Lin P, Lee J, et al. The epidemiology of molluscum contagiosum in children. J Am Acad Dermatol. 2006 Jan;54(1):47-54.

FDA, 2020

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. 2020 Apr 16

Olsen et al., 2015

Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Time to resolution and effect on quality of life of molluscum contagiosum in children in the UK: a prospective community cohort study. Lancet Infect Dis. 2015;15(2):190-5/

Olsen et al., 2014

Olsen J, Gallacher J, Piguet V, et al. Epidemiology of molluscum contagiosum in children: a systematic review. Fam Pract. 2014 Apr;31(2):130-6.

Osio et al., 2011

Osio A, Deslandes E, Saada V, Morel P, Guibal F. Clinical characteristics of molluscum contagiosum in children in a private dermatology practice in the greater Paris area, France: a prospective study in 661 patients. Dermatology. 2011;222:314–20.

Schofield et al., 2011

Schofield JK, Fleming D, Grindlay D, Williams H. Skin conditions are the commonest new reason people present to general practitioners in England and Wales. Br J Dermatol. 2011;165:1044–50.

APPENDIX 1 PROCEDURE FOR SUSPECTED SENSITIZATION

After treatment is reintroduced post-LSR, if a subject experiences a stronger LSR (second LSR event) than the first LSR event, allergic contact dermatitis may be suspected. In order to confirm whether the reaction is allergic contact dermatitis, patch testing should be conducted. If the investigator determines that patch testing is appropriate and the patient/caregiver consent to patch testing, he/she should contact the CRO medical monitor to discuss. Once the LSR has been completely resolved for a period of 2 weeks and up to 2 months, patch testing may commence. Novan will provide more detailed patch testing instructions once requested from the CRO medical monitor. The site will use a study drug kit already assigned to the subject in order to complete the testing. Additional drug product for patch testing may be supplied through IWRS if the currently assigned subject's investigational product was assigned more than 60 days prior to the patch testing date(s) or if the subject had previously returned all their drug product.

For patch testing:

- Discontinue study treatment (see Section 7.2.3 regarding LSRs)
- Document the event as an AE and consult with the CRO medical monitor. Detailed instructions for the patch testing will be provided after discussion with the medical monitor.
- When applicable, challenge patch testing should be performed after all signs and symptoms of the LSR have been resolved for approximately 2 weeks to 2 months.
- The randomized study treatment will be applied to a naïve area on the participant's back or arm. Use the subject's most recently assigned study drug kit to obtain material for testing.
- The participant will return to the site approximately 48 hours after the application of the patches. Approximately 30 minutes, 24 hours and 48 hours after patch removal, the patch site(s) will be evaluated using the scale in Table 9. If the 48-hour reading is equivocal, it is recommended to evaluate the site at 72 to 96 hours after removal. Take photographs at every time point and transmit them to the medical monitor. Further instructions will be given after review of the photos.
- At the last reading, the investigator will make the final interpretation of any challenge reactions. This last reading (at least 48 hours after patch removal) is critically important to distinguish irritant reactions (which fade) from true allergic reactions (which persist) and to identify allergic reactions that do not appear at the time of patch removal. See Table 10.

Table 9 Grading System for Patch Test Reactions (at each time point)

Score	Description
+/-	Doubtful reaction, faint macular erythema
+	Weak, non-vesicular reaction with erythema, infiltration, and papules
++	Strong vesicular reaction with erythema, infiltration, and papules
+++	Spreading bullous reaction
-	Negative reaction
IR	Irritant reaction

Table 10 Challenge Reaction Interpretation (based on the last reading (at least 48 hours after patch removal)

Score	Description
Negative	Might include an irritative reaction
Equivocal	Unable to determine
Positive*	Reaction definitely due to sensitization

*Judgement of "positive" reaction should be accompanied by ++ or greater reading at the last reading.