16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

This appendix includes

Document	Version, Date
NI-MC301 Protocol	Version 1.0, 26 March 2019

DRUG:	SB206/NVN1000
STUDY NUMBER(S):	NI-MC301
PROTOCOL(S) 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
IND NUMBER:	137015
SPONSOR:	Novan, Inc.
ORIGINAL PROTOCOL DATE:	26 March 2019
VERSION NUMBER:	Version 1.0

CLINICAL PROTOCOL APPROVAL FORM

Protocol 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

Study No: NI-MC301

Original Protocol Date: 26 March 2019

Protocol Version No: 1.0

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of Novan. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Approval	Signature	Date
Author: Hilary Partin, Associate Director, Clinical Operations	(Yes) No (circle one)		26 Mar 2019
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NI-MC301

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

CONFIDENTIALITY AND INVESTIGATOR'S STATEMENT

The information contained in this protocol and all other information relevant to SB206 are the confidential and proprietary information of Novan, Inc. (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, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations (CFR) for Good Clinical Practices (GCP) and International Conference on Harmonization (ICH) guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Novan, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about SB206 and the study.

_____	_____
Principal Investigator Name (printed)	Signature
_____	_____
Date	Site Number

STUDY 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

Rationale: Molluscum contagiosum (MC) is spread easily by close contact and autoinoculation from scratching or trauma. Although a single lesion of molluscum contagiosum is benign and generally self-limiting to about 2 months, many cases have an extended infection period, up to 2 years, due to autoinoculation. There is a significant unmet medical need to treat MC, considering most patients with MC are healthy young children and the disease is highly contagious. Ablative treatment often causes fear in children and may interfere in physician-patient relationships; repeated ablative treatments are difficult. Topical application of SB206 may accelerate resolution of MC without causing pain and/or scarring, decrease the need for ablative treatment and provide an effective, safe and convenient treatment option for MC.

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 340 subjects randomized.

Objectives: This study is being conducted to evaluate the efficacy and safety of SB206 12% QD for the treatment of MC.

Dosing Regimen Subjects 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 up to 12 weeks. If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24/ET2. Each dose of SB206 will consist of hydrogel thoroughly mixed with berdazimer sodium gel. Each dose of vehicle will consist of hydrogel thoroughly mixed with vehicle gel. The subject or caregiver will apply to the lesions and approximately 1 cm surrounding each lesion.

Periocular lesions will be treated if the lesions are at least 2 cm from the edge of the eye.

Study Design:

This is a Phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in up to approximately 340 subjects ≥6 months of age with MC. After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized 2:1 (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 into four strata corresponding to the cross-classification of household number of randomized subjects (1 subject per household vs 2 subjects per household) and investigator type (dermatologist vs other). Households randomizing 2 subjects would receive the same treatment assignment for both subjects.

Subjects or their caregivers will apply SB206 12% or Vehicle Gel once daily for a minimum of 4 weeks and 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. If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24/ET2. At Weeks 2, 4, and 8, the investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. At Weeks 2, 4, and 8, the investigator will determine if new lesions have occurred since the last visit, and the subject or caregiver will be instructed by the investigator to re-initiate treatment.

Subjects will visit the clinic at Screening/Baseline, Week 2, Week 4, Week 8, Week 12, and Week 24. 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 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 due to adverse events (AEs) or other reasons will be asked to complete the Week 12 visit assessments; this will be recorded as an Early Termination (ET1) visit. No study drug treatment will be provided after the Week 12 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 scarring/keloid, and urine pregnancy tests (UPTs). Safety assessments will be completed at specified site visits through Week 12. After Week 12, safety information for ongoing AEs and new AEs will be collected, along with information regarding household MC occurrence.

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. BOTE Inflammation Score and LSR score will be recorded at each visit. BOTE should not be considered an AE. When LSRs are clinically significant, the Investigator should report the condition as AE(s). At Baseline (30 min. post-dose) and Weeks 2 through Week 12, the Investigators will rate LSRs on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

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

LSR Score

	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

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 of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. The investigator may take photographs of the suspected allergic contact dermatitis and discuss possible confirmation of allergic contact dermatitis with the CRO medical monitor. The investigator should also discuss 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 contract

research organization (CRO) medical monitor to implement 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.

Scar formation will be assessed starting at the Week 4 visit through Week 12 and again at 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. The investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. If a scar is larger than 5mm in diameter and/or larger than 1 mm deep, this will be considered an adverse event for the purposes of this study. In addition, keloid/hypertrophic scars will also be recorded as adverse events. Any scars <5mm in diameter and/or <1mm deep will not be considered AEs since these are considered part of the normal healing.

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.

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 prior to initiating patch testing. Photography is not a protocol requirement and subjects must have documented consent for photographs to be taken.

When approximately 200 subjects (cumulative across studies MC301 and MC302) have completed 4 weeks of treatment, a Data Safety Monitoring Board (DSMB) will review all available unblinded safety data (including patch testing).

Inclusion / Exclusion Criteria:

Inclusion Criteria:

1. Be 6 months of age or older, and in good general health;
2. Have a written 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 at Baseline;

4. Female subjects age 9 and above must have a negative UPT at Baseline;

5. Female subjects age 9 and above must agree to practice a medically acceptable form of birth control during the study and for 30 days after Week 12/ET1;

6. Be willing and able to follow study instructions and likely to complete all study requirements.

Exclusion 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);

6. Have received surgical procedures related to MC (cryotherapy, curettage, other) 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 sodium product (SB204, SB206, SB208, SB414);

11. Have more than 1 family member currently participating in a study with a berdazimer sodium product (SB204, SB206, SB208, SB414).

12. Have participated in any other trial of an interventional investigational drug or device within 14 days or concurrent participation in another interventional research study.

13. 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.

Primary Endpoint:

- Proportion of subjects with complete clearance of all treatable MC at Week 12

Secondary Endpoint:

- Proportion of subjects with complete clearance of all treatable MC at Week 8

Exploratory endpoints

- Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed
- Proportion of subjects developing scar(s) after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Proportion of subjects with complete clearance of all treatable MC at each visit (Weeks 2, 4)
- Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)
- Change from baseline of the composite score from age-matched (at baseline) Dermatology Life Quality Index (DLQI) assessment at Week 12
- 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)
- Mean change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Mean percent change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)

- Time to complete clearance of all treatable MC

Statistics: **Statistical Methods**

Safety and efficacy endpoints will be displayed using descriptive statistics and graphical displays, where applicable. For categorical variables, frequencies, and percentages will be presented. The denominators for percentages will be based on the number of subjects appropriate for the purpose of analysis. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation (SD), minimum, and maximum). Where relevant, 95% confidence intervals will be calculated. All statistical tests of the primary and secondary endpoints will be conducted at the 0.05 significance level using 2-tailed tests. Nominal p-values will be reported for treatment comparisons of the exploratory endpoints.

The study treatment period is defined from randomization through completion of Week 12/ET1 visit and the safety follow-up period is from the completion of Week 12 through the completion of Week 24/ET2 visit.

The analysis populations include the following:

Safety Population (SAF): The Safety population will consist of all subjects who receive at least one application of study medication.

Intent-To-Treat Population (ITT): The ITT population will consist of all subjects who are randomized.

Per-Protocol Population (PP): The PP population will consist of all subjects in the ITT population who had no significant protocol deviations that impacted the analyses of the efficacy endpoints.

The primary efficacy endpoint, proportion of subjects with complete clearance of all treatable molluscum lesions at Week 12 in the ITT, 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), household number of randomized subjects (1 subject per household vs 2 subjects per household), age and Baseline lesion count as factors. The odds ratio between SB206 12% and vehicle gel, 95% CIs for the odds ratio, and *P*-value for the covariate-adjusted treatment comparison will be presented. Only subjects who achieve complete clearance at Week 12 will be counted as responders for the primary analysis; all other subjects (e.g., those

who discontinue the study before achieving complete clearance) will be reported as failures. As a sensitivity analysis, the primary efficacy analysis will also be reported for the PP population.

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

- Proportion of all study subjects demonstrating complete clearance of all treatable MC at Week 8

If the secondary efficacy endpoint fails to reach statistical significance at the alpha=0.05 level, it will be considered not statistically significant.

The dichotomous secondary efficacy endpoint will be analyzed using the GEE model described for the primary efficacy endpoint. The analyses methods to be used for the exploratory endpoints will be detailed in the Statistical Analysis Plan (SAP).

All safety and tolerability analyses will be based on the SAF population.

All AEs that occur during the study will be recorded and coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs that occurred any time on or after the first in-clinic application of study drug through the last application of study medication.

Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, SOC, preferred term, severity, relationship to study drug (causality), and seriousness.

Serious adverse events (SAEs) will be summarized by treatment group, severity, and relationship to study drug, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

Urine pregnancy tests results for females 9 years old and older will be presented in data listings by subject.

Sample Size Estimation

The sample size assumptions for this study were informed by the completed Phase 2 study NI-MC201 of subjects ≥2 years of age with 3-70 MC lesions at Baseline. In the ITT population of the Phase 2 study, the observed rates of clearance at Week 12 were 18% (12/66) for vehicle and 38% (18/48) for SB206 12% once daily (QD) and the covariate-adjusted treatment difference was 18%.

Approximately 340 subjects, 6 months of years of age and older, with a minimum of 3 and a maximum of 70 lesions at Baseline will be randomized in a 2:1 (active:vehicle) scheme.

A sample size of 340 subjects (227 subjects in the SB206 12% QD group and 113 subjects in the vehicle group) will provide 94% power for a 2-sided alpha test of size 0.05 to detect an absolute difference of 18% when the vehicle response rate is 18%. This same sample size provides 93% power to detect a treatment difference of 18% when the vehicle response rate is 20% and 83% power when the treatment difference is 15% and the vehicle response rate is 20%.

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LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
AE	Adverse Event
BID	Twice Daily
BOTE	Beginning-of-the-end
BSA	Body Surface Area
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRO	Clinical Research Organization
DLQI	Dermatology Life Quality Index
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EGW	External Genital Wart
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
GCP	Good Clinical Practice
hMAP3	Hydrolyzed N-Methylaminopropyl-trimethoxysilane
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LLOQ	Lower Limit of Quantitation
MC	Molluscum Contagiosum
MedDRA	Medical Dictionary of Regulatory Affairs
MMRM	Mixed-model Repeated Measures
NOAEL	No Observed Adverse Effect Level
NOVAN	Novan, Inc.
OTC	Over-the-counter
PAW	Perianal Wart
PK	Pharmacokinetic
PP	Per-Protocol Population
QD	Once Daily
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
UPT	Urine Pregnancy Test

1 INTRODUCTION AND RATIONALE

1.1 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% (Olsen et al, 2014).

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).

Extensive and persistent skin infection with the virus can indicate underlying immunodeficiency. 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 (Osio et al, 2011).

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 occur in 102 (41%) of 250 cases in the literature.

Novan has 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 or females, 2 years of age or older, with 3 to 70 MC lesions. Different concentrations and dosing frequency of SB206 was 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).

The primary endpoint for Study NI-MC201 was the proportion of subjects in the modified intent-to-treat population who achieved complete clearance of all MC lesions at Week 12. In this analysis, 8% BID and 12% QD groups of SB206 were statistically significantly superior to vehicle in the proportion of subjects with complete clearance at Week 12: 20.0% (vehicle BID/QD combined), 41.0% (8% BID: p=0.028), and 41.9% (12% QD: p=0.024). The 4% BID (13.2%, p=0.518) and

12% BID (35.1, p=0.144) were not statistically superior. The efficacy signals appeared as early as 2-4 weeks. 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). The ITT results will be the basis for the sample size criteria used in MC301.

Based on the clear treatment effect shown by the proportion of subjects achieving complete clearance of all molluscum lesions at Week 12 for SB206 12% once-daily, and favorable safety and tolerability profiles, Novan, Inc. (Novan) is conducting this Phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study of SB206 in subjects 6 months of age and older with molluscum contagiosum. SB206 is a topical gel, formed by mixing berdazimer sodium (NVN1000) gel with hydrogel. Berdazimer sodium gel contains berdazimer sodium, a nitric oxide-releasing macromolecule containing covalently bound N-diazeniumdiolate nitric oxide donors; nitric oxide release from the macromolecule is initiated by mixing berdazimer sodium gel with hydrogel.

Topical formulations of berdazimer sodium at concentrations ranging from 1-16% have been studied. Over 1600 healthy volunteers or subjects with MC, acne, genital warts or tinea pedis have been exposed to Vehicle and over 2700 exposed to berdazimer sodium as of December 31, 2018. In clinical studies completed to date, topical application of berdazimer sodium has generally been well-tolerated with no safety concerns identified.

1.1.1 Preclinical Pharmacology

During the development of SB204 (berdazimer sodium gel co-administered with hydrogel) for acne, SB206 (berdazimer sodium gel co-administered with hydrogel) for the treatment of external genital warts and perianal warts, SB208 (berdazimer sodium gel co-administered with hydrogel) for tinea pedis and SB414 (berdazimer sodium ointment co-administered with hydrogel), Novan has conducted over 90 nonclinical studies. In addition, specifically for SB206, Novan completed a 4-week daily dosing with 2-week recovery GLP dermal bridging study in miniature swine. Under the conditions of this study, the No Observed Adverse Effect Level (NOAEL) was considered to be greater than the nominal dose level evaluated (~48 mg/kg/day berdazimer sodium which equates to approximately 1.7 mg/cm^2/day), administered as BID 8% SB206 Gel or QD 12% SB206 Gel. There were no meaningful effects on mortality/moribundity, clinical observations, physical examination findings, food consumption, weekly body weight or weekly body weight change, clinical pathology parameters, ophthalmologic or electrocardiographic examinations, or organ weight findings. Microscopic changes, limited to the superficial dermis and epidermis, were minimal to mild but had not completely resolved following the 2-week recovery period. The induced changes included hyperkeratosis, epidermal hyperplasia and mononuclear dermal inflammation (mononuclear cell infiltration and dermal edema). Due to an insufficient number of plasma samples with quantifiable hydrolyzed n-methylaminopropyl-trimethoxysilane (hMAP3)

concentrations (values above the LOQ of 5 ng/mL), it was not possible to perform a noncompartmental TK analysis. There was no evidence of systemic nitric oxide exposure at any of the dose levels tested. This study with SB206 in miniature swine was successful in bridging the safety of topical administration of berdazimer sodium in the SB204 formulation with the SB206 formulation.

For additional information refer to the Investigator's Brochure (IB).

1.1.2 Pharmacokinetics

The systemic bioavailability of berdazimer sodium after dermal administration has been investigated in two maximal use studies 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 topical administration of SB204 4% was applied 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.

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 (NI-PS101) study, 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.

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

1.1.3 Potential for Drug-Drug Interactions

Since no quantifiable exposure has been observed to date with SB204 and SB206 clinically, the risk of drug-drug interactions is low.

1.1.4 Clinical Adverse Event Profile

As of December 31, 2018, topical formulations of berdazimer sodium at concentrations ranging from 1% to 16% have been studied in 21 completed studies. Almost 1600 healthy volunteers or subjects with acne, genital warts, tinea pedis, psoriasis and atopic dermatitis have been exposed to Vehicle and over 2700 exposed to berdazimer sodium.

Novan completed a Phase 2 ascending dose study of SB206 in 256 subjects with MC. No deaths or serious adverse events (SAEs) occurred during this study. Seven subjects were discontinued from treatment with the study drug due to an AE, all in active treatment groups (3 subjects in the 4% BID group; 2 in the 8% BID group; and 2 in the 12% BID group). Treatment discontinuation was due to application site reactions in 6 of these subjects and to worsening MC in the other. The active study drug (SB206) given at doses ranging from 4% BID to 12% QD was well tolerated. Most AEs were mild to moderate. The only AEs that appeared to be clearly associated with SB206 were those involving administration site reactions.

Novan completed a Phase 2 ascending dose study assessing the tolerability, safety, and efficacy of SB206 in subjects with external genital warts (EGW) and perianal warts (PAW). In this study, there were no safety concerns with single daily dose application; BID application of SB206 to the genitalia was associated with local application site reactions in some subjects which led to treatment discontinuation. The results of this study are supportive of the continued clinical development of SB206.

SB204 is in development for the treatment of acne vulgaris. The acne clinical program for SB204 includes 9 completed Phase 1 studies in healthy volunteers or subjects with acne vulgaris, 3 completed Phase 2 studies, and the completed Phase 3 program (two 12-week placebo-controlled studies and one 40-week open label long-term safety study in subjects ages 9 years old and older). Based on the clinical data acquired to date, topical application of berdazimer sodium to healthy volunteers or subjects with acne vulgaris has generally been well-tolerated with no safety concerns identified.

Novan has also completed a study in subjects with tinea pedis using SB208. There were no safety concerns identified with QD dosing to one or both feet; there were no application site AEs reported.

Novan has completed two studies in subjects with atopic dermatitis and psoriasis using SB414. In both studies, SB414 was generally well tolerated and the incidence of treatment-related treatment-emergent adverse events (TEAEs) was low. Administration site reactions were the most common treatment-related adverse events and tolerability (change in itch and burning/stinging) was similar across treatment groups. There was no evidence of meaningful trends in safety parameters. In completed studies, no clinically significant changes have been observed in laboratory assessments in subjects treated with topical berdazimer sodium. There have been no clinically significant changes in physical examination, including vital signs, in subjects treated with topical berdazimer sodium.

1.1.5 Elevations in Liver Function Tests

No clinically significant changes have been observed in laboratory assessments.

1.1.6 Potential Risk of Testicular Injury

In a nonclinical GLP study of fertility and early embryonic development in rats after daily oral administration of berdazimer sodium there was no adverse findings in male fertility parameters or reproductive parameters in either sex.

Additionally, since no quantifiable exposure has been observed to date after dermal administration of SB204 and SB206 clinically, the risk of testicular injury is low.

1.1.7 Potential Risk to Fetal Development

Oral administration of berdazimer sodium drug substance in GLP embryo-fetal developmental toxicity studies in rats and rabbits showed minor effects on fetal development only at the highest doses.

Additionally, due to the lack of systemic exposure after dermal administration of SB204 clinically and SB206 clinically observed to date, the risk to fetal development is low.

In prior studies using berdazimer sodium in different diseases, there have been 6 reported pregnancies; of those, two were completed to term with healthy babies. One woman had an elective termination of her pregnancy and one woman had a miscarriage. The outcome of the other two pregnancies is unknown.

1.2 Study Rationale

MC is benign and generally self-limiting. The average duration of a single lesion is about 2 months; however, since the lesions spread easily by autoinoculation from scratching or trauma, the mean duration of infection is often more than a year.

Nitric oxide, an endogenous small molecule, provides localized immunity against foreign organisms by acting both as a short-lived immune modulator and a direct broad-spectrum antimicrobial agent. Topical exogenous nitric oxide has been investigated as an antimicrobial agent due to its broad-spectrum activity, ability to inhibit viral replication, and the ability to readily diffuse through cell membranes.

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. 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.

1.2.1 Dosing Regimen

Subjects 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 up to 12 weeks. Each dose of SB206 will consist of hydrogel thoroughly mixed with berdazimer sodium gel. Each dose of vehicle will consist of hydrogel thoroughly mixed with vehicle gel. Subjects will be instructed on the correct use of study drug and the amount to apply during Baseline/Day 1 according to the corresponding subject instructions for use that will be provided to the subject. In addition, study personnel will ensure that the subjects or caregivers can identify the treatment area(s) and know where and how to apply the study drug. Dosing should be applied at home, except on the day of study visits when the dose should be applied in the clinic. The subject, caregiver, or study personnel will apply to the lesions and approximately 1 cm surrounding each lesion. Periocular lesions will be treated if the lesions are at least 2 cm from the edge of the eye.

If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. At Weeks 2, 4, and 8, the investigator will determine if new lesions have occurred since the last visit, and the subject or caregiver will be instructed by the investigator to re-initiate treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24/ET2. Subjects will be followed for recurrence/new lesions until Week 24. For the purpose of this study, a recurrence of MC will be documented as an AE.

1.2.2 Dose Selection Rationale

Novan completed a Phase 2 ascending dose study of SB206 in 256 subjects with MC. The primary endpoint for Study NI-MC201 was the proportion of subjects in the modified intent-to-treat population who achieved complete clearance of all MC lesions at Week 12. In this analysis, 8%

BID and 12% QD groups of SB206 were statistically significantly superior to vehicle in the proportion of subjects with complete clearance at Week 12: 20.0% (vehicle BID/QD combined), 41.0% (8% BID: p=0.028), and 41.9% (12% QD: p=0.024). The difference in proportion (95% CI) from vehicle was statistically significant for 8% BID (0.206 [0.022, 0.389], P = 0.028) and 12% QD (0.204 [0.027, 0.381], P = 0.024). A sensitivity analysis of the primary efficacy endpoint in the ITT population produced results consistent with the primary analysis results. Secondary and exploratory efficacy endpoints also support selection of 12% QD. In the Phase 2 study, 7 subjects were discontinued from treatment with the study drug due to an AE, all in active treatment groups (3 subjects in the 4% BID group; 2 in the 8% BID group; and 2 in the 12% BID group). Treatment discontinuation was due to application site reactions in 6 of these subjects and to worsening MC in the other. No subject discontinued treatment due to AEs in the 12% QD group.

Based on totality of the data, SB206 12% QD was selected for this Phase 3 study.

2 STUDY OBJECTIVE

This study is being conducted to evaluate the efficacy and safety of SB206 12% QD for the treatment of MC.

3 STUDY ENDPOINTS

The following endpoints will be assessed during the study.

3.1 Primary Efficacy Endpoint

- Proportion of subjects with complete clearance of all treatable MC at Week 12

3.2 Secondary Efficacy Endpoint

- Proportion of subjects with complete clearance of all treatable MC at Week 8

3.3 Exploratory Endpoints

- Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed
- Proportion of subjects developing scar(s) after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Proportion of subjects with complete clearance of all treatable MC at each visit (Weeks 2, 4)

- Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)

- Change from baseline of the composite score from age-matched (at baseline) Dermatology Life Quality Index (DLQI) assessment at Week 12 at Week 12

- 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)

- Mean change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)

- Mean percent change from Baseline in number treatable MC at each visit (Weeks 2, 4, 8, 12)

- Time to complete clearance of all treatable MC

3.4 Safety Endpoints

Safety assessments will be performed at scheduled timepoints throughout the study and include physical examination, urine pregnancy test, Beginning of the End (BOTE) Inflammation Score, Local Skin Reaction Scores (LSRs), concomitant medications, and adverse events (including scarring/keloid scarring).

4 STUDY PLAN

4.1 Study Design

This is a Phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in approximately 340 subjects with MC. After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized 2:1 (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 into four strata corresponding to the cross-classification of household number of randomized subjects (1 subject per household vs 2 subjects per household) and investigator type (dermatologist vs other). Households randomizing 2 subjects will receive the same treatment assignment for both subjects. Up to two subjects from the same household may be randomized on the same day, if both individually meet all inclusion/exclusion criteria. For subjects in the same household, Screening can occur on different days; however, the Baseline visit must occur on the same day.

Subjects or their caregivers will apply SB206 12% or Vehicle Gel once daily for a minimum of 4 weeks and 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. If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. At Weeks 2, 4, and 8, the investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. The investigator will also determine if new lesions have occurred since the last visit, and the subject or caregiver will be instructed by the investigator to re-initiate treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24.

Subjects will visit the clinic at Screening/Baseline, Week 2, Week 4, Week 8, Week 12, and Week 24. 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 AEs; at Week 24, the subject will be seen at the site for a final study visit. Subjects who discontinue the study prior to the Week 12 visit due to adverse events or other reasons will be asked to complete the Week 12 visit assessments; this will be recorded as an Early Termination (ET1) visit. No study drug treatment will be provided after the Week 12 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 Scores (LSRs), adverse event collection, including scarring/keloid and urine pregnancy tests (UPTs). Safety assessments will be completed at specified site visits through Week 12. After Week 12, safety information for ongoing AEs and new AEs will be collected, along with information regarding MC recurrence. For the purpose of this study, a recurrence of MC will be documented as an AE.

Inflammatory reactions around the MC 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. 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. BOTE Inflammation Score and LSR score will be recorded at each visit. BOTE should not be considered an AE. When LSRs are clinically significant at the application site, the Investigator should report the condition as AE(s).

At Baseline (30 min. post-dose) and Weeks 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 BOTE Inflammation Score (Section 7.2.3).

Local Skin Reaction (LSR) Scores

Clinically significant LSRs reported as AEs 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. If a drug holiday is prescribed, Investigational product (IP) will still be dispensed at the clinic visit to ensure the subject may resume dosing prior to the next clinic visit. The subject may reinitiate study drug treatment prior to the next scheduled visit. Upon re-initiation of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. The investigator may take photographs of the suspected allergic contact dermatitis and discuss possible confirmation of allergic contact dermatitis with the CRO medical monitor. The investigator should also discuss 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 clinical research organization (CRO) medical monitor to implement 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 occurs earlier.

Scar formation will be assessed starting at the Week 4 visit through Week 12 and again at 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. MC lesions may resolve with pitted scars (indentation), and the small scars that maintain original MC size (<5 mm) and less than 1 mm in depth will heal over time. Any pitted scars <5 mm in diameter and <1 mm in depth will not be considered AEs since these are considered part of the normal healing process. . If a scar is larger than 5 mm in diameter or greater than 1 mm in depth, this will be considered an adverse event for the purposes of this study. In addition, 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.

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 prior to initiating patch testing.

When approximately 200 subjects (cumulative across studies NI-MC302 and NI-MC302) have completed 4 weeks of treatment, a Data Safety Monitoring Board (DSMB) will review all available unblinded safety data (including completed patch testing results).

Table 1: Schedule of Assessments

	Screening	Treatment					
	Screening[1] (Day -14 to Day 1)	Visit 1[1] Baseline (Day 1)	V2 Telephone Contact (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						
Lesion Count or Recurrence	X	X		X	X	X	X
Physical Exam		X					X
Urine Pregnancy Test[3]	X	X			X	X	X
BOTE Inflammation Score[4]		X (pre-dose)		X	X	X	X
Local Skin Reactions (LSR) (post-dose)[4]		X		X	X	X	X
Scarring/Keloid Assessment					X	X	X
DLQI/CDLQI[5]		X					X
Review of Inclusion/Exclusion Criteria	X	X					
Drug Dispensed		X			X	X	
Dispense Subject Diary		X		X	X	X	
Review Subject Application Instructions		X		X	X	X	
In Clinic Study Drug Application[6]		X		X	X	X	X
Review Study Drug Compliance				X	X	X	X
Collect Study Drug					X	X	X
Collect Subject Diary				X	X	X	X
Record Adverse Event (AE) and Concomitant Medication (CM) Changes[7]		X	X	X	X	X	X

	Safety Follow-up		
	Visit 7[2] Week 16 Telephone Contact (Day 113±5)	Visit 8[2] Week 20 Telephone Contact (Day 141±5)	Visit 9[2] Week 24/ ET2 (Day 169±5)
Scarring/Keloid Assessment			X
Record Adverse Event (AE) and Concomitant Medication (CM) Changes[7]	X	X	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. If two members of the same household qualify for study participation, they must be randomized on the same day.

[2]All visit dates are in reference to Baseline, e.g. Week 2 occurs 14 days after Baseline Visit.

[3]Females 9 years of age and older.

[4]BOTE Inflammation Score will be assessed pre-dose at Baseline, and post-dose from Visit 3 through Visit 6. LSRs will be performed post-dose at each applicable visit.

[5]DLQI will be administered for subjects age 16 and older. The CDLQI will be administered for subjects ages 4 to age 16. If a subject turns 16 during the course of the study, the CDLQI will continue to be administered for consistency.

[6]Study drug application will occur in clinic at each study visit, from Baseline through Visit 5. Subjects will not apply the study drug at home on days where a study visit will occur.

[7]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 Screening and Day 2.

NOTE: Unscheduled visits are permitted as needed for medical reasons.

5 POPULATION

5.1 Number of Subjects

Approximately 340 males and females, 6 months of age and older, with a minimum of 3 and a maximum of 70 lesions of MC at baseline will be randomized in a 2:1 (active:vehicle) scheme.

5.2 Inclusion Criteria

1. Be 6 months of age or older, and in good general health;
2. Have a written 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 at Baseline;
4. Female subjects age 9 and above must have a negative UPT at Baseline;
5. Female subjects age 9 and above must agree to practice a medically acceptable form of birth control during the study and for 30 days after their final study visit;
6. Be willing and able to follow study instructions and likely to complete all study requirements.

5.3 Exclusion 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);

6. Have received surgical procedures related to MC (cryotherapy, curettage, other) 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 sodium product (SB204, SB206, SB208, SB414);

11. Have more than 1 family member currently participating in a study with a berdazimer sodium product (SB204, SB206, SB208, SB414)

12. Have participated in any other trial of an interventional investigational drug or device within 14 days or concurrent participation in another interventional research study.

13. 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 (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 without first obtaining consent. A subject wishing to participate must give written 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 contract research organization (CRO) for approval prior to submission to an Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) as appropriate. 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 of the above activities must be completed before any study related procedures are conducted.

5.4.1 Screening Failures

A subject is considered screened once they have a signed ICF/assent and completed one screening assessment. A screen failure subject will be any screened subject who does not get randomized to a treatment arm. Subjects will be allowed to rescreen once.

5.5 Deviation from Inclusion/Exclusion Criteria

Deviation from the Inclusion/Exclusion Criteria is not allowed. Any deviation identified during the study should be discussed with the CRO and/or Novan.

6 STUDY CONDUCT

6.1 General Instructions

Prospective subjects as defined by the eligibility criteria (Inclusion/Exclusion Criteria) will be considered for entry into this study. Subjects' ICF/assent must be obtained prior to conducting any procedures. Some Baseline procedures (i.e., review of inclusion/exclusion criteria, brief physical exam, adverse event assessment, concomitant medication review, and UPT) 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 on the same day.

After the required procedures are completed and study eligibility is confirmed, the subject will be randomized to treatment utilizing an Interactive Web Response System (IWRS) which will identify the study drug to be dispensed to the subject. 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, and application should also be done in clinic at Week 2, Week 4, Week 8, and Week 12.

6.2 Study Procedures by Time Point

6.2.1 Screening (Day-14 to Day 1)

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 written ICF/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, 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.

6.2.2 Visit 1/Baseline (Day 1)

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. Complete age-matched Dermatology Life Quality Index (DLQI) assessment, as applicable.
2. Perform a brief physical examination.
3. Perform lesion mapping and lesion count.*
4. Perform BOTE Inflammation Score (pre-dose).
5. Obtain urine pregnancy test, as applicable. If pregnancy test is positive, the subject may not participate in the study.
6. Update concomitant medication information.

7. Confirm eligibility and randomize subject.
8. Dispense subject diary and study drug.
9. Weigh and record study product tubes.
10. Instruct subject on dispensing, mixing, and application of study product and diary completion.
11. Have subject/caregiver apply first dose in clinic from kit assigned at randomization.
12. Complete Local Skin Reaction assessment approximately 30 minutes post dose.
13. Collect and record AE information for any AEs reported.

6.2.3 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.

6.2.4 Visit 3/Week 2 (Day 15 ±3)

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

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

6.2.5 Visit 4/Week 4 (Day 29 ±5)

The following procedures must be performed and recorded at the Week 4 visit.

1. Obtain pregnancy test and evaluate results, as applicable. If pregnancy test is positive, the subject may continue in the study; however, study drug should be discontinued.
2. Perform lesion counts and update lesion map with location for any new lesions.
3. Assess for subject recurrence of MC.
4. Perform scarring/keloid assessment.
5. Weigh returned study drug and review study compliance.
6. Weigh, record, and dispense new supply of study product and dispense subject diary.
7. Review dosing instructions and have subject/caregiver apply daily dose in clinic using the newly dispensed kit.
8. Perform BOTE Inflammation Score (post-dose).
9. Perform Local Skin Reaction Assessment (post-dose).
10. Collect and record AE information for AEs reported.
11. Update concomitant medication information and confirm if any new occurrences of MC were reported in the subject's household.

6.2.6 Visit 5/Week 8 (Day 57 ±5)

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

1. Obtain pregnancy test and evaluate results, as applicable. If pregnancy test is positive, the subject may continue in the study; however, study drug should be discontinued.
2. Perform lesion mapping and update lesion map with location for any new lesions.
3. Perform scarring/keloid assessment.
4. Weigh returned study drug and review study compliance.
5. Weigh, record, and dispense new supply of study product and dispense subject diary.

6. Review dosing instructions and have subject/caregiver apply daily dose in clinic using the newly dispensed kit.
7. Perform BOTE Inflammation Score (post-dose).
8. Perform Local Skin Reaction Assessment (post-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.

6.2.7 Visit 6/Week 12/ET (Day 85 ±5)

The following procedures must be performed and recorded at the Week 12/ET1 visit.

1. Complete age-matched Dermatology Life Quality Index (DLQI) assessment, as applicable.
2. Obtain pregnancy test and evaluate results, as applicable.
3. Perform lesion mapping and update lesion map with location for any new lesions.
4. Perform scarring/keloid assessment
5. Perform a brief physical examination.
6. Subject/caregiver administer final dose of study drug from previously dispensed kit.
7. Perform BOTE Inflammation Score (post-dose).
8. Perform Local Skin Reaction Assessment (post-dose).
9. Weigh returned study drug and review study compliance.
10. Collect and record AE information for AEs reported.
11. Update concomitant medication information and confirm if any new occurrences of MC were reported in the subject's household.

6.2.8 Visit 7/Week 16 and Visit 8/Week 20 (Day 113 +/- 7 days; Day 141 +/- 7 days)

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. Update concomitant medication information.

6.2.9 Visit 9/Week 24 (Day 169 +/- 7 days)

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

1. Perform scarring/keloid assessment.

2. Collect and record information for new and ongoing AEs, including subject recurrence of MC.

3. Update concomitant medication information.

6.3 Discontinuation

6.3.1 Treatment Discontinuation

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.

In addition, the investigator may instruct the subject to temporarily halt treatment of a specified region (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 and eCRF. The lesions in the impacted area should continue to be counted in the lesion count during the period of treatment modification.

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.

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:

- Completed (complete clearance prior to Week 12)
- Adverse Event (including LSRs deemed to be significant by investigator)
- Withdrawal by Subject/Caregiver
- Physician Decision
- Protocol Violation
- Lost to Follow-Up
- Pregnancy
- Lack of Efficacy
- Worsening of Molluscum Contagiosum
- Other

6.3.2 Study Discontinuation

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, (i.e., prior to Week 12/ET1) every effort should be made to have the subject return to the study center to complete the Week 12 evaluations (ET1 visit). Subjects who withdraw from the study will not be replaced. Subjects who discontinue from the study after Week 12 but prior to Week 24 will be asked to return to the study center to complete the Week 24 evaluations (ET2 visit).

All subjects who fail to return to the study center 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 two documented attempts (one attempt on two different days), a certified letter will be sent requesting that the

subject contacts the investigator. 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.

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

All premature discontinuations and their causes must be carefully documented in the subject's study record and in the study database.

All Week 12 or Week 24 evaluations should be performed at the time of premature discontinuation as applicable. 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 appropriate 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:

- Completed Treatment Per Investigator's Instructions and Completed All Study Visits
- Withdrawal by Subject/Caregiver
- Lost to Follow-Up

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.

7 DESCRIPTION OF STUDY PROCEDURES

Study procedures and their timings are summarized in the Schedule of Assessments (refer to Table 1).

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 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 active 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.

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.

Definition of Clearance: For the purpose of this study, "clear" means resolution of the active (raised, palpable) treatable molluscum lesion(s). After resolution, the residual surface changes such as pitted scar (indentation) < 1 mm in depth at the molluscum lesion area (<5 mm in diameter), hyper or hypopigmentation may remain. As these are considered part of the normal healing, they will not be captured as adverse events. Refer to the lesion count training for details.

The same evaluator should perform lesion counts at Screening, Baseline, and Weeks 2, 4, 8 and 12/ET1. In the event that this is not possible due to unforeseen circumstances, a different evaluator may evaluate the subject. The evaluator must pass the study training including lesion count training. It is particularly important to ensure the same evaluator performs the Baseline and Week 12/ET1 for lesion count for a subject and also Baseline and Week 24/ET2 assessment for scarring/keloid scarring.

7.1.2 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) questionnaire is designed for use in adults (i.e., subjects aged 16 years and above). The questions are designed to be completed with a one week recall period. It is self-explanatory and can be simply handed to the subject who is asked to fill it in without the need for detailed explanation. It is usually completed in one to two minutes. The Children's Dermatology Life Quality Index (CDLQI) questionnaire is the DLQI that is adapted for use in children (i.e., subjects from age 4 up to age 16).

Both the DLQI and the CDLQI are calculated by summing the score of each question resulting in a maximum score of 30 and a minimum score of 0.

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/ET1. Any clinically significant changes in the physical exam from baseline will be recorded as AEs.

7.2.2 Pregnancy Testing

Urine pregnancy testing for females 9 years of age and older will be collected at Screening, Baseline, Week 4, Week 8 and Week 12/ET1. In addition to having a negative UPT at Baseline, before the first application of study drug, females 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: abstinence with a documented acceptable method of birth control if the subject becomes sexually active, oral contraceptives, contraceptive patches, contraceptive implant, vaginal contraceptive, double-barrier methods (e.g., condom and spermicide), contraceptive injection, Intrauterine Device (IUD), hormonal IUD, permanent contraception, same sex partner or partner who has had a vasectomy. Tubal ligation is not considered to be surgical sterilization; women with tubal ligations will be required to complete UPTs at the required timepoints.

7.2.3 BOTE Inflammation Score

Inflammatory reactions around the MC has been associated with imminent resolution of MC (sometimes referred to as “beginning-of-the-end” [“BOTE”] signs). In most cases, clinical features can differentiate between BOTE and LSR. 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. BOTE should not be considered an AE since this is part of normal disease progression.

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

7.2.4 Local Skin Reaction Score

The investigator (or designated evaluator) will assess localized skin reactions (LSRs) at Baseline (at least 30 minutes post-dose), and 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, 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. When LSRs are clinically significant in the opinion of the investigator, s/he should report the condition as an AE(s) (e.g. application site erythema, application site edema).

In the event of an LSR, the investigator may choose to initiate a drug holiday for the study drug for up to 2 weeks; treatment with corticosteroids may be ordered during the drug holiday at the investigator's discretion. For very severe LSR, systemic corticosteroids may be considered. The subject should be instructed how many days to hold study drug and site staff should phone the

subject on the planned day of resuming study drug to ensure that the LSR has resolved. If the LSR has not resolved, the drug holiday may be extended as long as the total period of withholding study drug does not exceed 2 weeks. If the LSR has resolved, the subject may resume treatment. If the LSR flares again after re-introduction of study drug, allergic contact dermatitis may be suspected. The subject may again be treated with up to 2 weeks of corticosteroids.

If allergic contact dermatitis is suspected, study drug should be discontinued permanently and an AE of allergic contact dermatitis should be recorded as the reason for discontinuation. Week 12/ET1 assessments should be completed at the time of discontinuation, but the subject should continue in the study and complete study-related visits through Week 24.

Patch testing (see Section 7.2.5 and Section 20.2) should be offered to the subject.

LSR Score

	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

7.2.5 Patch Testing

In the event that a subject has an LSR that is felt to be suggestive of allergic contact dermatitis, patch testing may be initiated to confirm. This should be offered to 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. Novan will provide the patch testing instruction 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 has been assignment was > than 60 days of the patch testing date(s).

If allergic contact dermatitis is suspected, study drug should be discontinued permanently and an AE of allergic contact dermatitis should be recorded as the reason for discontinuation. Week 12/ET1 assessments should be completed at the time of discontinuation, but the subject should continue to participate in the study and complete study related visits through Week 24.

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 prior to initiating patch testing.

See Section 20.2 for further information.

7.2.6 Scarring/Keloid Assessment

Scar formation will be assessed starting at the Week 4 visit through Week 12, and again at Week 24. For the purposes of this study, scar is defined as follows: pitted scars with ≥ 5 mm in diameter or ≥ 1 mm in depth, and hypertrophic/keloid scars originated from MC lesion. Pitted scars < 5 mm in diameter and < 1 mm in depth originated from MC lesion are considered part of normal healing process and will not be captured as AEs.

7.3 Protocol Deviations

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 by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and the CRO.

8 STUDY DRUG MANAGEMENT

8.1 Description

8.1.1 Formulation

Investigational Drug: SB206 12%	Comparator Drug: Vehicle Gel
Dosing: Up to approximately 2mL of SB206 QD	Dosing: Up to approximately 2mL of Vehicle Gel QD

8.1.2 Storage

Upon receipt from Novan, or Novan's designee, a study staff member will place all study supplies in a refrigerated temperature-controlled and monitored area. The SB206/Vehicle study product should be refrigerated (2-8°C/36-46°F) until dispensed.

Access to study supplies should be strictly limited to the study staff. Neither the investigator nor any member of the study staff will distribute any of the study supplies to any person not participating in this study.

If a study staff member becomes aware that the study supplies have not been properly handled (i.e., supply arrives and was not placed in refrigerator upon receipt or there is a temperature excursion during shipment), the CRO must be contacted immediately. In such an event, study supplies should be quarantined and not be administered to any subject until Novan or Novan's designee provides further direction.

It is expected that the site staff will maintain refrigerator temperature logs in the refrigerated study drug storage area, recording the temperature at least once each working day. Excursions in temperature during storage should be discussed with the CRO immediately and study supplies should be quarantined and not administered until Novan provides approval for use. Other supplies will be stored at room temperature.

The study drug will be dispensed at the discretion of and by the direction of the designated study personnel in accordance with the conditions specified in this protocol. It is the investigator's responsibility to ensure that accurate records of study drug dispensing and return are maintained.

8.2 Packaging and Shipment

Novan, or designee, will provide all study drug to the sites. Sites are required to maintain all records of shipment and receipt in the Investigator Site File.

8.3 Method of Assigning Subjects to Treatment Groups

In this randomized, double-blind, vehicle-controlled study, subjects who meet study entry criteria will be randomly assigned in a 2:1 ratio (active: vehicle). The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central IWRS as subjects are entered into the study. At randomization, subjects will be stratified into four strata corresponding to the cross-classification of household number of randomized subjects (1 subject per household vs 2 subjects per household) and investigator type (dermatologist vs other). Households randomizing 2 subjects would receive the same treatment assignment for both subjects. Approximately 340 subjects, 6 months of years of age and older, with a minimum of 3 and a maximum of 70 lesions at Baseline will be randomized.

8.4 Blinding and Unblinding Treatment Assignment

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.

When approximately 200 subjects (cumulative across studies NI-MC302 and NI-MC302) have completed 4 weeks of treatment, a DSMB will review all available unblinded safety data (including patch testing). Personnel who are not otherwise involved in the study will prepare the unblinded data and summary tables for this analysis.

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

8.5 Dose and Administration

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 clinic visit, the treatment may stop. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24/ET2.

An increase in the number of MC lesions (with or without inflammatory reaction) during the early treatment phase 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 and applied to the lesions and approximately 1 cm surrounding each lesion. 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.

At the investigator's discretion, the subject may be placed on a drug holiday for up to 2 weeks at a time in the event of a significant local skin reaction (LSR). This will be captured in the electronic data capture (EDC) system and the subject's diary. The investigator should instruct the subject how long to hold study drug and the planned date to re-start treatment. Site staff should contact the subject on the day of the planned re-start and assess whether the LSR has resolved enough to resume treatment. If it has not resolved sufficiently, the drug holiday may be extended as long as the entire extension has not exceeded 2 weeks. If the LSR flares after re-introduction of study drug, the study drug should be permanently discontinued and the EDC system updated appropriately. Please see Section 7.2.4 for additional information.

8.6 Accountability

The dispensing and return of all study drug will be recorded on a dispensing log. The subject number/initials, and the initials and date of the person dispensing and receiving the returned medication will be documented on this form. All study product will be weighed at the time it is dispensed and when it is returned. The tube weights will be recorded in the electronic case report form (eCRF).

Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

Study drug returned by subjects at will be held on site until accountability has been completed. The site will be instructed on return or destruction of used and unused clinical supplies.

8.7 Prohibited Concomitant Medication/Therapy

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.

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 (cryotherapy, curettage, other) are prohibited during the study.

8.8 Compliance

Subjects will be provided a diary to record doses. Review of subject compliance will be conducted at each visit and missed doses recorded on the subject diary will be recorded on the eCRF.

No reconciliation will be performed on the diary compliance against the tube weights. Subject compliance will be based on calculation from the missed doses recorded from the subject diary only.

9 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. 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?*" Adverse events will be assessed and reported after the subject is dosed, beginning from Baseline through the end of the subject's 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. Treatment-related

adverse events will be followed up until resolution or up to one year after last treatment, whichever occurs earlier.

9.1 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 related SAEs to the Sponsor 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, 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) and scarring (pitted scars ≥ 1mm in depth), scars that are larger than the original MC and/or extend outside the treatment area, and hypertrophic/keloid scars will be captured as adverse events.

9.2 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

The investigator will follow all subjects who experience AEs as described in Section 9.4.

9.3 Assessment of Causality

Relationship of each AE to study drug must be assessed.

Several factors should be considered when assessing the relationship (causality) of an event to the study drug or administration of the study drug.

- Alternative etiology – Is the event due to an underlying disease/condition being treated or to another known, underlying disease/condition of the participant?

- Known relationship – Has the event been observed before in participants treated with this product or similar products?

- Temporal relationship – Is there a reasonable temporal relationship between the time of onset for the event and the administration of the study drug?

- Concomitant medication – Is the event a known side effect of a concomitant medication?

Per the Council for International Organizations of Medical Sciences (CIOMS) VI working group, the use of "cannot-be-ruled-out" to imply drug relatedness will lead to excessive over-reporting and excess noise in the system. It is virtually impossible to completely rule out the role of a drug in causing an adverse event in single-case reporting. Differentiating from the procedural causes may also be difficult. Hence, the review of aggregated controlled data is an important component for the determination of the safety profile of any investigation product. Aggregate review is completed by the Sponsor.

Therefore, given the above, 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 the table below:

Assessment of Causality	
Reasonable possibility: classification includes definitely, probably (likely), possibly 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.
No reasonable possibility: classification includes definitely not, probably not, unlikely related 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

The causal relationship will be recorded on a binary scale by answering yes or no the following questions: is there a reasonable possibility of a causal relationship between the study drug and the AE? The phrase "reasonable causal relationship" means to convey, in general, that there are facts, evidence or argument that support a causal relationship to the study drug.

9.4 Adverse Event Follow-up

9.4.1 Follow-Up of Non-Serious Adverse Events

Non-serious 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. No further follow-up will occur for any AEs that are not related to the study drug unless this is required by a health authority or the Medical Monitor.

Treatment related adverse events, including LSRs, pitted scars ≥ 5 mm in diameter or ≥ 1mm in depth originated from MC lesion and hypertrophic scars/keloid, will be followed up until resolution or up to 1 year after last treatment, whichever is sooner.

9.4.2 Follow-Up of Post Study Serious Adverse Events

Serious adverse events that are identified on the last scheduled contact (Week 24/ET2) must be recorded in the study database and reported to the CRO according to the reporting procedures outlined in Section 10. This may include unresolved previously reported SAEs, or new SAEs. The investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-

up. The investigator should continue to report any significant follow-up information to the Sponsor and the IRB up to the point the event has been resolved. 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.

9.5 Pregnancy

Females 9 years of age and older must use an effective method of birth control during the course of the study and for 30 days following their final study visit. The following are considered acceptable methods of birth control for this study: abstinence with a documented acceptable method of birth control if the subject becomes sexually active, oral contraceptives, contraceptive patches, contraceptive implant, vaginal contraceptive, double-barrier methods (e.g., condom and spermicide), contraceptive injection, Intrauterine Device (IUD), hormonal IUD, permanent contraception, same sex partner or partner who has had a vasectomy. Tubal ligation is not considered to be surgical sterilization; women with tubal ligations will be required to complete UPTs at the required timepoints.

A female is considered to be of childbearing potential unless she is post-menopausal (no menses for 24 consecutive months), surgically sterilized (documented hysterectomy, documented bilateral salpingectomy, documented bilateral oophorectomy) or under 9 years of age. Tubal ligation does not meet the definition of surgically sterile.

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 9 years of age and older 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 stop study drug treatment, continue with study visits through Week 24 and follow up with pregnancy outcome. Beyond Week 24, 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 anomaly/birth defect/ etc. are considered SAEs and require separate reporting per Section 10.)

9.6 Overdose

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 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

- Death

- Life-threatening event (i.e., the subject was at immediate risk of death from the event as it occurred. It does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.)

- Inpatient hospitalization or prolongation of existing hospitalization (AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything,

untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.)

- Persistent or significant disability/incapacity (if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions)

- Congenital anomaly/birth defect in the offspring of a subject who received SB206 or Vehicle Gel

- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

  - Intensive treatment in an emergency room or at home for allergic bronchospasm

  - Blood dyscrasias or convulsions that do not result in inpatient hospitalization

  - Development of drug dependency or drug abuse

10.2 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 safety office 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 share the same end date.

11 STATISTICS

11.1 General Procedures

The study treatment period is defined from randomization through completion of Week 12/ET1 visit and the safety follow-up period is from the completion of Week 12 through the completion of Week 24/ET2 visit.

After all subjects have completed their Week 12/ET1 visit, thus completing the Treatment Period of the study, the database through Week 12/ET1 will be frozen and unblinded for purposes of the primary analysis of efficacy and safety. While this analysis is being prepared, the subjects will continue through Week 24/ET2. After all subjects have completed their Week 24/ET2 visit, the database will be locked and the follow-up data will be analyzed. Prior to unblinding and the primary analysis of efficacy and safety, a detailed, finalized SAP will be completed and placed on file. The Statistical Analysis Plan will contain a more comprehensive explanation than that provided here of the methodology used in the statistical analyses, as well as the rules and data handling conventions used to perform the analyses and the procedure used to account for missing data.

Safety and efficacy endpoints will be displayed using descriptive statistics and graphical displays, where applicable. For categorical variables, frequencies, and percentages will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum). Where relevant, 95% confidence intervals will be calculated. Any statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and nominal p-values will be reported.

11.2 Sample Size

Approximately 340 subjects, 6 months of years of age and older, with a minimum of 3 and a maximum of 70 lesions at Baseline will be randomized in a 2:1 (active:vehicle) scheme. The sample size assumptions for this study were informed by the completed Phase 2 study NI-MC201 of subjects ≥2 years of age with 3-70 MC lesions at Baseline. In the ITT population of the Phase 2 study, the observed rates of clearance at Week 12 were 18% (12/66) for vehicle and 38% (18/48) for SB206 12% once daily (QD) and the covariate-adjusted treatment difference was 18%.

A sample size of 340 subjects (227 subjects in the SB206 12% QD group and 113 subjects in the vehicle group) will provide 94% power for a 2-sided alpha test of size 0.05 to detect an absolute difference of 18% when the vehicle response rate is 18%. This same sample size provides 93% power to detect a treatment difference of 18% when the vehicle response rate is 20% and 83% power when the treatment difference is 15% and the vehicle response rate is 20%.

11.3 Analysis Populations

The analysis populations include the following:

Safety Population: The Safety population will consist of all subjects who receive at least one application of study medication.

Intent-To-Treat Population (ITT): The ITT population will consist of all subjects who are randomized.

Per-Protocol Population (PP): The PP population will consist of all subjects in the ITT population. who had no significant protocol deviations that impacted the analyses of the efficacy endpoints.

12 STATISTICAL METHODS

12.1.1 Demographic and Baseline Characteristics

Subject demographic and Baseline characteristics will be summarized by treatment group for the SAF, ITT, and PP populations. Relevant medical history, current medical conditions, and any other relevant information will be listed by subject.

12.1.2 Efficacy Analysis

The primary efficacy endpoint, proportion of subjects with complete clearance of all treatable molluscum lesions at Week 12 in the ITT, 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), household number of randomized subjects (1 subject per household vs 2 subjects per household), age and Baseline lesion count as factors. The odds ratio between SB206 12% and vehicle gel, 95% CIs for the odds ratio, and *P*-value for the covariate-adjusted treatment comparison will be presented. Only subjects who achieve complete clearance at Week 12 will be counted as responders for the primary analysis; all other subjects (e.g., those who discontinue the study before achieving complete clearance) will be reported as failures. As a sensitivity analysis, the primary efficacy analysis will also be reported for the PP population.

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

- Proportion of all study subjects demonstrating complete clearance of all treatable MC at Week 8

If the secondary efficacy endpoint fails to reach statistical significance at the alpha=0.05 level, it will be considered not statistically significant.

The dichotomous secondary efficacy endpoint will be analyzed using the GEE model described for the primary efficacy endpoint. Other sensitivity analyses may be performed and will be specified in the SAP.

The analyses methods to be used for the exploratory endpoints will be detailed in the SAP, including any additional exploratory analyses that may be conducted. The SAP will be finalized before unblinding and database lock.

12.1.3 Analysis of Safety

12.1.3.1 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs that occurred any time on or after the first in-clinic application of study drug through the last application of study medication. Medical history noted prior to the first study drug administration that worsen after Baseline will also be reported as AEs and included in the summaries.

Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, System Organ Class (SOC), preferred term, severity, relationship to study drug (causality), and seriousness. When summarizing AEs by severity and relationship, each subject will be counted only once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs will be summarized by treatment group, severity, and relationship to study drug, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

12.1.3.2 Physical Examination

Changes in physical examination from baseline to end of treatment will be summarized. Any clinically significant changes from Baseline will be documented as an AE.

12.1.3.3 Urine Pregnancy Tests

Urine pregnancy tests results for females 9 years of age and older will be presented in data listings by subject.

13 ETHICS AND RESPONSIBILITIES

13.1 Good Clinical Practice

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 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 knowledge, it accurately describes the conduct and results of the study.

13.2 Data Safety Monitoring Board (DSMB)

When approximately 200 subjects (cumulative across studies MC301 and MC302) have completed 4 weeks of treatment, a Data Safety Monitoring Board (DSMB) will review all available unblinded safety data (including patch testing). All responsibilities of the DSMB and details of data to be reviewed will be detailed in the DSMB charter.

13.3 Institutional Review Board/Independent Ethics Committee

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.

13.4 Informed Consent

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. 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 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.

13.5 Records Management

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 – Essential Documents for the Conduct of a Clinical Trial of the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance and 21 CFR Part 312.

13.6 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.

13.7 Study Files and Record 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.

14 AUDITING AND MONITORING

14.1 Auditing

In addition to the routine monitoring procedures, audits of clinical research activities in accordance with standard operating procedures (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, investigational product, original, study-relevant medical records). All subject data will be treated confidentially.

14.2 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 C.F.R. § 50.20, 1999), and Institutional Review Board regulations, (21 C.F.R. § 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 C.F.R. § 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 visit the site regularly to check 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 center. 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 CRO and the responsible IRB with a study summary shortly after study completion.

15 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Novan. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Novan will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Novan, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

16 STUDY REPORT AND PUBLICATIONS

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.

17 STUDY DISCONTINUATION

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.

18 CONFIDENTIALITY

All information 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 written consent is gained from Novan. However, authorized regulatory officials, IRB/IEC personnel, Novan and its authorized representatives are allowed full access to the records.

Subject's 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.

19 REFERENCES

1. Chen X, Anstey AV, Bugert JJ. Molluscum contagiosum virus infection. Lancet Infect Dis **2013**; 13: 877–88.
2. Dohil M, Lin P, Lee J, Lucky AW, Paller AS, Eichenfield LF. The epidemiology of molluscum contagiosum in children. J Am Acad Dermatol **2006**; 54: 47-54.
3. Olsen, JR, Gallacher, J, Piguet, V, and Francis, NA. Epidemiology of molluscum contagiosum in children: a systematic review. Fam Pract. **2014**; 31: 130–136.
4. 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: 190–95.
5. 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.
6. 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.

20 APPENDICES

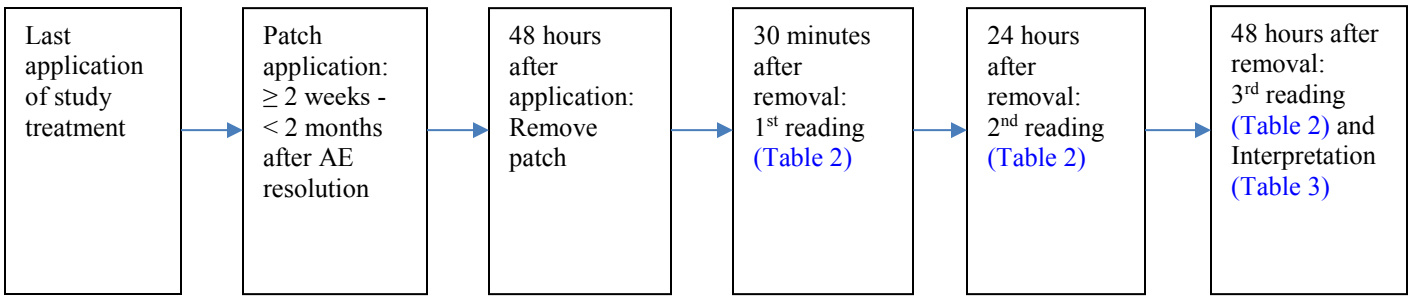
20.1 APPENDIX I Names of Study Personnel

Sponsor:	Novan, Inc. 4105 Hopson Road Morrisville, NC 27560
Clinical Research Organizations:	Synteract 5909 Sea Otter Place Carlsbad, CA 92010
Safety Number or Contact Email:	Tel: (760) 268-8080 Fax: (760) 268-6500 Email: SafetyFax@Synteract.com

20.2 APPENDIX II Procedure for Suspected Sensitization

In the event that a subject has a local skin reaction (LSR) severe enough that is felt to be suggestive of allergic contact dermatitis, patch testing may be initiated for confirmation after consultation with the CRO Medical Monitor and with the consent of the subject/caregiver. 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.

For patch testing:



- Discontinue study treatment (see Section 7.2.4 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 below (Table 2). If the 48-hour reading is equivocal, it is recommended to evaluate the site at 72 to 96 hours after removal. Take photographs if the reaction interpretation is positive or equivocal 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. See Table 3 below.

Table 2: Grading System for Patch Test Reactions

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 3: Challenge Reaction Interpretation

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

16.1.9 DOCUMENTATION OF STATISTICAL METHODS

This appendix includes

Document	Version, Date
Statistical Analysis Plan	Version 1.0, 16 August 2019
Statistical Analysis Plan	Version 2.0, 11 September 2019
Statistical Analysis Plan	Version 3.0, 18 November 2019

Statistical Analysis Plan

Novan, Inc.

NI-MC301

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 Version: 26Mar2019

Sponsor: Novan, Inc.
4105 Hopson Road
Morrisville, NC 27560

Prepared by: Christopher Tait
5909 Sea Otter Place, Suite 100
Carlsbad, CA 92010

Version	Date
Version 1	16 Aug 2019

Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
Tait, Christopher Senior Biostatistician I approve this document 19 Aug 2019 15:46:54 -05:00 cosign Christopher Tait, PhD Senior Biostatistician Synteract	19AUG2019
David Hebert, PhD Senior Director, Head of Biometrics Novan, Inc.	19AUG2019

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full Notation
AE	adverse event
ATC	anatomical/therapeutic/chemical
BOTE	beginning of the end
CDLQI	Children's Dermatology Life Quality Index
CRO	contract research organization
DLQI	Dermatology Life Quality Index
DSMB	data safety monitoring board
eCRF	electronic case report form
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LSR	local skin reaction
MC	molluscum contagiosum
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
QC	quality control
QD	once daily
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Novan, Inc. protocol version 1.0 [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]. The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report.

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol version 1.0, 26Mar2019
- Annotated electronic case report form (eCRF) version 3.0, 14Aug2019
- Data management plan version 1.0, 12Apr2019

3. STUDY OBJECTIVES

The objective of the study is to evaluate the efficacy and safety of SB206 12% once daily (QD) for the treatment of molluscum contagiosum (MC).

4. STUDY DESIGN AND PLAN

This is a Phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in approximately 340 subjects ≥6 months of age with MC. After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized to a 2:1 (active:vehicle) scheme. Subjects receiving current treatment for MC at the time of the Screening Visit will enter a washout period of up to 14 days prior to randomization. In the event no washout period is required, Screening and Baseline visit activities may be combined into a single visit. At randomization, subjects will be stratified into 4 strata corresponding to the cross-classification of household number of randomly assigned subjects (1 subject per household vs 2 subjects per household) and investigator type (dermatologist vs other). Households randomizing 2 subjects will receive the same treatment assignment for both subjects. Up to 2 subjects from the same household may be randomly assigned on the same day, if both individually meet all inclusion and exclusion criteria. For subjects in the same household, Screening can occur on different days; however, the baseline visit must occur on the same day.

Subjects or their caregivers will apply SB206 12% or Vehicle Gel QD for a minimum of 4 weeks and 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. If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. At Weeks 2, 4, 8 and 12, the investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. At Weeks 2, 4,

and 8, the investigator will determine if new lesions have occurred since the last visit, and the subject or caregiver will be instructed by the investigator to re-initiate treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24.

Subjects will visit the clinic at Screening/Baseline, Week 2, Week 4, Week 8, Week 12, and Week 24. 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 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. No study drug treatment will be provided after the Week 12 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 will be recorded as an ET2 visit.

Safety assessments include local skin reactions (LSRs), AE collection, including scarring/keloid, and urine pregnancy tests. Safety assessments will be completed at specified site visits through Week 12. After Week 12, safety information for ongoing AEs and new AEs will be collected, along with information regarding household MC occurrence.

Inflammatory reactions around the MC 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 (before dosing) and Weeks 2 through 12. 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, and 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. BOTE Inflammation Score and LSR score will be recorded at each visit. BOTE should not be considered an AE. When LSRs are clinically significant at the application site, the investigator should report the condition as an AE(s).

At Baseline (at least 30 minutes after dosing) and Weeks 2 through 12, the investigators will rate LSRs on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. At Baseline (pre-dose) and Weeks 2 through 12, the investigators will rate BOTE signs using the BOTE Inflammation Score.

The following tables describe the scoring parameters for the BOTE Inflammation Score and LSR score.

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

LSR Score

Score	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

Clinically significant LSRs that are reported as AEs 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 of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. The investigator may take photographs of the suspected allergic contact dermatitis and discuss possible confirmation of allergic contact dermatitis with the contract research organization's

(CRO) medical monitor. 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 with the CRO's medical monitor to implement 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 AEs will be followed up until resolution or up to 1 year after last treatment, whichever is sooner.

Scar formation will be assessed starting at the Week 4 visit through Week 12 and again at 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. The investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. If a new scar is noted after the subject treated with study drug, this will be considered an AE for the purposes of this study. In addition, keloid/hypertrophic scars will also be recorded as AEs.

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.

When approximately 200 subjects (cumulative across studies MC301 and MC302) have completed 4 weeks of treatment, a data safety monitoring board (DSMB) will review all available unblinded safety data (including patch testing).

5. DETERMINATION OF SAMPLE SIZE

Approximately 340 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 2:1 (active:vehicle) scheme. The sample size assumptions for this study were informed by the completed Phase 2 study NI-MC201 of subjects 2 years of age and older with between 3 and 70 MC lesions at Baseline. In the Intent-to-Treat (ITT) Population of the Phase 2 study, the observed rates of complete clearance at Week 12 were 18% (12/66) for vehicle and 38% (18/48) for SB206 12% QD and the covariate-adjusted treatment difference was 18%.

A sample size of 340 subjects (227 subjects in the SB206 12% QD group and 113 subjects in the vehicle group) will provide 94% power for a 2-sided alpha test of size 0.05 to detect an absolute difference of 18% when the vehicle response rate is 18%. This same sample size provides 93% power to detect a treatment difference of 18% when the vehicle response rate is 20% and 83% power when the treatment difference is 15% and the vehicle response rate is 20%.

Since the intra-cluster correlation is estimated to be small (<10%) and the average size of households is expected to be capped at roughly 1.3, the sample size is still sufficient when considering the fact that the subjects within the household may not be independent.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated *P*-value is ≤0.05.

Continuous variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Other statistics such as quartiles, confidence intervals (CIs), and number of missing values may be added as appropriate.

Categorical variable summaries will include the frequency and percentage of subjects who are in the category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population within each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

All summary tables will be presented by treatment group. Baseline summaries will also include an overall summary column.

Individual subject data obtained from the eCRFs and any derived data will generally be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to breaking the blind.

Any analyses performed subsequent to breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the clinical study report.

All analyses and tabulations will be performed using SAS® software Version 9.4 or higher. Tables, listings, and figures will be presented in RTF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS programming quality control." Study-specific QC requirements can be found in Appendix C: SAS Programming QC Requirements.

7. NOTATION OF TREATMENT GROUPS AND VISITS

Analysis visits

Baseline is defined as the last nonmissing value recorded prior to the first application of study drug. If time is not recorded and the assessment was on the same day as the first application of

study drug, then it will be assumed the assessment occurred prior to the application of study drug. The baseline record will have an analysis visit of "Baseline".

For all evaluations of all parameters, assessments will be analyzed according to the visit at which they occurred (i.e., per the eCRF visit label). In order to account for the fact that the Week 12 and Early Termination visits are collected on the same eCRF in the database, a check against the Study Exit form will be made to determine if the visit is a Week 12 or an Early Termination Visit. If the visit is an Early Termination visit, then the visit will be mapped according to the table below. If there is no corresponding Study Exit form on the same date, then it will be considered a Week 12 visit. However, if there is no assessment in a given visit, then the following visit windows will be applied to determine if an unscheduled visit may be used:

Visit	Analysis Visit	Target Study Day	Study Day Analysis Window
Week 2 (±3 days)	Week 2	15	Day 12 to 22
Week 4 (±5 days)	Week 4	29	Day 23 to 43
Week 8 (±5 days)	Week 8	57	Day 44 to 71
Week 12 (±5 days)	Week 12	85	Day 72 to 98

Days are measured from the date of randomization. Study days corresponding to measurements are calculated as:

- Assessment date – date of randomization + 1, if assessment date is on or after the date of randomization.
- Assessment date – date of randomization, if measurement date is before the date of randomization.

In the event of multiple unscheduled records falling in the same analysis window, the assessment which is closest to the target study day will be chosen for analysis.

8. ANALYSIS POPULATIONS

The following subject population will be used for disposition analyses:

- The Enrolled Population will consist of all subjects who sign informed consent. If a subject is randomly assigned to a treatment, then treatment assignment will be based on randomized treatment; otherwise, they will be deemed a screen failure and will only appear in the overall summary columns of output.

The following subject population will be used for safety analyses:

- The Safety Population will consist of all subjects who receive at least 1 application of study medication. Treatment assignment will be based on the treatment actually received. If a subject receives any amount of SB206, then they will be summarized in the SB206 12% QD arm.

The following subject populations will be used for efficacy analyses:

- The ITT Population will consist of all subjects who are randomized. Treatment assignment will be based on the randomized treatment.
- The Per-Protocol (PP) Population will consist of all subjects in the ITT Population who had no significant protocol deviations that impacted the analyses of efficacy endpoints. Final determination of subject inclusion in the PP Population will be made prior to unblinding. Treatment assignment will be based on the randomized treatment.

9. STUDY POPULATION

9.1 Subject 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 (defined as having an end of treatment reason of "Completed Treatment Per Protocol" or a reason of "Complete Clearance Prior to Week 12" and does not have a Study Exit date prior to the subject's), the number of subjects completed the study, and the primary reason for discontinuation.

A summary of the number of subjects in each center and each population will be presented.

9.2 Eligibility

A listing of subjects not fulfilling any eligibility criteria will be created.

9.3 Demographic and Baseline Characteristics

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

Other baseline characteristics include lesion counts at baseline, site type (dermatologist vs other), number of sites and a breakdown of site type, number of randomly assigned subjects in household (1 subject vs 2 subjects), number of households and breakdown of household size, age at diagnosis of the current molluscum episode and time since diagnosis. Descriptive statistics will be presented for ages and other continuous variables. Frequency counts and percentages will

be presented for sex, ethnicity, race and other categorical variables. Demographic and baseline characteristics will be summarized for the Safety, ITT, and PP Populations.

9.4 Extent of Exposure

Study drug exposure will be summarized for each treatment using the total number of applications, the duration of treatment, and the number of subjects requiring a treatment interruption and modification. Duration of treatment is defined as the last application date minus the first application date plus 1.

Study drug compliance will be summarized and calculated as follows:

Compliance [%] = (Actual applications applied)/(Planned applications) ×100, where

- Actual applications applied = Planned applications – the number of applications missed
- Planned applications = Number of applications (days) planned up to the point of treatment discontinuation.

This implies that if a subject treatment discontinues treatment prior to Week 12 due to complete clearance, then the number of applications takes this information into account and the subject is not penalized for having complete clearance.

Compliance will be further summarized into 2 groups:

1. Subjects who did not have any interruptions or modifications using the same formula as above, and
2. Subjects with modifications or interruptions. For these subjects, an adjusted compliance will be calculated in the following manner: the actual applications applied will be the same as above but the planned applications will exclude the time where the subject has dosing interrupted.

9.5 Protocol Deviations

Significant protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock and unblinding of individual subject treatment information. Significant protocol deviations may include, but are not limited to:

- Randomly assigned subjects who did not satisfy selected inclusion and exclusion criteria
- Randomly assigned subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who were randomized incorrectly including subjects of the same household who are randomized to different treatments
- Subjects who received the wrong treatment
- Subjects where the subject/site staff were unproperly unblinded

- Week 12 Lesion Count not performed
- Subjects who received an excluded concomitant treatment.

The decision whether a subject is excluded from the PP Population will be made during the data review meeting prior to unblinding and database lock. Reasons for exclusion of a subject from the analysis and protocol deviations will be listed.

A listing of all protocol deviations including the deviation designation (major or minor and significant or not), category, and indication of whether the deviation led to an exclusion of a subject from the PP Population will be presented in a data listing.

Major and significant protocol deviations will be summarized by deviation category and treatment group.

9.6 Medical History

Medical history verbatim terms in the eCRFs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. Subject incidence of unique medical history terms by MedDRA system organ class and preferred term will be presented. The summary will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

9.7 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to anatomical/therapeutic/chemical (ATC) class and preferred names using the WHODrug Global B3 (version March 2019). Prior medications are those medications started prior to the first application of study drug. Concomitant medications are those medications started on or after the date of first application of study drug or medications started prior to initial application of study drug and continued during the study. A medication can be classified as both prior and concomitant. If it cannot be determined whether the medication was a prior (or concomitant) medication due to a partial start or stop date, then it will be counted as both prior and concomitant; see Appendix B for the imputation of missing dates algorithm.

Prior and concomitant medications will be summarized for each treatment by WHODrug Global ATC class Level 3 and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

10. EFFICACY ANALYSES

The primary efficacy analysis will be based on the ITT Population. Additional supportive efficacy analyses will be performed using the PP Population.

10.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects with complete clearance of all treatable MC at Week 12.

The secondary efficacy endpoint is the proportion of subjects with complete clearance of all treatable MC at Week 8.

Complete clearance is defined as having a total number of lesions count of 0.

The exploratory endpoints are the following:

- Proportion of subjects with complete clearance of all treatable MC at Week 2 and Week 4 visits
- Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)
- Percent change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed, defined as the total lesion count being greater than 0 at any point after achieving a count of 0
- Time to complete clearance of all treatable MC, defined as the days between the date of first dose and the first date of clearance. Subjects who do not achieve complete clearance will be censored at the date of the last lesion count assessment.
- Proportion of subjects with scarring, defined as an answer of Yes to either question on the Scarring/Keloid Assessment eCRF page: “Was the presence of a scar > 1 mm deep and/or 5 mm wide noted?” or “Was the presence of a scar noted?”, after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Proportion of subjects with keloid or hypertrophic scar, defined as an answer of Yes to the Scarring/Keloid Assessment eCRF page question “Was the presence of a keloid or hypertrophic scar noted?”, after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Change from Baseline of the composite score from age-matched (at Baseline) Dermatology Life Quality Index (DLQI) or Children’s Dermatology Life Quality Index (CLDQI) assessment at Week 12

- 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, 16, 20, 24)

10.2 Baseline Values

Unless otherwise noted, baseline is defined as the last nonmissing value recorded prior to the first application of study drug. If time is not recorded and the assessment was on the same day as the first application of study drug, then it will be assumed the assessment occurred prior to the application of study drug.

10.3 Adjustments for Covariates

The model for the primary efficacy will include adjustments for the following covariates: investigator type (dermatologist vs other), household number of randomized subjects (1 subject per household vs 2 subjects per household), age, and baseline lesion count.

10.4 Handling of Dropouts or Missing Data

In analyses based on response, a missing response will be considered a nonresponder.

For a sensitivity analysis, subjects with missing lesion count at Week 12 but who demonstrated complete clearance at the last collected lesion assessment will be counted as responders.

10.5 Interim Analysis and Data Monitoring

When approximately 200 subjects (cumulative across studies NI-MC301 and NI-MC302) have completed 4 weeks of treatment, a DSMB will review all available unblinded safety data (including patch testing). All responsibilities of the DSMB and details of the analysis and data to be reviewed is detailed in the DSMB charter.

10.6 Examination of Subgroups

Subgroup analyses of complete clearance at Week 12 for investigator type (dermatologist vs other) and household number of randomized subjects (1 subject per household vs 2 subjects per household), and will be presented in a forest plot for the ITT Population. An additional subgroup analysis of complete clearance at Week 12 for age (≤1 year old, >1 to ≤2 years old, >2 to ≤6 years old, >6 to ≤12 years old, >12 to ≤18 years old, >18 years old) and MC disease duration prior to baseline (≤6 months vs >6 months) will be summarized descriptively for the ITT Population.

10.7 Multiple Comparison/Multiplicity

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

endpoint will be considered not significant. If the primary endpoint is statistically significant at the alpha=0.05 level, then the secondary efficacy endpoint will be analyzed. If the secondary efficacy endpoint fails to reach statistical significance at the alpha=0.05 level, it will be considered not statistically significant.

10.8 Multicenter Studies

This is a multicenter study, having approximately 35 centers participating in the study. The center effects will be investigated in the primary statistical analysis model.

11. METHODS OF EFFICACY ANALYSIS

11.1 Primary Efficacy Analysis

The primary efficacy comparison will test the following hypotheses:

H_0: The proportion of subjects with complete clearance is equal between SB206 12% QD and Vehicle;

H_1: The proportion of subjects with complete clearance is different between SB206 12% QD and Vehicle.

The primary efficacy model will be the following for π_{H_i} as the probability of complete clearance for the i^{th} subject in household H:

$$\pi_{H_i} = \frac{e^{(\beta_0+\beta_1*X_{H_{i1}} + \beta_2*X_{H_{i2}} + \beta_3*X_{H_{i3}} + \beta_4*X_{H_{i4}} + \beta_5*X_{H_{i5}})}}{1 + e^{(\beta_0+\beta_1*X_{H_{i1}} + \beta_2*X_{H_{i2}} + \beta_3*X_{H_{i3}} + \beta_4*X_{H_{i4}} + \beta_5*X_{H_{i5}})}}$$

where H = Household, i = subject within the household, β_0 is the intercept,

$$X_{H_{i1}} = \begin{cases} 1, if\ treatment\ is\ SB206 \\ 0, if\ treatment\ is\ Vehcile \end{cases}$$

$$X_{H_{i2}} = \begin{cases} 1, if\ subject\ is\ from\ a\ 2\ subject\ household \\ 0, if\ subject\ is\ from\ a\ 1\ subject\ household \end{cases}$$

$$X_{H_{i3}} = \begin{cases} 1, if\ subject\ is\ from\ a\ Dermatology\ site \\ 0, if\ subject\ is\ from\ an\ Other\ site \end{cases}$$

$X_{H_{i4}}$ is the subject's baseline lesion count, and $X_{H_{i4}}$ is the subject's age at baseline; treatment will be included in the class statement with PARAM=REF and REF=Vehicle. The working correlation will have an exchangeable structure. The model will include a repeated statement for subject household with household ID in the class statement. Also, the data structure will be ordered according to household ID and subject ID in household.

Treatment groups will be compared using a generalized estimating equation for logistic regression with an exchangeable working correlation structure. The model will include treatment, investigator type (dermatologist vs other), household number of randomly assigned subjects (1 subject per household vs 2 subjects per household), age, and baseline lesion count as factors. The odds ratio between SB206 12% and vehicle gel, 95% confidence intervals 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.

As a sensitivity analysis, the above primary analysis model will be applied to the PP Population. An additional sensitivity analysis counting subjects who discontinued prior to Week 12 or have a missing lesion count assessment but who demonstrated complete clearance at the last collected lesion assessment as responders will be presented. The impact of mis-stratifications may be explored via a sensitivity analysis.

An analysis where the complete clearance response probability for any dropouts prior to Week 12 will be varied across the following scenarios (Vehicle response probability, SB206 response probability):

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

An additional sensitivity analysis will be performed in a subset of the ITT population where only 1 subject from each household is chosen based on the subject with the highest number of baseline treatable MC and the oldest to break ties, if needed, to contribute to the model. A logistic regression model including treatment, investigator type, age, and baseline lesion counts will be utilized.

11.2 Secondary Efficacy Analyses

The secondary endpoint of the proportion of subjects with complete clearance of all treatable MC at Week 8 will be analyzed in the same manner as the primary endpoint. A sensitivity analysis using the PP Population will be provided.

11.3 Exploratory Analyses

The exploratory endpoints based on the proportion of subjects achieving complete clearance or 75% reduction will be analyzed in the same manner as the primary endpoint.

Since the within-household correlation is expected to be small and the change and percent change from Baseline in the number of treatable MC are exploratory, they 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; an unstructured covariance matrix will be utilized. If the calculation of the percent change from baseline is influenced by outliers with

calculated values >100%, then the influence of outliers will be avoided for analysis by censoring them so that all values were in the range of -100% to 100%.

Since the within-household correlation is expected to be small and time to first complete clearance of all MC is exploratory, it 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. Differences in Kaplan-Meier curves between the treatments will be tested for significance using a stratified log-rank test.

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

The change from Baseline of the composite score from age-matched (at Baseline) DLQI/CDLQI will be summarized descriptively and separately for each questionnaire. The scoring algorithms are detailed in Appendix A. Additionally, the changes from Baseline in the following subscales: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment, for DLQI, and Symptoms and Feelings, Leisure, School or Holidays, Personal Relationships, Sleep, and Treatment, for CDLQI, and each question will be summarized descriptively.

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.

12. OTHER ANALYSES

The following analyses of BOTE vs lesion count/complete clearance will be presented:

- Percent change from Baseline at Week 12 in relation to the highest BOTE score during treatment.
- Complete clearance at Week 12 in relation to the highest BOTE score during treatment.
- Percent change from Baseline at each visit in relation to BOTE score at Week 2.
- Complete clearance at each visit in relation to BOTE score at Week 2.

In these analyses, the BOTE scores will be analyzed in the ITT Population as follows:

1. Dichotomized:
    a. Score of 0 or 1: No to Mild
    b. Score of 2, 3, or 4: Moderate to Very Severe

A shift table comparing the baseline BOTE score to each scheduled postbaseline assessment will be presented for the Safety Population.

13. SAFETY ANALYSES

All safety analyses will be based on the Safety Population.

A listing of all deaths will be presented.

13.1 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are 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 medication 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; see Appendix B for the imputation of missing dates algorithm. Verbatim terms in the eCRFs will be mapped to preferred terms and system organ classes using the MedDRA Version 22.0.

Each AE summary will be displayed by treatment group. Summaries that are displayed by system organ classes and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs that contain an overview of each item below.
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and maximum severity. At each level of subject summarization, a subject is classified according to the maximum severity if the subject reported 1 or more events. Adverse events with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). Related AEs are those reported as “Definite,” “Probable,” or “Possible,” and unrelated AEs are those reported as “Unlikely” or “Unrelated.” At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to study drug discontinuation by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to death as an outcome by MedDRA system organ class and preferred term.

Separate listings of all AEs, all SAEs and all AEs leading to study drug discontinuation will be provided.

13.2 Local Skin Reaction

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.

13.3 Events of Special Interest

Events of Special Interest will include subjects with any TEAE where the preferred term contains "application site", subjects with at least 1 post-baseline occurrence of moderate BOTE inflammation score, or subjects with at least 1 post-baseline LSR component score ≥ 1. A summary including the number and percentage of subjects with at least 1 event of special interest, AEs of interest by MedDRA system organ class and preferred term, at least 1 moderate BOTE inflammation score, and any LSR component score ≥ 1 will be provided for the Safety Population. The analysis will also be repeated with the LSR criteria revised to include any post-baseline LSR component (excluding erythema) score ≥ 1.

13.4 Urine Pregnancy Test

Urine pregnancy test results will be included in a data listing only.

13.5 Physical Examination

A shift table summarizing the shift from Baseline to end of treatment in normal/abnormal will be presented.

13.6 Patch Testing

A table summarizing any patch testing results by time point will be presented.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following modifications and/or clarifications to the methodology specified in the protocol will be:

- The DLQI and CDLQI will be summarized separately
- The order of the exploratory endpoints was updated
- The Mean percent change in baseline endpoint was updated to be more generic in order to analyze the median in the case of skewness

15. REFERENCES

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16. APPENDICES

Appendix A: Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) Scoring

DLQI:

Question	Scoring	Subscale
1. Over the last week, how **itchy, sore, painful** or **stinging** has you skin been?	Very much = 3 A lot = 2 A little = 1 Not at all = 0	Symptoms and Feelings
2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much = 3 A lot = 2 A little = 1 Not at all = 0	Symptoms and Feelings
3. Over the last week, how has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Daily Activities
4. Over the last week, how much has your skin influenced the **clothes** you wear?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Daily Activities
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Leisure
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Leisure
7. Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes = 3 No Not Relevant = 0 A lot = 2 A little = 1 Not at all = 0	Work and School
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Personal Relationships

Question	Scoring	Subscale
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Personal Relationships
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Treatment

Note: DLQI is administered in subjects ≥ 16 years old.

The DLQI composite score is then the sum of the scores to all 10 questions and will range from 0 to 30. If 1 question is unanswered, this is allocated a score of 0 and the DLQI score is then summed. If 2 or more questions are unanswered, the questionnaire is not scored.

The subscales will be expressed as percentages of the maximum score:

Subscale	Maximum Score
Symptoms and Feelings	6
Daily Activities	6
Leisure	6
Work and School	3
Personal Relationships	6
Treatment	3

CDLQI:

Question	Scoring	Subscale
1. Over the last week, how **itchy**, **"scratchy"**, **sore**, or **painful** has your skin been?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Symptoms and Feelings
2. Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Symptoms and Feelings
3. Over the last week, how has your skin affected your **friendships**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Personal Relationships
4. Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
5. Over the last week, how much has your skin trouble affected **going out, playing,** or **doing hobbies**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
6. Over the last week, how much have you avoided swimming or **other sports** because of your skin trouble?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
7. Last week, was it **school time**? If **school time:** Over the last week, how much did your skin problem affect your **school work**? Was it **holiday time**? If **holiday time:** Over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school = 3 Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	School or Holidays
8. Over the last week, how much trouble have you had because of your skin with other people **calling you names, teasing, bullying, asking questions** or **avoiding you**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Personal Relationships

Question	Scoring	Subscale
9. Over the last week, how much has your **sleep** been affected by your skin problem?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Sleep
10. Over the last week, how much of a problem has the **treatment** for your skin been?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Treatment

Note: CDLQI is administered in subjects 4 years old up to 16 years old.

The CDLQI composite score is then the sum of the scores to all 10 questions and will range from 0 to 30. If a question is unanswered, this is allocated a score of 0 and the CDLQI score is then summed.

The subscales will be expressed as percentages of the maximum score:

Subscale	Maximum Score
Symptoms and Feelings	6
Leisure	9
School or Holidays	3
Personal Relationships	6
Sleep	3
Treatment	3

Appendix B: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, and shading will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., μ, α, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.
- Means and medians will be presented to 1 more decimal place than the raw data. Standard deviations will be presented to 2 more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source **table number**(s) if applicable (in case aggregated results like mean or median are plotted) or the source listing(s) (in case individual responses are plotted) and/or source dataset(s) (e.g., AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- For box plots, the horizontal line will represent the median, + represents the group mean, the length of the box represents the interquartile range (25^{th}-75^{th} percentiles), and the whiskers will represent the minimum and maximum.
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (e.g., AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Listings

- Formal organization of the listing may be changed during programming, if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Missing or incomplete dates (i.e., AEs and concomitant medications)
The most conservative approach will be systematically considered. If the AE onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a TEAE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first application of study drug, provided the start month and year are the same as the first application of study drug and the stop date is either after the first application of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first application of study drug, provided the start year is the same as the first application of study drug and the stop date is either after the first application of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013) or the subject's date of birth, whichever is latest.
- If the start date is completely missing and the stop date is either after the application of study drug or completely missing, the start date will be estimated to be the first day of study drug application. Otherwise, the start date will be estimated to be the first day of the same year as the stop date or the subject's date of birth, whichever is latest. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing and the event is not continuing, the event will be assumed to be after first application of study drug and will be imputed using the last known date on the study.

If the start date of current molluscum episode is partial, then the following imputation will be made:

- If only the day is unknown, the day will be assumed to be the first day of the month or the date of birth, whichever is later.
- If the day and month are missing, then the start date will be estimated to be June 1st or the date of birth, whichever is later.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days** – A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the formulas noted below:
  Duration in days = date2 – date1 + 1.
- **Months –** A duration expressed in months will be calculated as (later date – earlier date + 1)/(30.4167).
- **Years –** A duration expressed in years will be calculated as (later date – earlier date + 1)/(365).
- **Change from Baseline** – Change from Baseline will be calculated as follows:
  Change from Baseline = postbaseline value – baseline value.
- **Percent change from Baseline** – Change from Baseline will be calculated as follows:
  Percent change from Baseline = (postbaseline value – baseline value)/baseline value × 100.

Appendix C: SAS Programming QC Requirements

Derived datasets are independently programmed by two programmers. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study analysis dataset specifications provided to the client at study conclusion.

Tables are independently reprogrammed by a second programmer for numeric results.
Listings are checked for consistency against corresponding tables, figures, and derived datasets.
Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.

Appendix D: List of Tables, Figures, and Listings

The following proposal for section 14 and 16.2 is completed according to ICH E3 guidelines. The ICH heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.

The shells for the outputs below are contained in the file titled "Novan NI-MC301 SAP TLFs Version 1.0".

TABLES, FIGURES, AND GRAPHS

Table Number	Table Title	Analysis Population
14	**TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**	
14.1	**DEMOGRAPHIC DATA**	
14.1.1.1	Subject Disposition	Enrolled
14.1.1.2	Enrollment by Site	ITT
14.1.2.1	Demographic and Baseline Characteristics	Safety
14.1.2.2	Demographic and Baseline Characteristics	ITT
14.1.2.3	Demographic and Baseline Characteristics	PP
14.1.3.1	Study Drug Exposure	Safety
14.1.3.2	Study Drug Compliance	Safety
14.1.4.1	Significant and Major Protocol Deviations	ITT
14.1.5	Medical History	ITT
14.1.6.1	Prior Medications	ITT
14.1.6.2	Concomitant Medications	ITT
14.2	**Efficacy data**	
14.2.1.1	Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.2	Complete Clearance Lesion Count Response at Week 12	PP

Table Number	Table Title	Analysis Population
14.2.1.3	Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.4	Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	PP
14.2.1.6	Proportion of Subjects with Complete Clearance at Week 12 by Subgroup	ITT
14.2.1.7	Dropout Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.8	One Subject Per Household Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.2.1	Complete Clearance Lesion Count Response at Week 8	ITT
14.2.2.2	Complete Clearance Lesion Count Response at Week 8	PP
14.2.3.1	Complete Clearance Lesion Count Response at Weeks 2 and 4	ITT
14.2.3.2	Summary of a 75% Reduction in Lesion Counts from Baseline Response by Visit	ITT
14.2.3.3.1	Percent Change from Baseline in Lesion Count by Visit	ITT
14.2.3.4.1	Change from Baseline in Lesion Count by Visit	ITT
14.2.3.5	Summary of Recurrence after Complete Clearance	ITT
14.2.3.6.1	Kaplan-Meier Estimates of Time to Complete Clearance (Days) from Start of Dosing	ITT
14.2.3.7	Summary of Scarring and Keloid by Visit	ITT
14.2.3.8.1	Summary of the Dermatology Life Quality Index (DLQI) and Subscales by Visit	ITT
14.2.3.8.2	Summary of the Dermatology Life Quality Index (DLQI) Individual Questions by Visit	ITT
14.2.3.8.3	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT
14.2.3.8.4	Summary of the Children's Dermatology Life Quality Index (CDLQI) Individual Questions by Visit	ITT
14.2.3.9	Summary of Increase in Subject-Reported Spread to Household Members by Visit	ITT
14.2.3.10.1	Summary of Lesion Counts by Highest Dichotomized BOTE Score	ITT
14.2.3.10.3	Percent Change from Baseline in Lesion Count over Time by Dichotomized Week 2 BOTE Score	ITT
14.2.3.10.4	Summary of Complete Clearance by Visit and Dichotomized Week 2 BOTE Score	ITT
14.2.3.10.5	Summary of the Beginning of the End (BOTE) Inflammation Score Results by Visit	Safety
14.3	**Safety data**	
14.3.1	**Displays of Adverse Events**	
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety

Table Number	Table Title	Analysis Population
14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.3	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety
14.3.1.5	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.6	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term	Safety
14.3.1.7	Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety
14.3.2	**Listings of deaths, other serious and significant adverse events**	
14.3.2.1	Listing of Serious Adverse Events	Safety
14.3.2.2	Listing of Adverse Events Leading to Study Drug Discontinuation	Safety
14.3.2.3	Listing of Deaths	Safety
14.3.6	**Other safety data**	
14.3.6.1.1	Summary of Local Skin Reaction (LSR) Composite Score by Visit	Safety
14.3.6.1.2	Summary of Local Skin Reaction (LSR) Score Results by Visit	Safety
14.3.6.1.3	Shift Summary of Local Skin Reaction (LSR) Score Results by Visit	Safety
14.3.6.2	Summary of Events of Special Interest	Safety
14.3.6.3	Summary of Physical Examination Findings	Safety
14.3.6.4	Summary of Patch Testing Results	Safety

Figure Number	Figure Title	Analysis Population
14.2.1.5	Forest Plot: Odds Ratio (95% CI) of the Proportion of Subjects with Complete Clearance at Week 12	ITT
14.2.3.3.2	Percent Change from Baseline in Lesion Count over Time by Treatment Group	ITT
14.2.3.4.2	Mean Change from Baseline in Lesion Count over Time by Treatment Group	ITT
14.2.3.6.2	Kaplan-Meier Plot of Time to Complete Clearance (Days) from Start of Dosing	ITT
14.2.3.10.2	Plot of Complete Clearance at Week 12 by Highest Dichotomized Categorized BOTE Score	ITT

Section 16.2: **List of Data Listings**

ICH Listing Number	Listing Title	Analysis Population
16.1.7	Subject Randomization	
16.2	**SUBJECT DATA LISTINGS**	
16.2.1	**Discontinued subjects**	
16.2.1.1	Subject disposition	Enrolled
16.2.2	**Protocol deviations**	
16.2.2.1	Protocol Deviations	ITT
16.2.2.2	Inclusion/Exclusion Criteria	Enrolled
16.2.3	**Subjects excluded from the efficacy analysis**	
16.2.3.1	Analysis Populations	Enrolled
16.2.4	**Demographic data**	
16.2.4.1	Demographic and Baseline Characteristics	ITT
16.2.4.2	Patch Testing Consent/Assent	
16.2.4.3	Medical History	ITT
16.2.4.4	Prior and Concomitant Medications	ITT
16.2.5	**Compliance and/or drug concentration data**	
16.2.5.1	Study Drug Administration	Safety
16.2.5.2	Study Drug Accountability	Safety
16.2.5.3	Treatment Adjustment	Safety
16.2.6	**Individual efficacy response data**	
16.2.6.1	Lesion Counts	ITT
16.2.6.2	Lesion Count Derived Efficacy Variables and Time to Complete Clearance	ITT
16.2.6.3	Scarring/Keloid Assessment	ITT
16.2.6.4	Dermatology Life Quality Index (DLQI) and Subscales	ITT
16.2.6.5	Children's Dermatology Life Quality Index (CDLQI) and Subscales	ITT
16.2.6.6	Household Transmission	ITT
16.2.7	**Adverse events listings**	
16.2.7.1	All Adverse Events	Safety

ICH Listing Number	Listing Title	Analysis Population
16.2.8	**Listing of individual laboratory measurements by subject, when required by regulatory authorities**	
16.2.8.1	Urine Pregnancy Test	Safety
16.2.9	**Other data**	
16.2.9.1	Beginning-of-the-End (BOTE) Inflammation Score	Safety
16.2.9.2	Local Skin Reactions (LSR)	Safety
16.2.9.3	Physical Examination	Safety
16.2.9.4	Patch Testing	Safety
16.2.9.5	Telephone Contact	ITT

Statistical Analysis Plan

Novan, Inc.

NI-MC301

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 Version: 26Mar2019

Sponsor: Novan, Inc.
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Version	Date
Version 1	16 Aug 2019
Version 2	11 Sep 2019

Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
Tait, Christopher Senior Biostatistician I approve this document 12 Sep 2019 08:27:52 -05:00 cosign Christopher Tait, PhD Senior Biostatistician Synteract	12SEP2019
David Hebert, PhD Senior Director, Head of Biometrics Novan, Inc.	12SEP2019

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full Notation
AE	adverse event
ATC	anatomical/therapeutic/chemical
BOTE	beginning of the end
CDLQI	Children's Dermatology Life Quality Index
CRO	contract research organization
DLQI	Dermatology Life Quality Index
DSMB	data safety monitoring board
eCRF	electronic case report form
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LSR	local skin reaction
MC	molluscum contagiosum
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
QC	quality control
QD	once daily
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Novan, Inc. protocol version 1.0 [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]. The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report.

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol version 1.0, 26Mar2019
- Annotated electronic case report form (eCRF) version 3.0, 14Aug2019
- Data management plan version 1.0, 12Apr2019

3. STUDY OBJECTIVES

The objective of the study is to evaluate the efficacy and safety of SB206 12% once daily (QD) for the treatment of molluscum contagiosum (MC).

4. STUDY DESIGN AND PLAN

This is a Phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in approximately 340 subjects ≥6 months of age with MC. After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized to a 2:1 (active:vehicle) scheme. Subjects receiving current treatment for MC at the time of the Screening Visit will enter a washout period of up to 14 days prior to randomization. In the event no washout period is required, Screening and Baseline visit activities may be combined into a single visit. At randomization, subjects will be stratified into 4 strata corresponding to the cross-classification of household number of randomly assigned subjects (1 subject per household vs 2 subjects per household) and investigator type (dermatologist vs other). Households randomizing 2 subjects will receive the same treatment assignment for both subjects. Up to 2 subjects from the same household may be randomly assigned on the same day, if both individually meet all inclusion and exclusion criteria. For subjects in the same household, Screening can occur on different days; however, the baseline visit must occur on the same day.

Subjects or their caregivers will apply SB206 12% or Vehicle Gel QD for a minimum of 4 weeks and 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. If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. At Weeks 2, 4, 8 and 12, the investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. At Weeks 2, 4,

and 8, the investigator will determine if new lesions have occurred since the last visit, and the subject or caregiver will be instructed by the investigator to re-initiate treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24.

Subjects will visit the clinic at Screening/Baseline, Week 2, Week 4, Week 8, Week 12, and Week 24. 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 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. No study drug treatment will be provided after the Week 12 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 will be recorded as an ET2 visit.

Safety assessments include local skin reactions (LSRs), AE collection, including scarring/keloid, and urine pregnancy tests. Safety assessments will be completed at specified site visits through Week 12. After Week 12, safety information for ongoing AEs and new AEs will be collected, along with information regarding household MC occurrence.

Inflammatory reactions around the MC 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 (before dosing) and Weeks 2 through 12. 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, and 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. BOTE Inflammation Score and LSR score will be recorded at each visit. BOTE should not be considered an AE. When LSRs are clinically significant at the application site, the investigator should report the condition as an AE(s).

At Baseline (at least 30 minutes after dosing) and Weeks 2 through 12, the investigators will rate LSRs on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. At Baseline (pre-dose) and Weeks 2 through 12, the investigators will rate BOTE signs using the BOTE Inflammation Score.

The following tables describe the scoring parameters for the BOTE Inflammation Score and LSR score.

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

LSR Score

Score	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

Clinically significant LSRs that are reported as AEs 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 of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. The investigator may take photographs of the suspected allergic contact dermatitis and discuss possible confirmation of allergic contact dermatitis with the contract research organization's

(CRO) medical monitor. 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 with the CRO's medical monitor to implement 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 AEs will be followed up until resolution or up to 1 year after last treatment, whichever is sooner.

Scar formation will be assessed starting at the Week 4 visit through Week 12 and again at 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. The investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. If a new scar is noted after the subject treated with study drug, this will be considered an AE for the purposes of this study. In addition, keloid/hypertrophic scars will also be recorded as AEs.

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.

When approximately 200 subjects (cumulative across studies MC301 and MC302) have completed 4 weeks of treatment, a data safety monitoring board (DSMB) will review all available unblinded safety data (including patch testing).

5. DETERMINATION OF SAMPLE SIZE

Approximately 340 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 2:1 (active:vehicle) scheme. The sample size assumptions for this study were informed by the completed Phase 2 study NI-MC201 of subjects 2 years of age and older with between 3 and 70 MC lesions at Baseline. In the Intent-to-Treat (ITT) Population of the Phase 2 study, the observed rates of complete clearance at Week 12 were 18% (12/66) for vehicle and 38% (18/48) for SB206 12% QD and the covariate-adjusted treatment difference was 18%.

A sample size of 340 subjects (227 subjects in the SB206 12% QD group and 113 subjects in the vehicle group) will provide 94% power for a 2-sided alpha test of size 0.05 to detect an absolute difference of 18% when the vehicle response rate is 18%. This same sample size provides 93% power to detect a treatment difference of 18% when the vehicle response rate is 20% and 83% power when the treatment difference is 15% and the vehicle response rate is 20%.

Since the intra-cluster correlation is estimated to be small (<10%) and the average size of households is expected to be capped at roughly 1.3, the sample size is still sufficient when considering the fact that the subjects within the household may not be independent.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated *P*-value is ≤0.05.

Continuous variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Other statistics such as quartiles, confidence intervals (CIs), and number of missing values may be added as appropriate.

Categorical variable summaries will include the frequency and percentage of subjects who are in the category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population within each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

All summary tables will be presented by treatment group. Baseline summaries will also include an overall summary column.

Individual subject data obtained from the eCRFs and any derived data will generally be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to breaking the blind.

Any analyses performed subsequent to breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the clinical study report.

All analyses and tabulations will be performed using SAS® software Version 9.4 or higher. Tables, listings, and figures will be presented in RTF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS programming quality control." Study-specific QC requirements can be found in Appendix C: SAS Programming QC Requirements.

The study treatment period is defined from randomization through completion of Week 12/ET1 visit and the safety follow-up period is from the completion of Week 12 through the completion of Week 24/ET2 visit.

After all subjects have completed their Week 12/ET1 visit, thus completing the Treatment Period of the study, the database through Week 12/ET1 will be frozen and unblinded for purposes of the

primary analysis of efficacy and safety. While this analysis is being prepared, the subjects will continue through Week 24/ET2. After all subjects have completed their Week 24/ET2 visit, the database will be locked and the follow-up data will be analyzed.

7. NOTATION OF TREATMENT GROUPS AND VISITS

Analysis visits

Baseline is defined as the last nonmissing value recorded prior to the first application of study drug. If time is not recorded and the assessment was on the same day as the first application of study drug, then it will be assumed the assessment occurred prior to the application of study drug. The baseline record will have an analysis visit of "Baseline".

For all evaluations of all parameters, assessments will be analyzed according to the visit at which they occurred (i.e., per the eCRF visit label). In order to account for the fact that the Week 12 and Early Termination visits are collected on the same eCRF in the database, a check against the Study Exit form will be made to determine if the visit is a Week 12 or an Early Termination Visit. If the visit is an Early Termination visit, then the visit will be mapped according to the table below. If there is no corresponding Study Exit form on the same date, then it will be considered a Week 12 visit. If there is no assessment in a given visit, then the following visit windows will be applied to determine if an unscheduled visit may be used:

Visit	Analysis Visit	Target Study Day	Study Day Analysis Window
Week 2 (±3 days)	Week 2	15	Day 12 to 22
Week 4 (±5 days)	Week 4	29	Day 23 to 43
Week 8 (±5 days)	Week 8	57	Day 44 to 71
Week 12 (±5 days)	Week 12	85	Day 72 to 98

Days are measured from the date of randomization. Study days corresponding to measurements are calculated as:

- Assessment date – date of randomization + 1, if assessment date is on or after the date of randomization.
- Assessment date – date of randomization, if measurement date is before the date of randomization.

In the event of multiple unscheduled records falling in the same analysis window, the assessment which is closest to the target study day will be chosen for analysis.

8. ANALYSIS POPULATIONS

The following subject population will be used for disposition analyses:

- The Enrolled Population will consist of all subjects who sign informed consent. If a subject is randomly assigned to a treatment, then treatment assignment will be based on randomized treatment; otherwise, they will be deemed a screen failure and will only appear in the overall summary columns of output.

The following subject population will be used for safety analyses:

- The Safety Population will consist of all subjects who receive at least 1 application of study medication. Treatment assignment will be based on the treatment actually received. If a subject receives any amount of SB206, then they will be summarized in the SB206 12% QD arm.

The following subject populations will be used for efficacy analyses:

- The ITT Population will consist of all subjects who are randomized. Treatment assignment will be based on the randomized treatment.
- The Per-Protocol (PP) Population will consist of all subjects in the ITT Population who had no significant protocol deviations that impacted the analyses of efficacy endpoints. Final determination of subject inclusion in the PP Population will be made prior to unblinding. Treatment assignment will be based on the randomized treatment.

9. STUDY POPULATION

9.1 Subject 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 (defined as having an end of treatment reason of “Completed Treatment Per Protocol” or a reason of “Complete Clearance Prior to Week 12” and does not have a Study Exit date prior to the subject’s), the number of subjects completed the study, and the primary reason for discontinuation.

A summary of the number of subjects in each center and each population will be presented.

9.2 Eligibility

A listing of subjects not fulfilling any eligibility criteria will be created.

9.3 Demographic 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, site type (dermatologist vs other), number of sites and a breakdown of site type, number of randomly assigned subjects in household (1 subject vs 2 subjects), number of households and breakdown of household size, age at diagnosis of the current molluscum episode and time since diagnosis. Descriptive statistics will be presented for ages and other continuous variables. Frequency counts and percentages will be presented for sex, ethnicity, race and other categorical variables. Demographic and baseline characteristics will be summarized for the Safety, ITT, and PP Populations.

9.4 Extent of Exposure

Study drug exposure will be summarized for each treatment using the total number of applications, the duration of treatment, and the number of subjects requiring a treatment interruption and modification. Duration of treatment is defined as the last application date minus the first application date plus 1.

Study drug compliance will be summarized and calculated as follows:

Compliance [%] = (Actual applications applied)/(Planned applications) ×100, where

- Actual applications applied = Planned applications – the number of applications missed
- Planned applications = Number of applications (days) planned up to the point of treatment discontinuation.

This implies that if a subject treatment discontinues treatment prior to Week 12 due to complete clearance, then the number of applications takes this information into account and the subject is not penalized for having complete clearance.

Compliance will be further summarized into 2 groups:

1. Subjects who did not have any interruptions or modifications using the same formula as above, and
2. Subjects with modifications or interruptions. For these subjects, an adjusted compliance will be calculated in the following manner: the actual applications applied will be the same as above but the planned applications will exclude the time where the subject has dosing interrupted.

9.5 Protocol Deviations

Significant protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock and unblinding of individual subject treatment information. Significant protocol deviations may include, but are not limited to:

- Randomly assigned subjects who did not satisfy selected inclusion and exclusion criteria
- Randomly assigned subjects who developed withdrawal criteria during the study but were not withdrawn

- Subjects who were randomized incorrectly including subjects of the same household who are randomized to different treatments
- Subjects who received the wrong treatment
- Subjects where the subject/site staff were unproperly unblinded
- Week 12 Lesion Count not performed
- Subjects who received an excluded concomitant treatment.

The decision whether a subject is excluded from the PP Population will be made during the data review meeting prior to unblinding and database lock. Reasons for exclusion of a subject from the analysis and protocol deviations will be listed.

A listing of all protocol deviations including the deviation designation (major or minor and significant or not), category, and indication of whether the deviation led to an exclusion of a subject from the PP Population will be presented in a data listing.

Major and significant protocol deviations will be summarized by deviation category and treatment group.

9.6 Medical History

Medical history verbatim terms in the eCRFs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. Subject incidence of unique medical history terms by MedDRA system organ class and preferred term will be presented. The summary will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

9.7 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to anatomical/therapeutic/chemical (ATC) class and preferred names using the WHODrug Global B3 (version March 2019). Prior medications are those medications started prior to the first application of study drug. Concomitant medications are those medications started on or after the date of first application of study drug or medications started prior to initial application of study drug and continued during the study. A medication can be classified as both prior and concomitant. If it cannot be determined whether the medication was a prior (or concomitant) medication due to a partial start or stop date, then it will be counted as both prior and concomitant; see Appendix B for the imputation of missing dates algorithm.

Prior and concomitant medications will be summarized for each treatment by WHODrug Global ATC class Level 3 and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she

reported 1 or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

10. EFFICACY ANALYSES

The primary efficacy analysis will be based on the ITT Population. Additional supportive efficacy analyses will be performed using the PP Population.

10.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects with complete clearance of all treatable MC at Week 12.

The secondary efficacy endpoint is the proportion of subjects with complete clearance of all treatable MC at Week 8.

Complete clearance is defined as having a total number of lesions count of 0.

The exploratory endpoints are the following:

- Proportion of subjects with complete clearance of all treatable MC at Week 2 and Week 4 visits
- Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)
- Percent change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed, defined as the total lesion count being greater than 0 at any point after achieving a count of 0
- Time to complete clearance of all treatable MC, defined as the days between the date of first dose and the first date of clearance. Subjects who do not achieve complete clearance will be censored at the date of the last lesion count assessment.
- Proportion of subjects with scarring, defined as an answer of Yes to either question on the Scarring/Keloid Assessment eCRF page: “Was the presence of a scar > 1 mm deep and/or 5 mm wide noted?” or “Was the presence of a scar noted?”, after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Proportion of subjects with keloid or hypertrophic scar, defined as an answer of Yes to the Scarring/Keloid Assessment eCRF page question “Was the presence of a keloid or hypertrophic scar noted?”, after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)

- Change from Baseline of the composite score from age-matched (at Baseline) Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CLDQI) assessment at Week 12
- 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, 16, 20, 24)

10.2 Baseline Values

Unless otherwise noted, baseline is defined as the last nonmissing value recorded prior to the first application of study drug. If time is not recorded and the assessment was on the same day as the first application of study drug, then it will be assumed the assessment occurred prior to the application of study drug. If a subject was randomized but not treated, then baseline is defined as the last nonmissing value on or before the date of randomization.

10.3 Adjustments for Covariates

The model for the primary efficacy will include adjustments for the following covariates: investigator type (dermatologist vs other), household number of randomized subjects (1 subject per household vs 2 subjects per household), age, and baseline lesion count.

10.4 Handling of Dropouts or Missing Data

In analyses based on response, a missing response will be considered a nonresponder.

For a sensitivity analysis, subjects with missing lesion count at Week 12 but who demonstrated complete clearance at the last collected lesion assessment will be counted as responders.

10.5 Interim Analysis and Data Monitoring

When approximately 200 subjects (cumulative across studies NI-MC301 and NI-MC302) have completed 4 weeks of treatment, a DSMB will review all available unblinded safety data (including patch testing). All responsibilities of the DSMB and details of the analysis and data to be reviewed is detailed in the DSMB charter.

10.6 Examination of Subgroups

Subgroup analyses of complete clearance at Week 12 for investigator type (dermatologist vs other) and household number of randomized subjects (1 subject per household vs 2 subjects per household), and will be presented in a forest plot for the ITT Population. An additional subgroup analysis of complete clearance at Week 12 for age (≤1 year old, >1 to ≤2 years old, >2 to ≤6 years old, >6 to ≤12 years old, >12 to ≤18 years old, >18 years old) and MC disease duration prior to baseline (≤6 months vs >6 months) will be summarized descriptively for the ITT Population.

10.7 Multiple Comparison/Multiplicity

The familywise error rate with respect to the primary endpoint and secondary endpoint will be strongly controlled at the alpha=0.05 level using a fixed-sequence method testing strategy. If the primary endpoint is not statistically significant at the alpha=0.05 level, the secondary efficacy endpoint will be considered not significant. If the primary endpoint is statistically significant at the alpha=0.05 level, then the secondary efficacy endpoint will be analyzed. If the secondary efficacy endpoint fails to reach statistical significance at the alpha=0.05 level, it will be considered not statistically significant.

10.8 Multicenter Studies

This is a multicenter study, having approximately 35 centers participating in the study. The center effects will be investigated in the primary statistical analysis model.

11. METHODS OF EFFICACY ANALYSIS

11.1 Primary Efficacy Analysis

The primary efficacy comparison will test the following hypotheses:

H_0: The proportion of subjects with complete clearance is equal between SB206 12% QD and Vehicle;

H_1: The proportion of subjects with complete clearance is different between SB206 12% QD and Vehicle.

The primary efficacy model will be the following for π_{H_i} as the probability of complete clearance for the i^{th} subject in household H:

$$\pi_{H_i} = \frac{e^{(\beta_0+\beta_1*X_{H_{i1}}+\beta_2*X_{H_{i2}}+\beta_3*X_{H_{i3}}+\beta_4*X_{H_{i4}}+\beta_5*X_{H_{i5}})}}{1+e^{(\beta_0+\beta_1*X_{H_{i1}}+\beta_2*X_{H_{i2}}+\beta_3*X_{H_{i3}}+\beta_4*X_{H_{i4}}+\beta_5*X_{H_{i5}})}}$$

where H = Household, i = subject within the household, β_0 is the intercept,

$$X_{H_{i1}} = \begin{cases} 1, if\ treatment\ is\ SB206 \\ 0, if\ treatment\ is\ Vehcile \end{cases}$$

$$X_{H_{i2}} = \begin{cases} 1, if\ subject\ is\ from\ a\ 2\ subject\ household \\ 0, if\ subject\ is\ from\ a\ 1\ subject\ household \end{cases}$$

$$X_{H_{i3}} = \begin{cases} 1, if\ subject\ is\ from\ a\ Dermatology\ site \\ 0, if\ subject\ is\ from\ an\ Other\ site \end{cases}$$

$X_{H_{i4}}$ is the subject's baseline lesion count, and $X_{H_{i4}}$ is the subject's age at baseline; treatment will be included in the class statement with PARAM=REF and REF=Vehicle. The working

correlation will have an exchangeable structure. The model will include a repeated statement for subject household with household ID in the class statement. Also, the data structure will be ordered according to household ID and subject ID in household.

Treatment groups will be compared using a generalized estimating equation for logistic regression with an exchangeable working correlation structure. The model will include treatment, investigator type (dermatologist vs other), household number of randomly assigned subjects (1 subject per household vs 2 subjects per household), age, and baseline lesion count as factors. The odds ratio between SB206 12% and vehicle gel, 95% confidence intervals 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.

As a sensitivity analysis, the above primary analysis model will be applied to the PP Population. An additional sensitivity analysis counting subjects who discontinued prior to Week 12 or have a missing lesion count assessment but who demonstrated complete clearance at the last collected lesion assessment as responders will be presented. The impact of mis-stratifications may be explored via a sensitivity analysis.

An analysis where the complete clearance response probability for any dropouts prior to Week 12 will be varied across the following scenarios (Vehicle response probability, SB206 response probability):

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

An additional sensitivity analysis will be performed in a subset of the ITT population where only 1 subject from each household is chosen based on the subject with the highest number of baseline treatable MC and the oldest to break ties, if needed, to contribute to the model. A logistic regression model including treatment, investigator type, age, and baseline lesion counts will be utilized.

11.2 Secondary Efficacy Analyses

The secondary endpoint of the proportion of subjects with complete clearance of all treatable MC at Week 8 will be analyzed in the same manner as the primary endpoint. A sensitivity analysis using the PP Population will be provided.

11.3 Exploratory Analyses

The exploratory endpoints based on the proportion of subjects achieving complete clearance or 75% reduction will be analyzed in the same manner as the primary endpoint.

Since the within-household correlation is expected to be small and the change and percent change from Baseline in the number of treatable MC are exploratory, they 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; an unstructured covariance matrix will be utilized. If the calculation of the percent change from baseline is influenced by outliers with calculated values >100%, then the influence of outliers will be avoided for analysis by censoring them so that all values were in the range of -100% to 100%.

Since the within-household correlation is expected to be small and time to first complete clearance of all MC is exploratory, it 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. Differences in Kaplan-Meier curves between the treatments will be tested for significance using a stratified log-rank test.

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

The change from Baseline of the composite score from age-matched (at Baseline) DLQI/CDLQI will be summarized descriptively and separately for each questionnaire. The scoring algorithms are detailed in Appendix A. Additionally, the changes from Baseline in the following subscales: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment, for DLQI, and Symptoms and Feelings, Leisure, School or Holidays, Personal Relationships, Sleep, and Treatment, for CDLQI, and each question will be summarized descriptively.

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.

12. OTHER ANALYSES

The following analyses of BOTE vs lesion count/complete clearance will be presented:

- Percent change from Baseline at Week 12 in relation to the highest BOTE score during treatment.
- Complete clearance at Week 12 in relation to the highest BOTE score during treatment.
- Percent change from Baseline at each visit in relation to BOTE score at Week 2.
- Complete clearance at each visit in relation to BOTE score at Week 2.

In these analyses, the BOTE scores will be analyzed in the ITT Population as follows:

1. Dichotomized:
    a. Score of 0 or 1: No to Mild

b. Score of 2, 3, or 4: Moderate to Very Severe

A shift table comparing the baseline BOTE score to each scheduled postbaseline assessment will be presented for the Safety Population.

13. SAFETY ANALYSES

All safety analyses will be based on the Safety Population.

A listing of all deaths will be presented.

13.1 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are 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 medication 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; see Appendix B for the imputation of missing dates algorithm. Verbatim terms in the eCRFs will be mapped to preferred terms and system organ classes using the MedDRA Version 22.0.

Each AE summary will be displayed by treatment group. Summaries that are displayed by system organ classes and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs that contain an overview of each item below.
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and maximum severity. At each level of subject summarization, a subject is classified according to the maximum severity if the subject reported 1 or more events. Adverse events with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). Related AEs are those reported as “Definite,” “Probable,” or “Possible,” and unrelated AEs are those reported as “Unlikely” or “Unrelated.” At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.

- Subject incidence of TEAEs leading to study drug discontinuation by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to death as an outcome by MedDRA system organ class and preferred term.

Separate listings of all AEs, all SAEs and all AEs leading to study drug discontinuation will be provided.

13.2 Local Skin Reaction

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.

13.3 Events of Special Interest

Events of Special Interest will include subjects with any TEAE where the preferred term contains "application site", subjects with at least 1 post-baseline occurrence of moderate BOTE inflammation score, or subjects with at least 1 post-baseline LSR component score ≥ 1. A summary including the number and percentage of subjects with at least 1 event of special interest, AEs of interest by MedDRA system organ class and preferred term, at least 1 moderate BOTE inflammation score, and any LSR component score ≥ 1 will be provided for the Safety Population. The analysis will also be repeated with the LSR criteria revised to include any post-baseline LSR component (excluding erythema) score ≥ 1 and erythema score ≥ 2.

13.4 Urine Pregnancy Test

Urine pregnancy test results will be included in a data listing only.

13.5 Physical Examination

A shift table summarizing the shift from Baseline to end of treatment in normal/abnormal will be presented.

13.6 Patch Testing

A table summarizing any patch testing results by time point will be presented.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following modifications and/or clarifications to the methodology specified in the protocol will be:

- The DLQI and CDLQI will be summarized separately
- The order of the exploratory endpoints was updated
- The Mean percent change in baseline endpoint was updated to be more generic in order to analyze the median in the case of skewness

15. REFERENCES

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16. APPENDICES

Appendix A: Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) Scoring

DLQI:

Question	Scoring	Subscale
1. Over the last week, how **itchy, sore, painful** or **stinging** has you skin been?	Very much = 3 A lot = 2 A little = 1 Not at all = 0	Symptoms and Feelings
2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much = 3 A lot = 2 A little = 1 Not at all = 0	Symptoms and Feelings
3. Over the last week, how has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Daily Activities
4. Over the last week, how much has your skin influenced the **clothes** you wear?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Daily Activities
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Leisure
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Leisure
7. Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes = 3 No Not Relevant = 0 A lot = 2 A little = 1 Not at all = 0	Work and School
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Personal Relationships

Question	Scoring	Subscale
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Personal Relationships
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Treatment

Note: DLQI is administered in subjects ≥ 16 years old.

The DLQI composite score is then the sum of the scores to all 10 questions and will range from 0 to 30. If 1 question is unanswered, this is allocated a score of 0 and the DLQI score is then summed. If 2 or more questions are unanswered, the questionnaire is not scored.

The subscales will be expressed as percentages of the maximum score:

Subscale	Maximum Score
Symptoms and Feelings	6
Daily Activities	6
Leisure	6
Work and School	3
Personal Relationships	6
Treatment	3

CDLQI:

Question	Scoring	Subscale
1. Over the last week, how **itchy**, **"scratchy"**, **sore**, or **painful** has your skin been?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Symptoms and Feelings
2. Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Symptoms and Feelings
3. Over the last week, how has your skin affected your **friendships**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Personal Relationships
4. Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
5. Over the last week, how much has your skin trouble affected **going out, playing,** or **doing hobbies**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
6. Over the last week, how much have you avoided swimming or **other sports** because of your skin trouble?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
7. Last week, was it **school time**? If **school time:** Over the last week, how much did your skin problem affect your **school work**? Was it **holiday time**? If **holiday time:** Over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school = 3 Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	School or Holidays
8. Over the last week, how much trouble have you had because of your skin with other people **calling you names, teasing, bullying, asking questions** or **avoiding you**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Personal Relationships

Question	Scoring	Subscale
9. Over the last week, how much has your **sleep** been affected by your skin problem?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Sleep
10. Over the last week, how much of a problem has the **treatment** for your skin been?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Treatment

Note: CDLQI is administered in subjects 4 years old up to 16 years old.

The CDLQI composite score is then the sum of the scores to all 10 questions and will range from 0 to 30. If a question is unanswered, this is allocated a score of 0 and the CDLQI score is then summed.

The subscales will be expressed as percentages of the maximum score:

Subscale	Maximum Score
Symptoms and Feelings	6
Leisure	9
School or Holidays	3
Personal Relationships	6
Sleep	3
Treatment	3

Appendix B: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, and shading will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., μ, α, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.
- Means and medians will be presented to 1 more decimal place than the raw data. Standard deviations will be presented to 2 more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source **table number**(s) if applicable (in case aggregated results like mean or median are plotted) or the source listing(s) (in case individual responses are plotted) and/or source dataset(s) (e.g., AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- For box plots, the horizontal line will represent the median, + represents the group mean, the length of the box represents the interquartile range (25^{th}-75^{th} percentiles), and the whiskers will represent the minimum and maximum.
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (e.g., AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Listings

- Formal organization of the listing may be changed during programming, if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Missing or incomplete dates (i.e., AEs, concomitant medications, and start dates of current molluscum episode and initial diagnosis)
The most conservative approach will be systematically considered. If the AE onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a TEAE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first application of study drug, provided the start month and year are the same as the first application of study drug and the stop date is either after the first application of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first application of study drug, provided the start year is the same as the first application of study drug and the stop date is either after the first application of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013) or the subject's date of birth, whichever is latest.
- If the start date is completely missing and the stop date is either after the application of study drug or completely missing, the start date will be estimated to be the first day of study drug application. Otherwise, the start date will be estimated to be the first day of the same year as the stop date or the subject's date of birth, whichever is latest. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing and the event is not continuing, the event will be assumed to be after first application of study drug and will be imputed using the last known date on the study.

For the start dates of current molluscum episode and initial diagnosis, the day will be estimated as "01" if only day is missing. If both month and day are missing, then it will be estimated as "01-JUN-YYYY" or the subject's date of birth, whichever is latest.

If the start date of current molluscum episode is partial, then the following imputation will be made:

- If only the day is unknown, the day will be assumed to be the first day of the month or the date of birth, whichever is later.
- If the day and month are missing, then the start date will be estimated to be June 1st or the date of birth, whichever is later.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days** – A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the formulas noted below:
  Duration in days = date2 – date1 + 1.
- **Months –** A duration expressed in months will be calculated as (later date – earlier date + 1)/(30.4167).
- **Years –** A duration expressed in years will be calculated as (later date – earlier date + 1)/(365).
- **Change from Baseline** – Change from Baseline will be calculated as follows:
  Change from Baseline = postbaseline value – baseline value.
- **Percent change from Baseline** – Change from Baseline will be calculated as follows:
  Percent change from Baseline = (postbaseline value – baseline value)/baseline value × 100.

Appendix C: SAS Programming QC Requirements

Derived datasets are independently programmed by two programmers. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study analysis dataset specifications provided to the client at study conclusion.

Tables are independently reprogrammed by a second programmer for numeric results.
Listings are checked for consistency against corresponding tables, figures, and derived datasets.
Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.

Appendix D: List of Tables, Figures, and Listings

The following proposal for section 14 and 16.2 is completed according to ICH E3 guidelines. The ICH heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.

The shells for the outputs below are contained in the file titled "Novan NI-MC301 SAP TLFs Version 2.0".

TABLES, FIGURES, AND GRAPHS

Table Number	Table Title	Analysis Population
14	**TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**	
14.1	**DEMOGRAPHIC DATA**	
14.1.1.1	Subject Disposition	Enrolled
14.1.1.2	Enrollment by Site	ITT
14.1.2.1	Demographic and Baseline Characteristics	Safety
14.1.2.2	Demographic and Baseline Characteristics	ITT
14.1.2.3	Demographic and Baseline Characteristics	PP
14.1.3.1	Study Drug Exposure	Safety
14.1.3.2	Study Drug Compliance	Safety
14.1.4.1	Significant and Major Protocol Deviations	ITT
14.1.5	Medical History	ITT
14.1.6.1	Prior Medications	ITT
14.1.6.2	Concomitant Medications	ITT
14.2	**Efficacy data**	
14.2.1.1	Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.2	Complete Clearance Lesion Count Response at Week 12	PP

Table Number	Table Title	Analysis Population
14.2.1.3	Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.4	Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	PP
14.2.1.6	Proportion of Subjects with Complete Clearance at Week 12 by Subgroup	ITT
14.2.1.7	Dropout Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.8	One Subject Per Household Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.2.1	Complete Clearance Lesion Count Response at Week 8	ITT
14.2.2.2	Complete Clearance Lesion Count Response at Week 8	PP
14.2.3.1	Complete Clearance Lesion Count Response at Weeks 2 and 4	ITT
14.2.3.2	Summary of a 75% Reduction in Lesion Counts from Baseline Response by Visit	ITT
14.2.3.3.1	Percent Change from Baseline in Lesion Count by Visit	ITT
14.2.3.4.1	Change from Baseline in Lesion Count by Visit	ITT
14.2.3.5	Summary of Recurrence after Complete Clearance	ITT
14.2.3.6.1	Kaplan-Meier Estimates of Time to Complete Clearance (Days) from Start of Dosing	ITT
14.2.3.7	Summary of Scarring and Keloid by Visit	ITT
14.2.3.8.1	Summary of the Dermatology Life Quality Index (DLQI) and Subscales by Visit	ITT
14.2.3.8.2	Summary of the Dermatology Life Quality Index (DLQI) Individual Questions by Visit	ITT
14.2.3.8.3	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT
14.2.3.8.4	Summary of the Children's Dermatology Life Quality Index (CDLQI) Individual Questions by Visit	ITT
14.2.3.9	Summary of Increase in Subject-Reported Spread to Household Members by Visit	ITT
14.2.3.10.1	Summary of Lesion Counts by Highest Dichotomized BOTE Score	ITT
14.2.3.10.3	Percent Change from Baseline in Lesion Count over Time by Dichotomized Week 2 BOTE Score	ITT
14.2.3.10.4	Summary of Complete Clearance by Visit and Dichotomized Week 2 BOTE Score	ITT
14.2.3.10.5	Summary of the Beginning of the End (BOTE) Inflammation Score Results by Visit	Safety
14.3	**Safety data**	
14.3.1	**Displays of Adverse Events**	
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety

Table Number	Table Title	Analysis Population
14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.3	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety
14.3.1.5	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.6	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term	Safety
14.3.1.7	Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety
14.3.2	**Listings of deaths, other serious and significant adverse events**	
14.3.2.1	Listing of Serious Adverse Events	Safety
14.3.2.2	Listing of Adverse Events Leading to Study Drug Discontinuation	Safety
14.3.2.3	Listing of Deaths	Safety
14.3.6	**Other safety data**	
14.3.6.1.1	Summary of Local Skin Reaction (LSR) Composite Score by Visit	Safety
14.3.6.1.2	Summary of Local Skin Reaction (LSR) Score Results by Visit	Safety
14.3.6.1.3	Shift Summary of Local Skin Reaction (LSR) Score Results by Visit	Safety
14.3.6.2	Summary of Events of Special Interest	Safety
14.3.6.3	Summary of Physical Examination Findings	Safety
14.3.6.4	Summary of Patch Testing Results	Safety

Figure Number	Figure Title	Analysis Population
14.2.1.5	Forest Plot: Odds Ratio (95% CI) of the Proportion of Subjects with Complete Clearance at Week 12	ITT
14.2.3.3.2	Percent Change from Baseline in Lesion Count over Time by Treatment Group	ITT
14.2.3.4.2	Mean Change from Baseline in Lesion Count over Time by Treatment Group	ITT
14.2.3.6.2	Kaplan-Meier Plot of Time to Complete Clearance (Days) from Start of Dosing	ITT
14.2.3.10.2	Plot of Complete Clearance at Week 12 by Highest Dichotomized Categorized BOTE Score	ITT

Section 16.2: **List of Data Listings**

ICH Listing Number	Listing Title	Analysis Population
16.1.7	Subject Randomization	
16.2	**SUBJECT DATA LISTINGS**	
16.2.1	**Discontinued subjects**	
16.2.1.1	Subject disposition	Enrolled
16.2.2	**Protocol deviations**	
16.2.2.1	Protocol Deviations	ITT
16.2.2.2	Inclusion/Exclusion Criteria	Enrolled
16.2.3	**Subjects excluded from the efficacy analysis**	
16.2.3.1	Analysis Populations	Enrolled
16.2.4	**Demographic data**	
16.2.4.1	Demographic and Baseline Characteristics	ITT
16.2.4.2	Patch Testing Consent/Assent	
16.2.4.3	Medical History	ITT
16.2.4.4	Prior and Concomitant Medications	ITT
16.2.5	**Compliance and/or drug concentration data**	
16.2.5.1	Study Drug Administration	Safety
16.2.5.2	Study Drug Accountability	Safety
16.2.5.3	Treatment Adjustment	Safety
16.2.6	**Individual efficacy response data**	
16.2.6.1	Lesion Counts	ITT
16.2.6.2	Lesion Count Derived Efficacy Variables and Time to Complete Clearance	ITT
16.2.6.3	Scarring/Keloid Assessment	ITT
16.2.6.4	Dermatology Life Quality Index (DLQI) and Subscales	ITT
16.2.6.5	Children's Dermatology Life Quality Index (CDLQI) and Subscales	ITT
16.2.6.6	Household Transmission	ITT
16.2.7	**Adverse events listings**	
16.2.7.1	All Adverse Events	Safety

ICH Listing Number	Listing Title	Analysis Population
16.2.8	**Listing of individual laboratory measurements by subject, when required by regulatory authorities**	
16.2.8.1	Urine Pregnancy Test	Safety
16.2.9	**Other data**	
16.2.9.1	Beginning-of-the-End (BOTE) Inflammation Score	Safety
16.2.9.2	Local Skin Reactions (LSR)	Safety
16.2.9.3	Physical Examination	Safety
16.2.9.4	Patch Testing	Safety
16.2.9.5	Telephone Contact	ITT

Statistical Analysis Plan

Novan, Inc.

NI-MC301

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 Version: 26Mar2019

Sponsor: Novan, Inc.
4105 Hopson Road
Morrisville, NC 27560

Prepared by: Christopher Tait
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Carlsbad, CA 92010

Version	Date
Version 1	16 Aug 2019
Version 2	11 Sep 2019
Version 3	18 Nov 2019

Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
Christopher Tait Christopher Tait, PhD Senior Biostatistician Synteract	18 NOV 2019
David Hebert David Hebert, PhD Senior Director, Head of Biometrics Novan, Inc.	18NOV19

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full Notation
AE	adverse event
ATC	anatomical/therapeutic/chemical
BOTE	beginning of the end
CDLQI	Children's Dermatology Life Quality Index
CRO	contract research organization
DLQI	Dermatology Life Quality Index
DSMB	data safety monitoring board
eCRF	electronic case report form
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LSR	local skin reaction
MC	molluscum contagiosum
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
QC	quality control
QD	once daily
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Novan, Inc. protocol version 1.0 [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]. The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report.

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol version 1.0, 26Mar2019
- Annotated electronic case report form (eCRF) version 3.0, 14Aug2019
- Data management plan version 1.0, 12Apr2019

3. STUDY OBJECTIVES

The objective of the study is to evaluate the efficacy and safety of SB206 12% once daily (QD) for the treatment of molluscum contagiosum (MC).

4. STUDY DESIGN AND PLAN

This is a Phase 3 multi-center, randomized, double-blind, vehicle-controlled, parallel group study to be conducted in approximately 340 subjects ≥6 months of age with MC. After obtaining informed consent/assent, subjects who satisfy entry criteria will be randomized to a 2:1 (active:vehicle) scheme. Subjects receiving current treatment for MC at the time of the Screening Visit will enter a washout period of up to 14 days prior to randomization. In the event no washout period is required, Screening and Baseline visit activities may be combined into a single visit. At randomization, subjects will be stratified into 4 strata corresponding to the cross-classification of household number of randomly assigned subjects (1 subject per household vs 2 subjects per household) and investigator type (dermatologist vs other). Households randomizing 2 subjects will receive the same treatment assignment for both subjects. Up to 2 subjects from the same household may be randomly assigned on the same day, if both individually meet all inclusion and exclusion criteria. For subjects in the same household, Screening can occur on different days; however, the baseline visit must occur on the same day.

Subjects or their caregivers will apply SB206 12% or Vehicle Gel QD for a minimum of 4 weeks and 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. If the investigator determines all lesions are cleared at a clinic visit, the treatment may stop. At Weeks 2, 4, 8 and 12, the investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. At Weeks 2, 4,

and 8, the investigator will determine if new lesions have occurred since the last visit, and the subject or caregiver will be instructed by the investigator to re-initiate treatment. If treatment is stopped due to clearance, subjects will continue regularly scheduled visits through Week 24.

Subjects will visit the clinic at Screening/Baseline, Week 2, Week 4, Week 8, Week 12, and Week 24. 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 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. No study drug treatment will be provided after the Week 12 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 will be recorded as an ET2 visit.

Safety assessments include local skin reactions (LSRs), AE collection, including scarring/keloid, and urine pregnancy tests. Safety assessments will be completed at specified site visits through Week 12. After Week 12, safety information for ongoing AEs and new AEs will be collected, along with information regarding household MC occurrence.

Inflammatory reactions around the MC 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 (before dosing) and Weeks 2 through 12. 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, and 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. BOTE Inflammation Score and LSR score will be recorded at each visit. BOTE should not be considered an AE. When LSRs are clinically significant at the application site, the investigator should report the condition as an AE(s).

At Baseline (at least 30 minutes after dosing) and Weeks 2 through 12, the investigators will rate LSRs on individual features including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. At Baseline (pre-dose) and Weeks 2 through 12, the investigators will rate BOTE signs using the BOTE Inflammation Score.

The following tables describe the scoring parameters for the BOTE Inflammation Score and LSR score.

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

LSR Score

Score	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

Clinically significant LSRs that are reported as AEs 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 of study drug treatment, if a subject develops worsening LSRs, allergic contact dermatitis may be suspected. The investigator may take photographs of the suspected allergic contact dermatitis and discuss possible confirmation of allergic contact dermatitis with the contract research organization's

(CRO) medical monitor. 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 with the CRO's medical monitor to implement 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 AEs will be followed up until resolution or up to 1 year after last treatment, whichever is sooner.

Scar formation will be assessed starting at the Week 4 visit through Week 12 and again at 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. The investigator will count and record the number of active (raised, treatable) molluscum lesions per body area. If a new scar is noted after the subject treated with study drug, this will be considered an AE for the purposes of this study. In addition, keloid/hypertrophic scars will also be recorded as AEs.

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.

When approximately 200 subjects (cumulative across studies MC301 and MC302) have completed 4 weeks of treatment, a data safety monitoring board (DSMB) will review all available unblinded safety data (including patch testing).

5. DETERMINATION OF SAMPLE SIZE

Approximately 340 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 2:1 (active:vehicle) scheme. The sample size assumptions for this study were informed by the completed Phase 2 study NI-MC201 of subjects 2 years of age and older with between 3 and 70 MC lesions at Baseline. In the Intent-to-Treat (ITT) Population of the Phase 2 study, the observed rates of complete clearance at Week 12 were 18% (12/66) for vehicle and 38% (18/48) for SB206 12% QD and the covariate-adjusted treatment difference was 18%.

A sample size of 340 subjects (227 subjects in the SB206 12% QD group and 113 subjects in the vehicle group) will provide 94% power for a 2-sided alpha test of size 0.05 to detect an absolute difference of 18% when the vehicle response rate is 18%. This same sample size provides 93% power to detect a treatment difference of 18% when the vehicle response rate is 20% and 83% power when the treatment difference is 15% and the vehicle response rate is 20%.

Since the intra-cluster correlation is estimated to be small (<10%) and the average size of households is expected to be capped at roughly 1.3, the sample size is still sufficient when considering the fact that the subjects within the household may not be independent.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated *P*-value is ≤0.05.

Continuous variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Other statistics such as quartiles, confidence intervals (CIs), and number of missing values may be added as appropriate.

Categorical variable summaries will include the frequency and percentage of subjects who are in the category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population within each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

All summary tables will be presented by treatment group. Baseline summaries will also include an overall summary column.

Individual subject data obtained from the eCRFs and any derived data will generally be presented by subject in data listings. Additionally, a listing of the subjects requiring a narrative because they experience one of the following events: serious adverse event, death, discontinued the study due to an AE, hypertrophic or keloid scarring, unresolved scars, or LSR suggestive of allergic contact dermatitis will be presented.

The analyses described in this plan are considered a priori, in that they have been defined prior to breaking the blind.

Any analyses performed subsequent to breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the clinical study report.

All analyses and tabulations will be performed using SAS® software Version 9.4 or higher. Tables, listings, and figures will be presented in RTF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS programming quality control." Study-specific QC requirements can be found in Appendix C: SAS Programming QC Requirements.

The study treatment period is defined from randomization through completion of Week 12/ET1 visit and the safety follow-up period is from the completion of Week 12 through the completion of Week 24/ET2 visit.

After all subjects have completed their Week 12/ET1 visit, thus completing the Treatment Period of the study, the database through Week 12/ET1 will be frozen and unblinded for purposes of the primary analysis of efficacy and safety. While this analysis is being prepared, the subjects will continue through Week 24/ET2. After all subjects have completed their Week 24/ET2 visit, the database will be locked and the follow-up data will be analyzed.

7. NOTATION OF TREATMENT GROUPS AND VISITS

Analysis visits

Baseline is defined as the last nonmissing value recorded prior to the first application of study drug. If time is not recorded and the assessment was on the same day as the first application of study drug, then it will be assumed the assessment occurred prior to the application of study drug. The baseline record will have an analysis visit of "Baseline".

For all evaluations of all parameters, assessments will be analyzed according to the visit at which they occurred (i.e., per the eCRF visit label). In order to account for the fact that the Week 12 and Early Termination visits are collected on the same eCRF in the database, a check against the Study Exit form will be made to determine if the visit is a Week 12 or an Early Termination Visit. If the visit is an Early Termination visit, then the visit will be mapped according to the table below. If there is no corresponding Study Exit form on the same date, then it will be considered a Week 12 visit. If there is no assessment in a given visit, then the following visit windows will be applied to determine if an unscheduled visit may be used:

Visit	Analysis Visit	Target Study Day	Study Day Analysis Window
Week 2 (±3 days)	Week 2	15	Day 12 to 22
Week 4 (±5 days)	Week 4	29	Day 23 to 43
Week 8 (±5 days)	Week 8	57	Day 44 to 71
Week 12 (±5 days)	Week 12	85	Day 72 to 98

Days are measured from the date of randomization. Study days corresponding to measurements are calculated as:

- Assessment date – date of randomization + 1, if assessment date is on or after the date of randomization.
- Assessment date – date of randomization, if measurement date is before the date of randomization.

In the event of multiple unscheduled records falling in the same analysis window, the assessment which is closest to the target study day will be chosen for analysis.

8. ANALYSIS POPULATIONS

The following subject population will be used for disposition analyses:

- The Enrolled Population will consist of all subjects who have a signed informed consent or assent. If a subject is randomly assigned to a treatment, then treatment assignment will be based on randomized treatment; otherwise, they will be deemed a screen failure and will only appear in the overall summary columns of output.

The following subject population will be used for safety analyses:

- The Safety Population will consist of all subjects who receive at least 1 application of study medication. Treatment assignment will be based on the treatment actually received. If a subject receives any amount of SB206, then they will be summarized in the SB206 12% QD arm.

The following subject populations will be used for efficacy analyses:

- The ITT Population will consist of all subjects who are randomized. Treatment assignment will be based on the randomized treatment.
- The Per-Protocol (PP) Population will consist of all subjects in the ITT Population who had no significant protocol deviations that impacted the analyses of efficacy endpoints. Final determination of subject inclusion in the PP Population will be made prior to unblinding. Treatment assignment will be based on the randomized treatment.

9. STUDY POPULATION

9.1 Subject 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 (defined as having an end of treatment reason of “Completed Treatment Per Protocol” or a reason of “Complete Clearance Prior to Week 12” and does not have a Study Exit date prior to the subject’s Week 12 visit date), the number of subjects completed the study, and the primary reason for discontinuation.

A summary of the number of subjects in each center and each population will be presented.

9.2 Eligibility

A listing of subjects not fulfilling any eligibility criteria will be created.

9.3 Demographic 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, site type (dermatologist vs other), number of sites and a breakdown of site type, number of randomly assigned subjects in household (1 subject vs 2 subjects), number of households and breakdown of household size, age at and time since initial clinical diagnosis of the current molluscum episode and age at and time since onset of symptoms of current molluscum episode. Descriptive statistics will be presented for ages and other continuous variables. Frequency counts and percentages will be presented for sex, ethnicity, race and other categorical variables. Demographic and baseline characteristics will be summarized for the Safety, ITT, and PP Populations.

9.4 Extent of Exposure

Study drug exposure will be summarized for each treatment using the total number of applications, the duration of treatment, and the number of subjects requiring a treatment interruption and modification. Duration of treatment is defined as the last application date minus the first application date plus 1.

Study drug compliance will be summarized and calculated as follows:

Compliance [%] = (Actual applications applied)/(Planned applications) ×100, where

- Actual applications applied = Planned applications – the number of applications missed
- Planned applications = Number of applications (days) planned up to the point of treatment discontinuation or date of Week 12 visit, whichever is later.

This implies that if a subject treatment discontinues treatment prior to Week 12 due to complete clearance, then the number of applications takes this information into account and the subject is not penalized for having complete clearance.

Compliance will be further summarized into 2 groups:

1. Subjects who did not have any interruptions or modifications using the same formula as above, and
2. Subjects with modifications or interruptions. For these subjects, an adjusted compliance will be calculated in the following manner: the actual applications applied will be the same as above but the planned applications will exclude the time where the subject has dosing interrupted.

9.5 Protocol Deviations

Significant protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock and unblinding of individual subject treatment information. Significant protocol deviations may include, but are not limited to:

- Randomly assigned subjects who did not satisfy selected inclusion and exclusion criteria
- Randomly assigned subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who were randomized incorrectly including subjects of the same household who are randomized to different treatments
- Subjects who received the wrong treatment
- Subjects where the subject/site staff were unproperly unblinded
- Week 12 Lesion Count not performed
- Subjects who received an excluded concomitant treatment.

The decision on the criteria for whether a subject is excluded from the PP Population will be made during the data review meeting prior to unblinding and database lock. Reasons for exclusion of a subject from the analysis will be listed.

A listing of all protocol deviations including the deviation designation (major or minor and significant or not), category, and indication of whether the deviation led to an exclusion of a subject from the PP Population will be presented in a data listing.

Major and significant protocol deviations will be summarized by deviation category and treatment group.

9.6 Medical History

Medical history verbatim terms in the eCRFs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. Subject incidence of unique medical history terms by MedDRA system organ class and preferred term will be presented. The summary will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

9.7 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to anatomical/therapeutic/chemical (ATC) class and preferred names using the WHODrug Global B3 (version March 2019). Prior medications are those medications started prior to the first application of study drug. Concomitant medications are those medications started on or after the date of first application of study drug or medications started prior to initial application of study

drug and continued during the study. A medication can be classified as both prior and concomitant. If it cannot be determined whether the medication was a prior (or concomitant) medication due to a partial start or stop date, then it will be counted as both prior and concomitant; see Appendix B for the imputation of missing dates algorithm.

Prior and concomitant medications will be summarized for each treatment by WHODrug Global ATC class Level 3 and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

10. EFFICACY ANALYSES

The primary efficacy analysis will be based on the ITT Population. Additional supportive efficacy analyses will be performed using the PP Population.

10.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects with complete clearance of all treatable MC at Week 12.

The secondary efficacy endpoint is the proportion of subjects with complete clearance of all treatable MC at Week 8.

Complete clearance is defined as having a total number of lesions count of 0.

The exploratory endpoints are the following:

- Proportion of subjects with complete clearance of all treatable MC at Week 2 and Week 4 visits
- Proportion of subjects achieving at least a 95% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)
- Proportion of subjects achieving at least a 90% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)
- Proportion of subjects achieving at least a 75% reduction from Baseline in the number of all treatable MC at each visit (Weeks 2, 4, 8, 12)
- Percent change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Change from Baseline in number of treatable MC at each visit (Weeks 2, 4, 8, 12)
- Proportion of subjects who have a recurrence of MC after the first visit at which complete clearance was observed, defined as the total lesion count being greater than 0 at any point after achieving a count of 0

- Time to complete clearance of all treatable MC, defined as the days between the date of first dose and the first date of clearance. Subjects who do not achieve complete clearance will be censored at the date of the last lesion count assessment.
- Proportion of subjects with scarring, defined as an answer of Yes to either question on the Scarring/Keloid Assessment eCRF page: "Was the presence of a scar > 1 mm deep and/or 5 mm wide noted?" or "Was the presence of a scar noted?", after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Proportion of subjects with keloid or hypertrophic scar, defined as an answer of Yes to the Scarring/Keloid Assessment eCRF page question "Was the presence of a keloid or hypertrophic scar noted?", after clearance of lesion(s) at each visit (Weeks 4, 8, 12, 24)
- Change from Baseline of the composite score from age-matched (at Baseline) Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CLDQI) assessment at Week 12
- 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, 16, 20, 24)

10.2 Baseline Values

Unless otherwise noted, baseline is defined as the last nonmissing value recorded prior to the first application of study drug. If time is not recorded and the assessment was on the same day as the first application of study drug, then it will be assumed the assessment occurred prior to the application of study drug. If a subject was randomized but not treated, then baseline is defined as the last nonmissing value on or before the date of randomization.

10.3 Adjustments for Covariates

The model for the primary efficacy will include adjustments for the following covariates: investigator type (dermatologist vs other), household number of randomized subjects (1 subject per household vs 2 subjects per household), age, and baseline lesion count. If there are not at least 3 responders and non-responders at each level of the stratification factors, then that stratification factor will be removed from the model. If there are fewer than 10 responders/non-responders, then neither investigator type nor household number of randomized subjects will be included in the model.

10.4 Handling of Dropouts or Missing Data

In analyses based on response, a missing response will be considered a nonresponder.

For a sensitivity analysis, subjects with missing lesion count at Week 12 but who demonstrated complete clearance at the last collected lesion assessment will be counted as responders.

10.5 Interim Analysis and Data Monitoring

When approximately 200 subjects (cumulative across studies NI-MC301 and NI-MC302) have completed 4 weeks of treatment, a DSMB will review all available unblinded safety data (including patch testing). All responsibilities of the DSMB and details of the analysis and data to be reviewed is detailed in the DSMB charter.

10.6 Examination of Subgroups

Subgroup analyses of complete clearance at Week 12 for investigator type (dermatologist vs other) and household number of randomized subjects (1 subject per household vs 2 subjects per household), and will be presented in a forest plot for the ITT Population. An additional subgroup analysis of complete clearance at Week 12 for age (<1 year old, ≥1 to <2 years old, ≥2 to <6 years old, ≥6 to <12 years old, ≥12 to <18 years old, ≥18 years old) and onset of MC symptoms duration prior to baseline (≤6 months vs >6 months) will be summarized descriptively for the ITT Population.

10.7 Multiple Comparison/Multiplicity

The familywise error rate with respect to the primary endpoint and secondary endpoint will be strongly controlled at the alpha=0.05 level using a fixed-sequence method testing strategy. If the primary endpoint is not statistically significant at the alpha=0.05 level, the secondary efficacy endpoint will be considered not significant. If the primary endpoint is statistically significant at the alpha=0.05 level, then the secondary efficacy endpoint will be analyzed. If the secondary efficacy endpoint fails to reach statistical significance at the alpha=0.05 level, it will be considered not statistically significant.

10.8 Multicenter Studies

This is a multicenter study, having approximately 35 centers participating in the study. The center effects will be investigated in the primary statistical analysis model by including the treatment by investigator type interaction. As exploratory analyses to examine the variability of the treatment effect across centers, the following analyses will be performed:

- Pool the centers into self-standing center pools of at least 17 subjects. The pooling will sort by investigator type and number of randomized subjects. Then, the centers with fewer than 17 subjects will be pooled until the self-standing center pool is at least 17 subjects. The treatment effect will be explored using a logistic model including treatment, household number of randomly assigned subjects, age, baseline lesion counts, and a strata statement which will include the pooling identified and examining the residual score statistics. To address treatment*center interaction, each pooling center will have a corresponding variable coded as 1 if on SB206 and 0 otherwise. Some pooled centers may have a p-value of less than 0.05 by chance since there will be multiple pooled centers.

- Pool the centers using the method above but the self-standing center pools will contain at least 10 subjects. This analysis should be interpreted with caution due to the small sample size within pooled centers.

11. METHODS OF EFFICACY ANALYSIS

11.1 Primary Efficacy Analysis

The primary efficacy comparison will test the following hypotheses:

H_0: The proportion of subjects with complete clearance is equal between SB206 12% QD and Vehicle;

H_1: The proportion of subjects with complete clearance is different between SB206 12% QD and Vehicle.

The primary efficacy model will be the following for π_{H_i} as the probability of complete clearance for the i^{th} subject in household H:

$$\pi_{H_i} = \frac{e^{(\beta_0+\beta_1*X_{H_{i1}} + \beta_2*X_{H_{i2}} + \beta_3*X_{H_{i3}} + \beta_4*X_{H_{i4}} + \beta_5*X_{H_{i5}})}}{1 + e^{(\beta_0+\beta_1*X_{H_{i1}} + \beta_2*X_{H_{i2}} + \beta_3*X_{H_{i3}} + \beta_4*X_{H_{i4}} + \beta_5*X_{H_{i5}})}}$$

where H = Household, i = subject within the household, β_0 is the intercept,

$$X_{H_{i1}} = \begin{cases} 1, if\ treatment\ is\ SB206 \\ 0, if\ treatment\ is\ Vehcile \end{cases}$$

$$X_{H_{i2}} = \begin{cases} 1, if\ subject\ is\ from\ a\ 2\ subject\ household \\ 0, if\ subject\ is\ from\ a\ 1\ subject\ household \end{cases}$$

$$X_{H_{i3}} = \begin{cases} 1, if\ subject\ is\ from\ a\ Dermatology\ site \\ 0, if\ subject\ is\ from\ an\ Other\ site \end{cases}$$

$X_{H_{i4}}$ is the subject's baseline lesion count, and $X_{H_{i4}}$ is the subject's age at baseline; treatment will be included in the class statement with PARAM=REF and REF=Vehicle. The working correlation will have an exchangeable structure. The model will include a repeated statement for subject household with household ID in the class statement. Also, the data structure will be ordered according to household ID and subject ID in household.

Treatment groups will be compared using a generalized estimating equation for logistic regression with an exchangeable working correlation structure. The model will include treatment, investigator type (dermatologist vs other), household number of randomly assigned subjects (1 subject per household vs 2 subjects per household), age, and baseline lesion count as factors. The odds ratio between SB206 12% and vehicle gel, 95% confidence intervals 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. The difference in proportion confidence interval will be calculated using the following formula:

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

Where the SE =

$$\sqrt{p_{SB206}^2(1-p_{SB206})^2\, s_{SB206}^2 + p_{Vehicle}^2(1-p_{Vehicle})^2\, s_{Vehicle}^2 - 2p_{SB206}(1-p_{SB206})p_{Vehicle}(1-p_{Vehicle}) * \left(\frac{s_{SB206}^2 + s_{Vehicle}^2 - s_{Odds\ Ratio}^2}{2}\right)}$$

The p_{SB206} and $p_{Vehicle}$ are the transformed predicted log odds at the mean of the covariates, s^2's are the standard errors of the predicted log odds and the odds ratio.

As a sensitivity analysis, the above primary analysis model will be applied to the PP Population. An additional sensitivity analysis counting subjects who discontinued prior to Week 12 or have a missing lesion count assessment but who demonstrated complete clearance at the last collected lesion assessment as responders will be presented. The impact of mis-stratifications may be explored via a sensitivity analysis.

An analysis where the complete clearance response probability for each dropout prior to Week 12 will be independently generated across the following scenarios (Vehicle response probability, SB206 response probability):

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

The analysis will be produced 100 times and then the results for the estimated log odds ratio for treatment and its estimated standard error from each of the imputations will be combined using PROC MIANALYZE.

An additional sensitivity analysis will be performed in a subset of the ITT population where only 1 subject from each household is chosen to contribute to the model based on the subject with the highest number of baseline treatable MC and the oldest to break ties, if needed. A logistic regression model including treatment, investigator type, age, and baseline lesion counts will be utilized.

11.2 Secondary Efficacy Analyses

The secondary endpoint of the proportion of subjects with complete clearance of all treatable MC at Week 8 will be analyzed in the same manner as the primary endpoint. A sensitivity analysis using the PP Population will be provided.

11.3 Exploratory Analyses

The exploratory endpoints based on the proportion of subjects achieving complete clearance or 75%, 90%, or 95% reductions will be analyzed in the same manner as the primary endpoint.

Since the within-household correlation is expected to be small and the change and percent change from Baseline in the number of treatable MC are exploratory, they 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; an unstructured covariance matrix will be utilized. If the calculation of the percent change from baseline is influenced by outliers with calculated values >100%, then the influence of outliers will be avoided for analysis by censoring them so that all values were in the range of -100% to 100%. If the model fails to converge, then other correlation structures will be explored.

Since the within-household correlation is expected to be small and time to first complete clearance of all MC is exploratory, it 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. Differences in Kaplan-Meier curves between the treatments will be tested for significance using a stratified log-rank test.

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

The change from Baseline of the composite score from age-matched (at Baseline) DLQI/CDLQI will be summarized descriptively and separately for each questionnaire. The scoring algorithms are detailed in Appendix A. The CDLQI will be examined in the following Week 12 response categories: complete clearance, 95% reduction in lesion counts, 90% reduction in lesion counts, and subjects who did not achieve complete clearance. Additionally, the changes from Baseline in the following subscales: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment, for DLQI, and Symptoms and Feelings, Leisure, School or Holidays, Personal Relationships, Sleep, and Treatment, for CDLQI, and each question will be summarized descriptively.

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.

12. OTHER ANALYSES

The following analyses of BOTE vs lesion count/complete clearance will be presented:

- Percent change from Baseline at Week 12 in relation to the highest BOTE score during treatment.
- Complete clearance at Week 12 in relation to the highest BOTE score during treatment.

- Percent change from Baseline at each visit in relation to BOTE score at Week 2.
- Complete clearance at each visit in relation to BOTE score at Week 2.

In these analyses, the BOTE scores will be analyzed in the ITT Population as follows:

1. Dichotomized:
    a. Score of 0 or 1: No to Mild
    b. Score of 2, 3, or 4: Moderate to Very Severe

A shift table comparing the baseline BOTE score to each scheduled postbaseline assessment will be presented for the Safety Population.

13. SAFETY ANALYSES

All safety analyses will be based on the Safety Population.

A listing of all deaths will be presented.

13.1 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are 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 medication 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; see Appendix B for the imputation of missing dates algorithm. Verbatim terms in the eCRFs will be mapped to preferred terms and system organ classes using the MedDRA Version 22.0.

Each AE summary will be displayed by treatment group. Summaries that are displayed by system organ classes and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs that contain an overview of each item below.
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and maximum severity. At each level of subject summarization, a subject is classified according to the maximum severity if the subject reported 1 or more events. Adverse events with missing severity will be considered severe for this summary.

- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). Related AEs are those reported as "Definite," "Probable," or "Possible," and unrelated AEs are those reported as "Unlikely" or "Unrelated." At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to study drug discontinuation by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to death as an outcome by MedDRA system organ class and preferred term.

Separate listings of all AEs, all SAEs and all AEs leading to study drug discontinuation will be provided.

13.2 Local Skin Reaction

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.

13.3 Events of Special Interest

Events of Special Interest will include subjects with any TEAE where the preferred term contains "application site", subjects with at least 1 post-baseline occurrence of moderate BOTE inflammation score, or subjects with at least 1 post-baseline LSR component score ≥ 1. A summary including the number and percentage of subjects with at least 1 event of special interest, AEs of interest by MedDRA system organ class and preferred term, at least 1 moderate BOTE inflammation score, and any LSR component score ≥ 1 will be provided for the Safety Population. The analysis will also be repeated with the LSR criteria revised to include any post-baseline LSR component (excluding erythema) score ≥ 1 and erythema score ≥ 2.

13.4 Urine Pregnancy Test

Urine pregnancy test results will be included in a data listing only.

13.5 Physical Examination

A shift table summarizing the shift from Baseline to end of treatment in normal/abnormal will be presented.

13.6 Patch Testing

A table summarizing any patch testing results by time point may be presented.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following modifications and/or clarifications to the methodology specified in the protocol will be:

- The DLQI and CDLQI will be summarized separately
- The order of the exploratory endpoints was updated
- The Mean percent change in baseline endpoint was updated to be more generic in order to analyze the median in the case of skewness
- Proportion of subjects with 90% and 95% clearance exploratory endpoints were added in order to provide additional clinically meaningful categories for analysis

15. REFERENCES

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16. APPENDICES

Appendix A: Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) Scoring

DLQI:

Question	Scoring	Subscale
1. Over the last week, how **itchy, sore, painful** or **stinging** has you skin been?	Very much = 3 A lot = 2 A little = 1 Not at all = 0	Symptoms and Feelings
2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much = 3 A lot = 2 A little = 1 Not at all = 0	Symptoms and Feelings
3. Over the last week, how has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Daily Activities
4. Over the last week, how much has your skin influenced the **clothes** you wear?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Daily Activities
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Leisure
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Leisure
7. Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes = 3 No Not Relevant = 0 A lot = 2 A little = 1 Not at all = 0	Work and School
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Personal Relationships

Question	Scoring	Subscale
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Personal Relationships
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much = 3 A lot = 2 A little = 1 Not at all/Not Relevant = 0	Treatment

Note: DLQI is administered in subjects ≥ 16 years old.

The DLQI composite score is then the sum of the scores to all 10 questions and will range from 0 to 30. If 1 question is unanswered, this is allocated a score of 0 and the DLQI score is then summed. If 2 or more questions are unanswered, the questionnaire is not scored.

The subscales will be expressed as percentages of the maximum score:

Subscale	Maximum Score
Symptoms and Feelings	6
Daily Activities	6
Leisure	6
Work and School	3
Personal Relationships	6
Treatment	3

CDLQI:

Question	Scoring	Subscale
1. Over the last week, how **itchy**, **"scratchy"**, **sore**, or **painful** has your skin been?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Symptoms and Feelings
2. Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Symptoms and Feelings
3. Over the last week, how has your skin affected your **friendships**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Personal Relationships
4. Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
5. Over the last week, how much has your skin trouble affected **going out, playing,** or **doing hobbies**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
6. Over the last week, how much have you avoided swimming or **other sports** because of your skin trouble?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Leisure
7. Last week, was it **school time**? If **school time:** Over the last week, how much did your skin problem affect your **school work**? Was it **holiday time**? If **holiday time:** Over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school = 3 Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	School or Holidays
8. Over the last week, how much trouble have you had because of your skin with other people **calling you names, teasing, bullying, asking questions** or **avoiding you**?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Personal Relationships

Question	Scoring	Subscale
9. Over the last week, how much has your **sleep** been affected by your skin problem?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Sleep
10. Over the last week, how much of a problem has the **treatment** for your skin been?	Very much = 3 Quite a lot = 2 Only a little = 1 Not at all = 0	Treatment

Note: CDLQI is administered in subjects 4 years old up to 16 years old.

The CDLQI composite score is then the sum of the scores to all 10 questions and will range from 0 to 30. If a question is unanswered, this is allocated a score of 0 and the CDLQI score is then summed.

The subscales will be expressed as percentages of the maximum score:

Subscale	Maximum Score
Symptoms and Feelings	6
Leisure	9
School or Holidays	3
Personal Relationships	6
Sleep	3
Treatment	3

Appendix B: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, and shading will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., μ, α, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.
- Means and medians will be presented to 1 more decimal place than the raw data. Standard deviations will be presented to 2 more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source **table number**(s) if applicable (in case aggregated results like mean or median are plotted) or the source listing(s) (in case individual responses are plotted) and/or source dataset(s) (e.g., AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- For box plots, the horizontal line will represent the median, + represents the group mean, the length of the box represents the interquartile range (25^{th}-75^{th} percentiles), and the whiskers will represent the minimum and maximum.
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (e.g., AdaM).
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Listings

- Formal organization of the listing may be changed during programming, if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be
  - "PROGRAM SOURCE: …\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

  where extract date (e.g., data cut off, database lock) is the date stamp of the data snapshot used.

Missing or incomplete dates (i.e., AEs, concomitant medications, and start dates of current molluscum episode and initial diagnosis)
The most conservative approach will be systematically considered. If the AE onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a TEAE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first application of study drug, provided the start month and year are the same as the first application of study drug and the stop date is either after the first application of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first application of study drug, provided the start year is the same as the first application of study drug and the stop date is either after the first application of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013) or the subject's date of birth, whichever is latest.
- If the start date is completely missing and the stop date is either after the application of study drug or completely missing, the start date will be estimated to be the first day of study drug application. Otherwise, the start date will be estimated to be the first day of the same year as the stop date or the subject's date of birth, whichever is latest. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing and the event is not continuing, the event will be assumed to be after first application of study drug and will be imputed using the last known date on the study.

For the start dates of current molluscum episode and initial diagnosis, the day will be estimated as "01" if only day is missing. If both month and day are missing, then it will be estimated as "01-JUN-YYYY" or the subject's date of birth, whichever is latest.

If the start date of current molluscum episode is partial, then the following imputation will be made:

- If only the day is unknown, the day will be assumed to be the first day of the month or the date of birth, whichever is later.
- If the day and month are missing, then the start date will be estimated to be June 1st or the date of birth, whichever is later.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days** – A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the formulas noted below:
  Duration in days = date2 – date1 + 1.
- **Months –** A duration expressed in months will be calculated as (later date – earlier date + 1)/(30.4167).
- **Years –** A duration expressed in years will be calculated as (later date – earlier date + 1)/(365).
- **Change from Baseline** – Change from Baseline will be calculated as follows:
  Change from Baseline = postbaseline value – baseline value.
- **Percent change from Baseline** – Change from Baseline will be calculated as follows:
  Percent change from Baseline = (postbaseline value – baseline value)/baseline value × 100.

Appendix C: SAS Programming QC Requirements

Derived datasets are independently programmed by two programmers. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study analysis dataset specifications provided to the client at study conclusion.

Tables are independently reprogrammed by a second programmer for numeric results.
Listings are checked for consistency against corresponding tables, figures, and derived datasets.
Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.

Appendix D: List of Tables, Figures, and Listings

The following proposal for section 14 and 16.2 is completed according to ICH E3 guidelines. The ICH heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.

The shells for the outputs below are contained in the file titled "Novan NI-MC301 SAP TLFs Version 3.0".

TABLES, FIGURES, AND GRAPHS

Table Number	**Table Title**	**Analysis Population**
14	**TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**	
14.1	**DEMOGRAPHIC DATA**	
14.1.1.1	Subject Disposition	Enrolled
14.1.1.2	Enrollment by Site	ITT
14.1.2.1	Demographic and Baseline Characteristics	Safety
14.1.2.2	Demographic and Baseline Characteristics	ITT
14.1.2.3	Demographic and Baseline Characteristics	PP
14.1.3.1	Study Drug Exposure	Safety
14.1.3.2	Study Drug Compliance	Safety
14.1.4	Significant and Major Protocol Deviations	ITT
14.1.5	Medical History	ITT
14.1.6.1	Prior Medications	ITT
14.1.6.2	Concomitant Medications	ITT
14.2	**Efficacy data**	
14.2.1.1	Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.2	Complete Clearance Lesion Count Response at Week 12	PP

Table Number	Table Title	Analysis Population
14.2.1.3	Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.4	Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	PP
14.2.1.6	Proportion of Subjects with Complete Clearance at Week 12 by Subgroup	ITT
14.2.1.7	Dropout Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.8	One Subject Per Household Sensitivity Analysis: Complete Clearance Lesion Count Response at Week 12	ITT
14.2.1.9	Exploratory Analysis of the Variability of Treatment Effect of Complete Clearance Lesion Count Response at Week 12 Across Pools of at Least 17 Subjects	ITT
14.2.1.10	Exploratory Analysis of the Variability of Treatment Effect of Complete Clearance Lesion Count Response at Week 12 Across Pools of at Least 10 Subjects	ITT
14.2.2.1	Complete Clearance Lesion Count Response at Week 8	ITT
14.2.2.2	Complete Clearance Lesion Count Response at Week 8	PP
14.2.3.1	Complete Clearance Lesion Count Response at Weeks 2 and 4	ITT
14.2.3.2.1	Summary of a 95% Reduction in Lesion Counts from Baseline Response by Visit	ITT
14.2.3.2.2	Summary of a 90% Reduction in Lesion Counts from Baseline Response by Visit	ITT
14.2.3.2.3	Summary of a 75% Reduction in Lesion Counts from Baseline Response by Visit	ITT
14.2.3.3.1	Percent Change from Baseline in Lesion Count by Visit	ITT
14.2.3.4.1	Change from Baseline in Lesion Count by Visit	ITT
14.2.3.5	Summary of Recurrence after Complete Clearance	ITT
14.2.3.6.1	Kaplan-Meier Estimates of Time to Complete Clearance (Days) from Start of Dosing	ITT
14.2.3.7	Summary of Scarring and Keloid by Visit	ITT
14.2.3.8.1	Summary of the Dermatology Life Quality Index (DLQI) and Subscales by Visit	ITT
14.2.3.8.2	Summary of the Dermatology Life Quality Index (DLQI) Individual Questions by Visit	ITT
14.2.3.8.3.1	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT
14.2.3.8.3.2	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT: Complete Responders at Week 12
14.2.3.8.3.3	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT: Subjects with at least a 95% Reduction in

Table Number	Table Title	Analysis Population
		Lesion Counts at Week 12
14.2.3.8.3.4	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT: Subjects with at least a 90% Reduction in Lesion Counts at Week 12
14.2.3.8.3.5	Summary of the Children's Dermatology Life Quality Index (CDLQI) and Subscales by Visit	ITT: Subjects who did not Achieve Complete Clearance at Week 12
14.2.3.8.4	Summary of the Children's Dermatology Life Quality Index (CDLQI) Individual Questions by Visit	ITT
14.2.3.9	Summary of Increase in Subject-Reported Spread to Household Members by Visit	ITT
14.2.3.10.1	Summary of Lesion Counts by Highest Dichotomized BOTE Score	ITT
14.2.3.10.3	Percent Change from Baseline in Lesion Count over Time by Dichotomized Week 2 BOTE Score	ITT
14.2.3.10.4	Summary of Complete Clearance by Visit and Dichotomized Week 2 BOTE Score	ITT
14.2.3.10.5	Summary of the Beginning of the End (BOTE) Inflammation Score Results by Visit	Safety
14.3	**Safety data**	
14.3.1	**Displays of Adverse Events**	
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.3	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety
14.3.1.5	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.6	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term	Safety

Table Number	Table Title	Analysis Population
14.3.1.7	Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety
14.3.2	**Listings of deaths, other serious and significant adverse events**	
14.3.2.1	Listing of Serious Adverse Events	Safety
14.3.2.2	Listing of Adverse Events Leading to Study Drug Discontinuation	Safety
14.3.2.3	Listing of Deaths	Safety
14.3.6	**Other safety data**	
14.3.6.1.1	Summary of Local Skin Reaction (LSR) Composite Score by Visit	Safety
14.3.6.1.2	Summary of Local Skin Reaction (LSR) Score Results by Visit	Safety
14.3.6.1.3	Shift Summary of Local Skin Reaction (LSR) Score Results by Visit	Safety
14.3.6.2	Summary of Events of Special Interest	Safety
14.3.6.3	Summary of Physical Examination Findings	Safety
14.3.6.4	Summary of Patch Testing Results	Safety

Figure Number	Figure Title	Analysis Population
14.2.1.5	Forest Plot: Odds Ratio (95% CI) of the Proportion of Subjects with Complete Clearance at Week 12	ITT
14.2.3.3.2	Percent Change from Baseline in Lesion Count over Time by Treatment Group	ITT
14.2.3.4.2	Mean Change from Baseline in Lesion Count over Time by Treatment Group	ITT
14.2.3.6.2	Kaplan-Meier Plot of Time to Complete Clearance (Days) from Start of Dosing	ITT
14.2.3.10.2	Plot of Complete Clearance at Week 12 by Highest Dichotomized Categorized BOTE Score	ITT

Section 16.2: **List of Data Listings**

ICH Listing Number	Listing Title	Analysis Population
16.1.7	Subject Randomization	ITT
16.2	**SUBJECT DATA LISTINGS**	
16.2.1	**Discontinued subjects**	
16.2.1.1	Subject disposition	Enrolled
16.2.2	**Protocol deviations**	
16.2.2.1	Protocol Deviations	ITT
16.2.2.2	Inclusion/Exclusion Criteria	Enrolled
16.2.3	**Subjects excluded from the efficacy analysis**	
16.2.3.1	Analysis Populations	Enrolled
16.2.4	**Demographic data**	
16.2.4.1	Demographic and Baseline Characteristics	ITT
16.2.4.2	Patch Testing Consent/Assent	Enrolled
16.2.4.3	Medical History	ITT
16.2.4.4	Prior and Concomitant Medications	ITT
16.2.5	**Compliance and/or drug concentration data**	
16.2.5.1	Study Drug Administration	Safety
16.2.5.2	Study Drug Accountability	Safety
16.2.5.3	Treatment Adjustment	Safety
16.2.5.4	Treatment Compliance	Safety
16.2.6	**Individual efficacy response data**	
16.2.6.1	Lesion Counts	ITT
16.2.6.2	Lesion Count Derived Efficacy Variables and Time to Complete Clearance	ITT
16.2.6.3	Scarring/Keloid Assessment	ITT
16.2.6.4	Dermatology Life Quality Index (DLQI) and Subscales	ITT
16.2.6.5	Children’s Dermatology Life Quality Index (CDLQI) and Subscales	ITT
16.2.6.6	Household Transmission	ITT
16.2.7	**Adverse events listings**	

ICH Listing Number	Listing Title	Analysis Population
16.2.7.1	All Adverse Events	Safety
16.2.8	**Listing of individual laboratory measurements by subject, when required by regulatory authorities**	
16.2.8.1	Urine Pregnancy Test	Safety
16.2.9	**Other data**	
16.2.9.1	Beginning-of-the-End (BOTE) Inflammation Score	Safety
16.2.9.2	Local Skin Reactions (LSR)	Safety
16.2.9.3	Physical Examination	Safety
16.2.9.4	Patch Testing	Safety
16.2.9.5	Telephone Contact	ITT
16.2.9.6	Subjects who Require a Narrative	ITT