DRUG:	SB206/NVN1000
STUDY NUMBER(S):	NI-MC201
PROTOCOL(S) TITLE:	A PHASE 2 MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, ASCENDING DOSE STUDY OF SB206 IN SUBJECTS WITH MOLLUSCUM CONTAGIOSUM
IND NUMBER:	137015
SPONSOR:	Novan, Inc
ORIGINAL PROTOCOL DATE:	10 November 2017
VERSION NUMBER:	Version 3.0
AMENDMENT VERSION DATE:	29 June 2018

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A PHASE 2 MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, ASCENDING DOSE STUDY OF SB206 IN SUBJECTS WITH MOLLUSCUM CONTAGIOSUM

Study No: NI-MC201

Original Protocol Date: 10 November 2017

Protocol Version No: 3.0

Protocol Amendment Version Date: 29 June 2018

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: Teresa Reams, Clinical Study Manager	(Yes) No (circle one)	Teresa Reams	
Clinical Operations: Emily de Leon, Director of Clinical Development	(Yes) No (circle one)	Emily de Leon	29 Jun 2018
Biometrics: Todd Durham, Head of Biostatistics	(Yes) No (circle one)	Todd Durham	29 JUN 2018
Medical Lead: Tomoko Maeda-Chubachi, VP, Medical Dermatology	Yes No (circle one)		
Regulatory Affairs: Kevin Barber, VP, Regulatory Affairs	(Yes) No (circle one)	Kevin Barber	29 JUN 2018
Quality Assurance: Liz Troll, Head of Clinical Quality Assurance	Yes No (circle one)		

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Clinical Operations: Emily de Leon, Director of Clinical Development	Yes No (circle one)		
Biometrics: Todd Durham, Head of Biostatistics	Yes No (circle one)		
Medical Lead: Tomoko Maeda-Chubachi, VP, Medical Dermatology	Yes No (circle one)		6/29/18
Regulatory Affairs: Kevin Barber, VP, Regulatory Affairs	Yes No (circle one)		
Quality Assurance: Liz Troll, Head of Clinical Quality Assurance	Yes No (circle one)		

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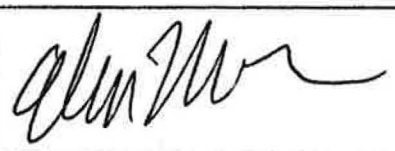
Clinical Operations: Emily de Leon, Director of Clinical Development	Yes No (circle one)		
Biometrics: Todd Durham, Head of Biostatistics	Yes No (circle one)		
Medical Lead: Tomoko Maeda-Chubachi, VP, Medical Dermatology	Yes No (circle one)		
Regulatory Affairs: Kevin Barber, VP, Regulatory Affairs	Yes No (circle one)		
Quality Assurance: Liz Troll, Head of Clinical Quality Assurance	(Yes) No (circle one)		24 JUN 2018

RATIONALE FOR AMENDMENT

This protocol amendment is to 1) add collection of blood samples for analysis of hMAP3 to confirm the level of systemic exposure to SB206 and 2) to add an unblinded analysis after all subjects have completed Cohort 3. Administrative changes and clarifications have also been included in this amendment.

IDENTIFICATION OF CHANGES

Any changes to the original protocol are identified below and are incorporated into this protocol amendment. All additions are identified using **bold underlined** text. Any deletions are identified using strikethrough text. The Table of Contents and internal references are updated to reflect current section numbers. Minor administrative changes were made as well to correct grammar, punctuation, etc.

Change 1: STUDY SUMMARY:

STUDY DESIGN:

Subjects will be treated once daily, twice daily or three times a week for up to 12 weeks to all lesions identified at Baseline and new lesions that arise during treatment. If a subject clears all lesions (confirmed by the Investigator at the next regular scheduled visit), the treatment period will end, and subjects will be followed for recurrence/new lesions until Week 12/ Early Termination (ET). **All QD dosing should be applied in the morning at home or in the clinic. All subjects should apply their last dose to accommodate the 1 to 6 hour window for blood draws. The exact time of the last dose preceding any scheduled visit will be collected.** Subjects will visit the clinic at Screening, Baseline, Week 1, Week 2, Week 4, Week 8, and Week 12.

Change 2: STUDY SUMMARY:

SECONDARY EFFICACY ENDPOINTS:

Proportion of subjects **achieving** at least a ~~achieving~~ 75% reduction from baseline in the number of MC at each visit.

Change 3: STUDY SUMMARY:

Exposure Endpoint

- **Determination of the hMAP3 plasma concentration at end of treatment, if quantifiable.**

Change 4: LIST OF ABBREVIATIONS

hMAP3 – Hydrolyzed N-Methylaminopropyl-trimethoxysilane

Change 5: 1.1 BACKGROUND

~~Clinical studies~~ **A clinical study** involving subjects with psoriasis **just completed** and **one in subjects with** atopic dermatitis ~~are~~ **is** ongoing.

Change 6: 1.1.1 PHARMACOKINETICS

In the recently completed study in subjects with psoriasis (NI-PS101) who were administered a cream formulation, SB414 6% (NVN1000 Ointment 12% co-administered with hydrogel), 6 of 23 subjects (26.0%) had at least one quantifiable hMAP3 plasma concentration following dosing. The mean (SD) Cmax of hMAP3 (18.89 [15.02] ng/mL) occurred at 1 hour postdose in the 6 subjects with quantifiable hMAP3 plasma concentrations. The plasma concentration gradually decreased after the peak and hMAP3 was below the the lower limit of quantitation (LLOQ) in all subjects at 12 hours postdose. Systemic exposure to the investigational product was negligible in the study. The clinical study report is under preparation. Analyses are currently ongoing to determine systemic exposure in a study of subjects with atopic dermatitis (NI-AD101) administered SB414 2% (NVN1000 Ointment 4% co-administered with buffered hydrogel) or 6% (NVN1000 Ointment 12% co-administed with buffered hydrogel).

Change 7: 1.2.1: DOSING REGIMEN

All QD dosing should be applied in the morning at home or in the clinic. All subjects should apply their last dose to accommodate the 1 to 6 hour window for blood draws. The exact time of the last dose preceding any scheduled visit will be collected. Each dose will consist of NVN1000 Gel or Vehicle Gel with an equal volume of hydrogel mixed thoroughly 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. Lesions on the labia and penis will not be treated.

Change 8: EXPOSURE ENDPOINT

3.5 Exposure Endpoint

Blood for determination of the hMAP3 plasma concentration will be collected at a single time point at the end of treatment to evaluate if quantifiable concentrations can be measured following repeated application.

Change 9: 4.1 STUDY DESIGN

Subjects will be treated once daily, twice daily or three times a week for up to 12 weeks to all lesions identified at Baseline and new lesions that arise during treatment. If a subject clears all lesions (confirmed by the Investigator at the next regular scheduled visit), the treatment period will end, and subjects will be followed for recurrence/new lesions until Week 12/ET. **All QD dosing should be applied in the morning at home or in the clinic. All subjects should apply their last dose to accommodate the 1 to 6 hour window for blood draws. The exact time of the**

last dose preceding any scheduled visit will be collected. Subjects will visit the clinic at Screening, Baseline, Week 1, Week 2, Week 4, Week 8, and Week 12/ET.

Change 10: Table 1: Schedule of Assessments

	Screening[1] (Day -28 to Day 1)	Visit 1[1] Baseline (Day 1)	Visit 2[2] Week 1 (Day 8 ±3)	Visit 3[2] Week 2 (Day 15 ±3)	Visit 4[2] Week 4 (Day 29 ±3)	Visit 5[2] Week 8 (Day 57 ±3)	Visit 6[2] Week 12/ET (Day 85 ±7)
Informed Consent (Assent)	X						
Demographics	X						
Medical and Medication History	X	X					
Lesion Counts	X	X	X	X	X	X	X
Physical Exam		X					X
Vital Signs		X	X	X	X	X	X
Chemistry & Hematology[3]		X					X
Methemoglobin[3,4]		X	X	X	X	X	X
Assessment of hMAP3 plasma concentration[5,6]							**X**
Urine Pregnancy Test[5,7]	X	X			X	X	X
Tolerability Evaluation		X	X	X	X	X	X
Photographs[6]		X			X		X
In Clinic Study Drug Application and Provide Subject Instructions		X					
Dispense Subject Diary		X			X	**X**	
Review Study Compliance			X	X	X	X	X
Collect Subject Diary					X	**X**	X
Drug Dispensed		X			X	X	
Collect Study Drug					X	X	X
Randomization		X					
Review Concomitant Medications and Adverse Events		X	X	X	X	X	X

[1] Screening and Baseline may occur on the same day.
[2] All visit dates are in reference to Baseline, e.g. Week 1 occurs 7 days after Baseline Visit.
[3]Collected at the last day of treatment.
[4]Collected via pulse co-oximetry at site.
[5] Blood for determination of the hMAP3 plasma concentration will be collected at a single time approximately 1 to 6 hours following last dose application. The time of the sample collection and the time of last dose preceding the scheduled visit will be recorded. The blood sample may be collected at the same time as the chemistry and hematology sample.
[56]Selected sites and subjects.
[7]Females 10 years of age and older. Subjects whose Baseline is within 7 days of Screening do not require UPT retesting.
~~[67]Selected sites and subjects.~~

Change 11: 5.4.1 SCREENING FAILURES

Subjects will ~~not~~ be allowed to rescreen.

Change 12: 6.1 GENERAL INSTRUCTIONS

The first application should be done at the clinic. ~~All study drug applications will be done at home except for the first dose on Day 1.~~

Change 13: 6.2.1: SCREENING (DAY -28 TO Day 1)

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)**, medication history and concomitant medication information.

Change 14: 6.2.4: VISIT 3/WEEK 2 (DAY 15±3)

6. If subject discontiues treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.

Change 15: 6.2.5: VISIT 4/WEEK 4 (DAY 29±3)

6. If subject discontiues treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.

Change 16: 6.2.6: VISIT 5/WEEK 8 (DAY 57±3)

6. If subject discontiues treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.

Change 17: 6.2.7 VISIT 6/WEEK 12/ET (DAY 85 ±7)

3. If subject is still on treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.

~~3. Collect blood samples for chemistry and hematology.~~

Change 18: 7.3.3 CLINICAL LABORATORY TESTS

Chemistry and hematology will be collected at Baseline and ~~Week 12/ET~~ **on the last day of treatment**. Clinically significant changes in laboratory values will be recorded as AEs.

Change 19: 7.4 EXPOSURE ASSESSMENT

7.4 EXPOSURE ASSESSMENT

At select sites, a blood sample will be collected at the Week 12 visit from those subjects who have not previously discontinued treatment. The sample will be collected at a single time point approximately 1 to 6 hours following application of study drug. The final dose may be either be done at home or in the clinic. The time of dose application and sample collection should be recorded. Blood may be collected at the same time as the chemistry and hematology sample, but the chemistry and hematology samples should be drawn first. If a subject discontinues treatment for any reason (e.g., lesion clearance, subject withdrawal, physician decision) before Visit 6, blood should be collected on the last day of treatment.

Instructions for processing and transporting plasma samples for analysis will be described separately.

Change 20: 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 ~~from Premier Research~~ 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.

Several analyses of unblinded data are planned throughout the study. A Data Safety Monitoring Board (DSMB) will conduct an unblinded review of safety and tolerability data after 30 subjects are enrolled and treated for two weeks within in each cohort. ~~Unblinded personnel who are not otherwise involved in the study will prepare the data for review.~~ **After all subjects in Cohort 3 have completed their last study visits, the database for all subjects in Cohorts 1-3 will be frozen for purposes of an interim analysis of safety and efficacy data. While this interim analysis is being prepared, the study will complete through Cohort 4 and the final analysis will be based on all subjects in Cohorts 1-4: Cohort 4 (QD dosing of SB206 8% or 12% vs. vehicle). Personnel who are not otherwise involved in the study will prepare the unblinded data and summary tables for the interim analysis.**

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. **Individual** ~~T~~**t**reatment unblinding is discouraged since knowledge of the treatment assignment will not materially change the planned management of a medical emergency.

Change 21: 8.6 ACCOUNTABILITY

Study drug returned by subjects at Weeks 4 and 8 will be held on site until ~~final~~ accountability has been completed. ~~Upon completion or termination of the study, t~~**T**he site will be instructed on return or destruction of used and unused clinical supplies.

Change 22: 11.1 General Procedures

Prior to the ~~database lock~~ **release of unblinded information through Cohort 3**, a detailed, finalized Statistical Analysis Plan (SAP) will be completed and placed on file.

Change 23: 11.3 ANALYSIS POPULATIONS

The exposure population will consist of all subjects who receive at least 1 application of active study medication and had a blood sample collected and successfully analyzed for the hMAP3 plasma concentration.

The per-protocol population (PP) will consist of all subjects in the mITT population and have no significant protocol deviations **that impact the analyses of the efficacy endpoints.**

Change 24:11.4.1 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

Change 25: 11.4.2 EFFICACY ANALYSIS

Secondary endpoints will be analyzed on the mITT **and ITT** population as follows:

Change 26: 11.4.3.4 LABORATORY ASSESSMENTS

Blood chemistry and hematology values will be reported individually at Baseline and **day of last dose, which may occur at any time during the study. Therefore, the study day of the last dose will be used to assign the laboratory values to the closest study visit (**Week **1, 2, 4, 8, or** 12~~/ET~~**)**. Laboratory test results will be summarized descriptively at Baseline and ~~Week 12/ET~~ **each visit**. Additionally, shifts from Baseline to ~~Week 12/ET~~ **each visit** in laboratory test results based on normal ranges will be summarized with descriptive statistics. The last laboratory evaluation prior to the first dose of study drug will be used as Baseline for all laboratory analyses. Any clinically significant changes from Baseline will be documented as an AE.

Change 27:11.5 ANALYSIS OF hMAP3 PLASMA CONCENTRATIONS

11.5 Analysis of hMAP3 Plasma Concentrations

Plasma concentrations of hMAP3, a silicon-containing hydrolyzed monomer of the polymeric NVN1000 drug substance will be determined. Results will be presented in data listings by subject. If quantifiable concentrations are observed, the results will be summarized descriptively.

Change 28: 11.6 INTERIM ANALYSIS

~~No interim analyses are planned for this study.~~

After all subjects in Cohort 3 have completed their last study visits, the database for all subjects in Cohorts 1-3 will be frozen for purposes of an interim analysis of safety and efficacy data. While this interim analysis is being prepared, the study will complete through Cohort 4 and the final analysis will be based on all subjects in Cohorts 1-4: Cohort

4 (QD dosing of SB206 8% or 12% vs. vehicle). Personnel who are not otherwise involved in the study will prepare the unblinded data and summary tables for the interim analysis. The interim analysis will not impact the final analysis since the study does not involve any formal hypothesis testing.

Change 29: 12.1 GOOD CLINICAL PRACTICE

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 ~~Premier Research~~ **the CRO** before investigational product will be shipped to the study site.

Change 30: 13.2 MONITORING

All aspects of the study will be monitored by ~~Premier~~ **the CRO** or Novan according to Good Clinical Practices (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)).

NI-MC201

A Phase 2 Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Ascending Dose Study of SB206 in Subjects with 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 SUMMARY

Title: A Phase 2 Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Ascending Dose Study of SB206 in Subjects with Molluscum Contagiosum

Rationale: Molluscum Contagiosum (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 duration of infection is often more than a year.

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 interfere in physician-patient relationships. Repeated ablative treatment become difficult. Topical application of SB206 which releases nitric oxide may accelerate resolution of MC without causing pain, and provide an effective, safe and convenient treatment option of MC.

Target Population: Males and females, 2 years of age and older, with a minimum of 3 and a maximum of 70 MC lesions at baseline.

Number of Subjects: Approximately 192 subjects with a possibility to increase up to 256 subjects.

Objectives: This study is being conducted to evaluate the efficacy, safety and tolerability of SB206 for the topical treatment of MC. Results will be used to determine the dose(s) for future studies.

Study Design: This is a phase 2 multi-center, randomized, double-blind, vehicle-controlled ascending dose study to be conducted in up to approximately 192 or 256 non-immunocompromised subjects with molluscum contagiosum. After obtaining informed consent, subjects who satisfy entry criteria will be randomized 3:1 (active: vehicle) to ascending, sequential dose cohorts of SB206. The highest tolerated dose will also be run in a cohort once daily. Approximately 64 subjects will be randomized to each cohort (see study schematic). At randomization, subjects will be stratified by number of lesions at Baseline (3-18; 19-70) and atopic dermatitis (AD) history (with AD history vs w/o AD history). A maximum of 16 adult subjects, ages 18 and above, will be randomized into each cohort.

Subjects will be treated once daily, twice daily or three times a week for up to 12 weeks to all lesions identified at Baseline and new lesions that arise during treatment. If a subject clears all lesions (confirmed by the Investigator at the next regular scheduled visit), the treatment period will end, and subjects will be followed for recurrence/new lesions until Week 12/ Early Termination (ET). All QD dosing should be applied in the morning at home or in the clinic.

All subjects should apply their last dose to accommodate the 1 to 6 hour window for blood draws. The exact time of the last dose preceding any scheduled visit will be collected. Subjects will visit the clinic at Screening, Baseline, Week 1, Week 2, Week 4, Week 8, and Week 12.

After 30 subjects randomized in a cohort have completed 2 weeks of treatment, the Data Safety Monitoring Board (DSMB) will review the available unblinded safety and tolerability data. Using predetermined criteria documented in the DSMB charter, the DSMB will determine if the data supports escalating to the next highest dose for the next cohort or if the data shows the dose is not tolerable decreasing to the next lower dose or frequency for the next cohort. After 64 subjects are randomized to a cohort, the next cohort will be opened. Once a subject is randomized to a cohort, the subject will stay in the cohort. If a subject discontinues treatment, the subject will continue in the study and be followed until Week 12 unless the subject/caregiver withdraws consent.

Primary Efficacy Endpoint:

Proportion of subjects achieving complete clearance of all molluscum contagiosum at Week 12 (Subjects who achieved complete clearance before Week 12 need to maintain complete clearance at Week 12).

Secondary / Exploratory Endpoints:

Secondary Efficacy Endpoints

- Proportion of subjects achieving complete clearance of all MC at each visit
- Time to complete clearance of all MC
- Proportion of subjects achieving at least a 75% reduction from baseline in the number of MC at each visit
- Mean change from baseline in number of MC at each visit
- Mean percent change from baseline in number of MC at each visit

Exploratory Endpoints

- Proportion of subjects whose lesion count decreases and increases from baseline at each visit
- Absolute number of subjects who show new lesions after once achieving complete clearance at each visit

Safety Endpoints

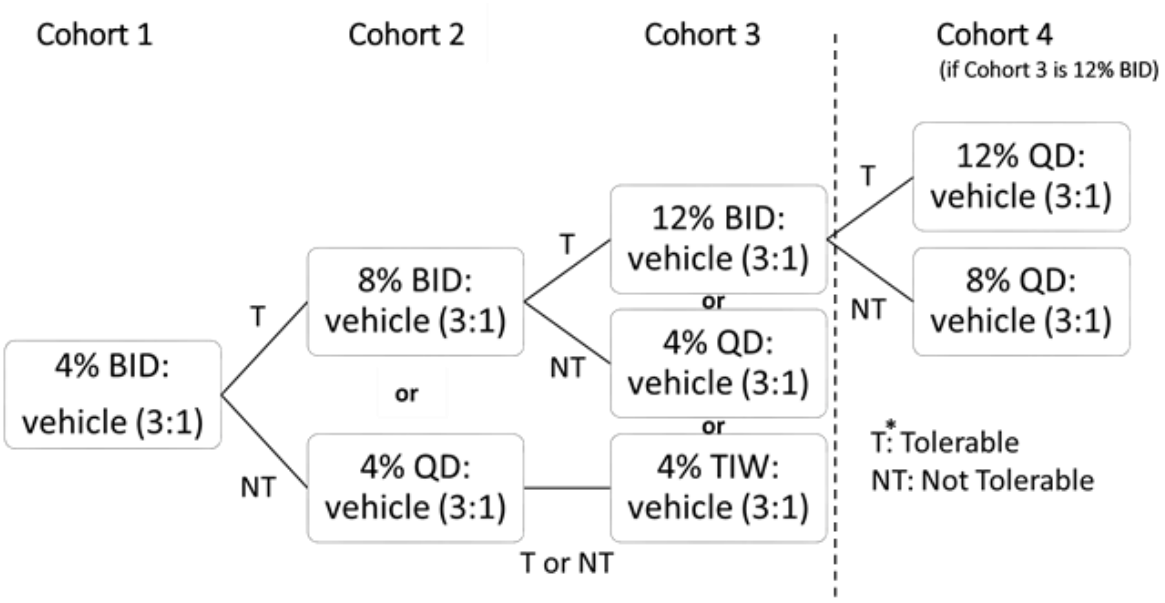
- Tolerability assessment (Investigator, Subject)

- Adverse Events

Exposure Endpoint

- Determination of hMAP3 plasma concentration at end of treatment, if quantifiable

STUDY SCHEMATIC



*Note: T or NT is decided on a cohort basis, not on a subject level, after 30 subjects have completed 2 weeks of treatment.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
AD	Atopic Dermatitis
BID	Twice Daily
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Clinical Research Organization
DSMB	Data and Safety Monitoring Board
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
mITT	Modified Intent-to-Treat
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
MC	Molluscum Contagiosum
MedDRA	Medical Dictionary of Regulatory Affairs
NOVAN	Novan, Inc

PP	Per-Protocol Population
QD	Once Daily
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
TIW	Three Times a Week
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 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.

Acidified nitrite was used in a double-blind, group-sequential clinical trial to demonstrate the efficacy of nitric oxide donor in treating MC (Ormerod et al, 1999). In the study, subjects received either 5% sodium nitrite co-applied with 5% salicylic acid under occlusion, or identical cream with 5% salicylic acid, omitting sodium nitrite. Completion was defined as 3 months, or when the patient was cured or dropped out, if sooner. The study demonstrated that a 75% cure rate in the active treatment group and 21% cure with control treatment ($P = 0.01$). The mean time to cure was 1.83 months. Staining of the skin and irritation were frequent side-effects but did not prevent successful treatment.

Novan, Inc. (Novan) is conducting this Phase 2 multi-center, randomized, double-blind, vehicle-controlled, ascending dose study of SB206 in subjects 2 years of age and older with molluscum contagiosum. SB206 is a topical gel, formed by mixing NVN1000 Gel with hydrogel. NVN1000 Gel contains NVN1000, a nitric oxide-releasing macromolecule containing covalently bound N-diazeniumdiolate nitric oxide donors; nitric oxide release from the macromolecule is initiated by mixing NVN1000 Gel with hydrogel.

Topical formulations of NVN1000 at concentrations ranging from 1-16% have been studied in 19 completed studies. Over 1900 healthy volunteers or subjects with acne, genital warts or tinea pedis

have been exposed to Vehicle and 2600 exposed to NVN1000. In clinical studies completed to date, topical application of NVN1000 has generally been well-tolerated with no safety concerns identified. A clinical study involving subjects with psoriasis just completed and one in subjects with atopic dermatitis is ongoing.

1.1.1 Pharmacokinetics

The systemic bioavailability of NVN1000 after dermal administration has been investigated in two maximum use studies in adults and adolescent subjects with moderate to severe acne vulgaris, and no detectable systemic exposure was observed. In adult subjects with moderate to severe acne vulgaris (NI-AC101) administration of SB204 8% (NVN1000 Gel 16% co-administered with hydrogel) or Vehicle Gel daily for 5 days to the face, chest, back, upper shoulders twice daily (BID) (17% BSA) showed no detectable systemic exposure on Day 1 or Day 5 to 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 PK, study (NI-AC103) in adolescents (ages 9-16 years) with moderate to severe acne vulgaris topical administration of SB204 4% was applied 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 ECG effects following SB204 application (NI-AC104), there was no detectable systemic exposure to hMAP3 and no difference in plasma nitrate levels in 48 subjects with moderate to severe acne treated with SB204 (NVN1000) Gel 4%, SB204 (NVN1000) Gel 12% or Vehicle Gel applied to 17% BSA. No changes in ECG were observed with therapeutic or supratherapeutic doses of SB204.

In the recently completed study in subjects with psoriasis (NI-PS101) who were administered a cream formulation, SB414 6% (NVN1000 Ointment 12% co-administered with hydrogel), 6 of 23 subjects (26.0%) had at least one quantifiable hMAP3 plasma concentration following dosing. The mean (SD) Cmax of hMAP3 (18.89 [15.02] ng/mL) occurred at 1 hour postdose in the 6 subjects with quantifiable hMAP3 plasma concentrations. The plasma concentration gradually decreased after the peak and hMAP3 was below the the lower limit of quantitation (LLOQ) in all subjects at 12 hours postdose. Systemic exposure to the investigational product was negligible in the study. The clinical study report is under preparation. Analyses are currently ongoing to determine systemic exposure in a study of subjects with atopic dermatitis (NI-AD101) administered SB414 2% (NVN1000 Ointment 4% co-administered with buffered hydrogel) or 6% (NVN1000 Ointment 12% co-administed with buffered hydrogel).

1.1.2 Preclinical Pharmacology

During the development of SB204 (NVN1000 Gel) for acne, SB206 (NVN1000 Gel) for the treatment of external genital warts and perianal warts, SB208 (NVN1000 Gel) for tinea pedis and SB414 (NVN1000 Ointment), Novan has conducted over 90 nonclinical studies. With 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 NVN1000), administered as twice daily 8% SB206 Gel or once daily 16% 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). There was no evidence of systemic nitric oxide or hMAP3 exposure at any of the dose levels tested. This study with SB206 Gel in miniature swine was successful in bridging the safety of topical administration of NVN1000 in the SB204 formulation with the SB206 formulation.

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

1.1.3 Potential for Drug-Drug Interactions

Due to the low systemic exposure observed to date with SB204 clinically and with SB206 nonclinically the risk of drug-drug interactions is low.

1.1.4 Clinical Adverse Event Profile

Topical formulations of NVN1000 at concentrations ranging from 1-16% have been studied in 19 completed studies. Over 1900 healthy volunteers or subjects with acne, genital warts or tinea pedis have been exposed to Vehicle and 2600 exposed to NVN1000.

Novan has 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; twice daily 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 nine completed Phase 1 studies in healthy volunteers or subjects with acne vulgaris, three 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 NVN1000 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 once daily dosing to one or both feet; there were no application site adverse events reported.

In completed studies, no clinically significant changes have been observed in laboratory assessments, including methemoglobin, in subjects treated with topical NVN1000. The percent

methemoglobin in blood has been measured using pulse co-oximetry in the Phase 1 and Phase 2 studies in the acne, external genital wart, and anti-fungal programs. There have been no reports of methemoglobinemia or observed methemoglobin levels greater than 3% in subjects treated with topical NVN1000 in completed studies. Fluctuations in methemoglobin during treatment have been similar in subjects treated with topical NVN1000 or Vehicle. There have been no clinically significant changes in physical examination, including vital signs, in subjects treated with topical NVN1000.

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 NVN1000 there was no adverse findings in male fertility parameters or reproductive parameters in either sex.

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

1.1.7 Potential Risk to Fetal Development

Oral administration of NVN1000 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 nonclinically observed to date, the risk to fetal development is low.

In prior studies using NVN1000 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 interfere in physician-patient relationships. Repeated ablative treatment become difficult. Using anesthesia involves safety risk and costs. Not treating increases further dissemination of the disease. Topical application of SB206 which releases nitric oxide may accelerate resolution of MC without causing pain, and provide an effective, convenient treatment option of MC. Prevention of further dissemination of the disease is also important from public health perspective.

1.2.1 Dosing Regimen

A thin layer of SB206 4%, SB206 8%, SB206 12% or Vehicle Gel will be applied once daily, twice daily, or three times a week depending on the assigned cohort, to all affected areas of MC for 12 consecutive weeks (84 days). Subjects/caregivers will apply the study drug to all lesions identified at Baseline and new lesions that arise during treatment. If a subject clears all lesions (confirmed by the Investigator at the next regular scheduled visit), the treatment period will end and subjects will be followed for recurrence/new lesions until Week 12/ET.

All QD dosing should be applied in the morning at home or in the clinic. All subjects should apply their last dose to accommodate the 1to 6 hour window for blood draws. The exact time of the last dose preceding any scheduled visit will be collected. Each dose will consist of NVN1000 Gel or Vehicle Gel with an equal volume of hydrogel mixed thoroughly 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. Lesions on the labia and penis will not be treated.

Study personnel will ensure that the subjects or caregivers can identify the treatment area(s) and know where to apply the study drug. 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.

1.2.2 Dose Selection Rationale

Based on the previous nonclinical and clinical safety profiles of NVN1000 topical formulations and a nonclinical NOAEL approximately 1.8 fold higher than the highest dose of SB206 to be applied in this study, these doses are expected to be safe and well tolerated.

2 STUDY OBJECTIVES

- To evaluate the efficacy of SB206 over vehicle gel for up to 12 weeks of topical treatment of MC
- To evaluate the safety and tolerability of SB206 for up to 12 weeks treatment of MC
- To evaluate and determine a safe and efficacious SB206 dose level for future studies

3 STUDY ENDPOINTS

The following endpoints will be assessed during the study.

3.1 Primary Efficacy Endpoint

- Proportion of subjects achieving complete clearance of all MC at Week 12 (Subjects who achieved complete clearance before Week 12 need to maintain complete clearance at Week 12)

3.2 Secondary Efficacy Endpoints

- Proportion of subjects achieving complete clearance of all MC at each visit
- Time to complete clearance of all MC
- Proportion of subjects achieving at least a 75% reduction from baseline in number of MC at each visit
- Mean change from baseline in number of MC at each visit
- Mean percent change from baseline in number of MC at each visit

3.3 Exploratory Endpoints

- Proportion of subjects whose lesion count decreases and increases from baseline at each visit
- Absolute number of subjects who show new lesions after once achieving complete clearance at each visit

3.4 Safety Endpoints

Safety assessments will be performed at scheduled timepoints throughout the study and include physical examination, vital signs, standard clinical laboratory testing (hematology, serum chemistry), methemoglobin measurement, pregnancy test, tolerability evaluation, concomitant medications, and adverse events.

3.5 Exposure Endpoint

Blood for determination of the hMAP3 plasma concentration will be collected at a single time point at the end of treatment to evaluate if quantifiable concentrations can be measured following repeated application.

4 STUDY PLAN

4.1 Study Design

This is a phase 2 multi-center, randomized, double-blind, vehicle-controlled ascending dose study to be conducted in up to approximately 192 or 256 non-immunocompromised subjects with MC. After obtaining informed consent, subjects who satisfy entry criteria will be randomized 3:1 (active: vehicle) to ascending, sequential dose cohorts of SB206. The highest tolerated dose will also be run in a cohort once daily. Approximately 64 subjects will be randomized to each cohort (see study schematic). At randomization, subjects will be stratified by number of lesions at Baseline (3-18; 19-70) and atopic dermatitis (AD) history (with AD history vs w/o AD history). A maximum of 16 adult subjects, ages 18 and above, will be randomized into each cohort.

Subjects will be treated once daily, twice daily or three times a week for up to 12 weeks to all lesions identified at Baseline and new lesions that arise during treatment. If a subject clears all lesions (confirmed by the Investigator at the next regular scheduled visit), the treatment period will end, and subjects will be followed for recurrence/new lesions until Week 12/ET. All QD dosing should be applied in the morning at home or in the clinic. All subjects should apply their last dose to accommodate the 1 to 6 hour window for blood draws. The exact time of the last dose preceding any scheduled visit will be collected. Subjects will visit the clinic at Screening, Baseline, Week 1, Week 2, Week 4, Week 8, and Week 12/ET.

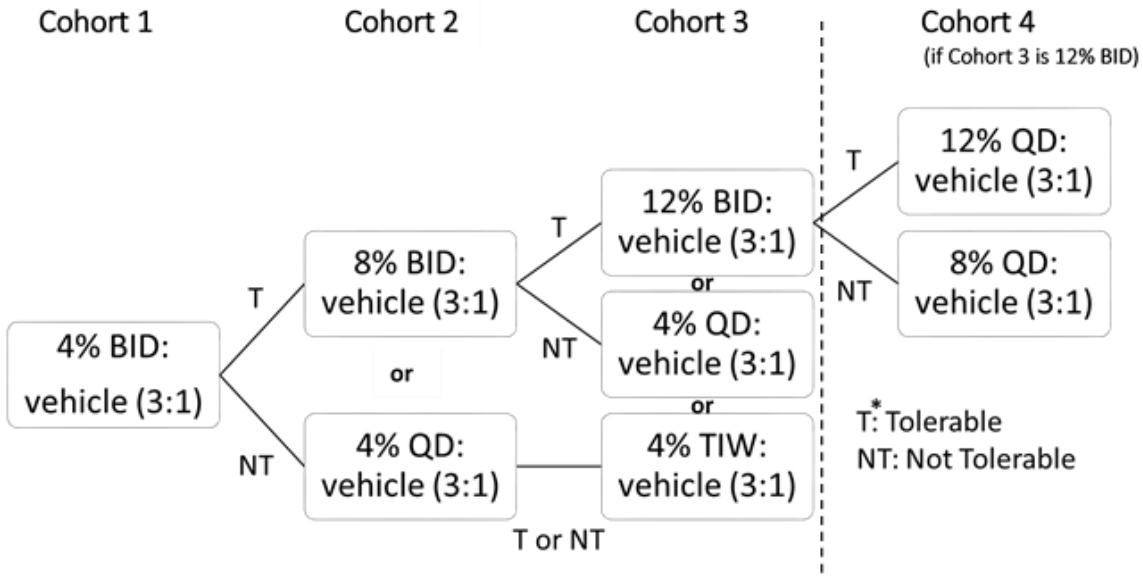
After 30 subjects randomized in a cohort have completed 2 weeks of treatment, the DSMB will review the available unblinded safety (Methemoglobin, AE, SAE) and tolerability data. Using predetermined criteria documented in the DSMB charter, the DSMB will determine if the data supports escalating to the next highest dose for the next cohort or if the data shows the dose is not tolerable, decreasing to the next lower dose or frequency for the next cohort. After 64 subjects are randomized to a cohort, the next cohort will be opened. Once a subject is randomized to a cohort, the subject will stay in the cohort. If a subject discontinues treatment, the subject will continue in the study and be followed until Week 12 unless the subject/caregiver withdraws the consent.

The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Novan.

4.2 Study Schematic

Figure 1: Ascending Dose Design

Once a subject is randomized to a cohort, the subject will stay in the assigned cohort.



*Note: T or NT is decided on a cohort basis, not on a subject level, after 30 subjects have completed 2 weeks of treatment.

Table 1: Schedule of Assessments

	Screening[1] (Day -28 to Day 1)	Visit 1[1] Baseline (Day 1)	Visit 2[2] Week 1 (Day 8 ±3)	Visit 3[2] Week 2 (Day 15 ±3)	Visit 4[2] Week 4 (Day 29 ±3)	Visit 5[2] Week 8 (Day 57 ±3)	Visit 6[2] Week 12/ET (Day 85 ±7)
Informed Consent (Assent)	X						
Demographics	X						
Medical and Medication History	X	X					
Lesion Counts	X	X	X	X	X	X	X
Physical Exam		X					X
Vital Signs		X	X	X	X	X	X
Chemistry & Hematology[3]		X					X
Methemoglobin[4]		X	X	X	X	X	X
Assessment of hMAP3 plasma concentration[5,6]							X
Urine Pregnancy Test[7]	X	X			X	X	X
Tolerability Evaluation		X	X	X	X	X	X
Photographs[6]		X			X		X
In Clinic Study Drug Application and Provide Subject Instructions		X					
Dispense Subject Diary		X			X	X	
Review Study Compliance			X	X	X	X	X
Collect Subject Diary					X	X	X
Drug Dispensed		X			X	X	
Collect Study Drug					X	X	X
Randomization		X					
Review Concomitant Medications and Adverse Events		X	X	X	X	X	X

[1] Screening and Baseline may occur on the same day.
[2] All visit dates are in reference to Baseline, e.g. Week 1 occurs 7 days after Baseline Visit.
[3] Collected at the last day of treatment.
[4] Collected via pulse co-oximetry at site.
[5] Blood for determination of the hMAP3 plasma concentration will be collected at a single time approximately 1 to 6 hours following last dose application. The time of the sample collection and the time of last dose preceding the scheduled visit will be recorded. The blood sample may be collected at the same time as the chemistry and hematology sample.
[6] Selected sites and subjects.
[7] Females 10 years of age and older. Subjects whose Baseline is within 7 days of Screening do not require UPT retesting.

5 POPULATION

5.1 Number of Subjects

Up to approximately 192 males and females, 2 years of age and older, with a minimum of 3 and a maximum of 70 lesions of MC at baseline will be randomized across a minimum of 3 cohorts. If the third cohort is administered 12% BID then up to an additional 64 subjects will be randomized in a fourth cohort (see Figure 1).

5.2 Inclusion Criteria

1. Be 2 years of age or older, and in good general health;
2. Have a signed written informed consent form by a parent or legal guardian (assent form where required);
3. Have between 3 and 70 MC at baseline, excluding periocular (within 2 cm circumference of the eye) and lesions on the labia and penis;
4. Females **10 years of age** and older must have a negative urine pregnancy test (UPT) prior to randomization;
5. Females **10 years of age** and older must agree to use an effective method of birth control during the course of 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. Are immunosuppressed (e.g. HIV, cancer or solid organ transplant), have immunodeficiency disorder, or are on immunosuppressive treatment;
2. Have agminated MC that could make it difficult to provide accurate lesion counts;
3. Have **active** atopic dermatitis with intense erythema and/or excoriations that impact currently or could impact at any point during the study the ability to count MC lesions;

   Note: History of atopic dermatitis is not an exclusion but will be captured and used for stratification. Diagnosis of atopic dermatitis for this study purpose can be based on the 2 essential features (Eichenfield, 2014): Pruritus and Eczema (acute, subacute, chronic) with typical morphology and age-specific patterns and chronic or relapsing history.*

**Patterns include:*

- *Facial, neck, and extensor involvement in infants and children*
- *Current or previous flexural lesions in any age group*
- *Sparing of the groin and axillary regions*

4. Have significant eczematous reactions or other skin disease surrounding MC that may impact ability to count lesions;
5. Have received treatment with topical calcineurin inhibitors or steroids on MC or within 2 cm of MC lesions within 14 days prior to baseline;
6. 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 OTC products including, but not limited to, Zymaderm and tea tree oil, cimetidine and other histamine H2 receptor antagonists;
7. Have received surgical procedures (cryotherapy, curettage, other) within 28 days prior to Baseline;
8. Have MC only in periocular area;
9. Have MC only on the labia or penis;
10. Female subjects who are pregnant, planning a pregnancy or breastfeeding;
11. Have a confirmed methemoglobin level of > 3.0% at Baseline using a pulse co-oximeter;
12. Have known hypersensitivity to any ingredients of SB206 or Vehicle Gel including excipients;
13. Have participated in a previous study with NVN1000;
14. Have participated in any other trial of an interventional investigational drug or device within 30 days or 5 half-lives (whichever is longer) or concurrent participation in another interventional research study.

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 clinical research organization (CRO) for approval prior to submission to an Institutional Review Board (IRB) 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.

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, blood pressure and pulse rate, methemoglobin assessment, 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.

6.2 Study Procedures by Time Point

6.2.1 Screening (Day-28 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)), medication history and concomitant medication information.

4. Obtain urine pregnancy test and evaluate results. If pregnancy test is positive, the subject may not participate in the study.

5. Perform lesion counts.

6.2.2 Visit 1/Baseline (Day 1)

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

1. Update medication history and concomitant medication information.

2. Perform lesion counts.

3. Collect vital signs.

4. Perform a brief physical examination.

5. Collect blood samples for chemistry and hematology.

6. Measure percent methemoglobin using Masimo handheld pulse co-oximeter device and instructions provided by Novan.

7. Obtain urine pregnancy test. If pregnancy test is positive, the subject may not participate in the study.

8. Selected sites obtain photographs of all areas where lesions appear (only areas that have at least 3 lesions).

9. Confirm eligibility and randomize subject.

10. Dispense subject diary and study drug. Weigh and record study product tubes. Instruct subject on dispensing, mixing, and application of study product and diary completion.

11. Have subject/caregiver apply first dose in clinic.

12. Perform tolerability assessments 30 minutes post dose.

13. Collect and record AE information for AEs reported.

6.2.3 Visit 2/Week 1 (Day 8 ±3)

The following procedures must be performed and recorded at the Week 1 visit.

1. Update concomitant medication information.

2. Perform lesion counts.

3. Collect vital signs.

4. Measure percent methemoglobin using Masimo handheld pulse co-oximeter device and instructions provided by Novan.

5. Perform tolerability assessments.

6. Review study compliance.

7. Collect and record AE information for AEs reported.

6.2.4 Visit 3/Week 2 (Day 15 ±3)

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

1. Update concomitant medication information.
2. Perform lesion counts.
3. Collect vital signs.
4. Measure percent methemoglobin using Masimo handheld pulse co-oximeter device and instructions provided by Novan.
5. Perform tolerability assessments.
6. If subject discontinues treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.
7. Review study compliance.
8. Collect and record AE information for AEs reported.

6.2.5 Visit 4/Week 4 (Day 29 ±3)

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

1. Update concomitant medication information.
2. Perform lesion counts.
3. Collect vital signs.
4. Measure percent methemoglobin using Masimo handheld pulse co-oximeter device and instructions provided by Novan.
5. Obtain pregnancy test and evaluate results. If pregnancy test is positive, the subject may not continue in the study.
6. Perform tolerability assessments.
7. If subject discontinues treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.
8. Selected sites obtain photographs of all areas where Baseline photographs were collected.
9. Collect subject diaries and returned study medication. Weigh and record study product tubes. Review study compliance.

10. Weigh, record and dispense new supply of study product and dispense subject diary.

11. Collect and record AE information for AEs reported.

6.2.6 Visit 5/Week 8 (Day 57 ±3)

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

1. Update concomitant medication information.

2. Perform lesion counts.

3. Collect vital signs.

4. Measure percent methemoglobin using Masimo handheld pulse co-oximeter device and instructions provided by Novan.

5. Perform tolerability assessment.

6. If subject discontinues treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.

7. Collect subject diaries and returned study medication. Weigh and record study product tubes. Review study compliance.

8. Weigh, record and dispense new supply of study product and dispense subject diary.

9. Collect and record AE information for AEs reported.

6.2.7 Visit 6/Week 12/ET (Day 85 ±7)

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

1. Update concomitant medication information.

2. Perform a brief physical exam.

3. If subject is still on treatment, collect blood samples for chemistry, hematology and hMAP3 and confirm time of last dose with subject/caregiver or apply dose in clinic.

4. Perform lesion counts.

5. Collect vital signs.

6. Measure percent methemoglobin using Masimo handheld pulse co-oximeter device and instructions provided by Novan.

7. Obtain pregnancy test and evaluate results.

8. Perform tolerability assessments.

9. Select sites obtain photographs of all areas where Baseline photographs were collected.

10. Collect subject diaries and returned study medication. Weigh and record study product tubes. Review study compliance.

11. Collect and record AE information for AEs reported.

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 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 is encouraged to follow the visit schedule and complete all assessments.

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 (due to clearance of all MC or 12 weeks of treatment)

- Adverse Event

- Withdrawal by Subject/caregiver

- Physician Decision

- Protocol Violation

- Lost to Follow-Up
- Pregnancy
- Lack of Efficacy
- 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/ET) every effort should be made to have the subject return to the study center to complete the Week 12/ET evaluations. Subjects who withdraw from the study will not be replaced.

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 by the Investigator on the subject's study record and in the study database.

All Week 12/ET evaluations should be performed at the time of premature discontinuation. All data gathered on the subject prior to termination will be made available to the CRO.

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
- 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.

For this clinical trial purpose, only active MC lesions are counted. Active MC lesions are dome-shaped, pearly and shiny white top centered papules. They may have a central dimple (umbilication). In order to correctly diagnose, the evaluator should confirm the papular nature of molluscum by touching and feeling and using a magnifier, if necessary. Training on how to accurately count the number of MC lesions will be provided.

Definition of Clearance: "Clear" means, in the study, resolution of the active molluscum lesion with dome-shaped, pearly and shiny white top centered papule, with or without umbilication. After resolution, the residual surface changes such as pitting, scar, and hyper/hypo pigmentation may remain. These signs should not be counted as active lesions. Inflammatory reaction may also occur during the natural healing process. Refer to the lesion count training for details.

The same blinded evaluator should perform lesion counts at Screening, Baseline, and Weeks 1, 2, 4, 8 and 12/ET. In the event that this is not possible due to unforeseen circumstances, a different blinded evaluator may evaluate the subject. However, the same evaluator should evaluate subjects at the Baseline and Week 12/ET evaluations.

Periocular lesions that are not treated will not be included in the lesion count. Lesions on the labia and penis will not be treated and will not be included in the lesion count.

7.2 Local Tolerability Assessments (Investigator, Subject/Caregiver)

Inflammatory reaction around the MC is considered as a predictor of imminent resolution of MC (beginning-of-the-end sign, BOTE sign). The Investigator needs to carefully assess and if possible, differentiate the irritation symptom and sign (tolerability) from the BOTE sign (Butala, 2013).

Subjects will be assessed at each visit from Baseline through Week 12/ET for local tolerability. At Baseline, the subject must remain at least 30 minutes after the initial application of study product for the local tolerability assessments. The Investigator (or designated evaluator) will assess the presence and overall degree of irritation (dryness, erythema, and peeling) at the application sites and the score will reflect what the investigator/evaluator sees at the time of the assessment. The score will ideally represent an "average" across all application sites. To the fullest extent possible

the same investigator (or designated evaluator) will perform all tolerability assessments for an individual subject throughout the study. Scores of 3 or 4 (Severe or Very Severe) should be reported as an AE. The score will be a global assessment based on all parameters. There will not be a unique score for each parameter.

Investigator Assessment of Dryness, Erythema, and Peeling

Score	Severity	Description
0	No irritation	No evidence of local irritation/intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking but does not require treatment modification
3	Severe (report as an AE)	Erythema, edema glazing with fissures, few vesicles or papules
4	Very severe (report as an AE)	Strong reaction spreading beyond the treated area, bullous reaction, erosions

At Baseline and all post baseline visits, subjects will use a 5-point tolerability scale to assess the presence and degree of burning/stinging and itching.

At the Baseline visit, 30 minutes post-dose, the subject will be asked to rate the overall severity of their itching and burning/stinging. The assessment will apply only to the time since application of study drug. At Week 1 through Week 12/ET the subject will be asked to rate the overall severity of their itching and burning/stinging at the treatment areas since their previous visit. The score will ideally represent an "average" across all application sites. The subject's caregiver can assist in providing a score as needed. If the subject reports scores of 4 (Strong/Severe) at any visit, the investigator should assess for accompanying signs and symptoms (erythema, edema, vesicles, papules, or erosions, etc.) and report as an AE accordingly. The following scores, severity and descriptions will be used to score subject reported tolerability. There will be one score based on a full assessment of both burning/stinging and itching. There will not be a unique score for each parameter.

Subject Assessment of Burning/Stinging and Itching

Score	Severity	Description
0	None	Normal, no discomfort
1	Slight	An awareness, but no discomfort and no intervention required
2	Mild	A noticeable discomfort that causes intermittent awareness
3	Moderate	A noticeable discomfort that causes intermittent awareness and interferes occasionally with normal daily activities
4	Strong/Severe	A definite continuous discomfort that interferes with normal daily activities

7.3 Safety Assessments

7.3.1 Physical Exam

A brief physical examination will include heart, lung, and abdomen evaluation. This physical examination will be performed at Baseline and at Week 12/ET. Height and weight will only be collected at Baseline. Any clinically significant changes in the physical exam from baseline will be recorded as AEs.

7.3.2 Vital Signs

Blood pressure and pulse rate will be collected at Baseline, Week 1, Week 2, Week 4, Week 8 and Week 12/ET. Any clinically significant changes in vital signs from baseline will be recorded as AEs.

7.3.3 Clinical Laboratory Tests

Chemistry and hematology will be collected at Baseline and on the last day of treatment. Clinically significant changes in laboratory values will be recorded as AEs.

Methemoglobin will be measured at Baseline, Weeks 1, 2, 4, 8 and Week 12/ET using a Masimo Rainbow® SET® Rad-57™ pulse co-oximeter. The percent methemoglobin will be displayed on the pulse co-oximeter and recorded in the subject's source documents and in the case report form (CRF). Subjects with methemoglobin greater than 3.0% at baseline are not eligible for the study.

Subjects with a confirmed methemoglobin > 5.0% at any post-baseline visit will be discontinued from the study. A confirmed methemoglobin is defined as at least 2 readings within 0.5% of each other taken within a 30-minute period. Methemoglobin levels will not be collected as AEs; however, if a subject has signs/symptoms of methemoglobinemia and an elevated methemoglobin level, methemoglobinemia should be reported as an AE.

7.3.4 Pregnancy Testing

Urine pregnancy testing for females 10 years of age and older will be collected at Screening, Baseline, Week 4, Week 8 and Week 12/ET. In addition to having a negative UPT at Baseline (and Screening unless Visit 1 is within 7 days of Screening) before the first application of study drug, females 10 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.

7.4 Exposure Assessment

At select sites, a blood sample will be collected at the Week 12 visit from those subjects who have not previously discontinued treatment. The sample will be collected at a single time point approximately 1 to 6 hours following application of study drug. The final dose may be either be done at home or in the clinic. The time of dose application and sample collection should be recorded. Blood may be collected at the same time as the chemistry and hematology sample, but the chemistry and hematology samples should be drawn first. If a subject discontinues treatment for any reason (e.g., lesion clearance, subject withdrawal, physician decision) before Visit 6, blood should be collected on the last day of treatment.

Instructions for processing and transporting plasma samples for analysis will be described separately.

7.5 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 4%, 8% or 12%	Comparator Drug: Vehicle Gel
Dosing: Approximately 1.0g of SB206 QD, BID or TIW	Dosing: Approximately 1.0g of Vehicle Gel QD, BID or TIW

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 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 3:1 ratio (active: vehicle) to ascending, sequential dose cohorts of SB206. 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 interactive web response system (IWRS) as subjects are entered into the study (Cohort 1, then Cohort 2, then Cohort 3). Randomization will be stratified by number of lesions at baseline (3-18, 19-70) and atopic dermatitis history (with AD history vs w/o AD history). A maximum of 16 adult subjects, ages 18 and above, will be randomized into each cohort.

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.

Several analyses of unblinded data are planned throughout the study. A Data Safety Monitoring Board (DSMB) will conduct an unblinded review of safety and tolerability data after 30 subjects are enrolled and treated for two weeks within in each cohort. After all subjects in Cohort 3 have completed their last study visits, the database for all subjects in Cohorts 1-3 will be frozen for purposes of an interim analysis of safety and efficacy data. While this interim analysis is being prepared, the study will complete through Cohort 4 and the final analysis will be based on all subjects in Cohorts 1-4: Cohort 4 (QD dosing of SB206 8% or 12% vs. vehicle). Personnel who are not otherwise involved in the study will prepare the unblinded data and summary tables for the interim 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 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 CRF 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, twice daily or three times a week for up to 12 weeks to all lesions identified at baseline and new lesions that arise during treatment depending on the frequency of the cohort plus the dose selected for the cohort. If a subject clears all lesions (confirmed by the Investigator at the next regular scheduled visit), the treatment period will end and subjects will be followed for recurrence/new lesions until Week 12/ET.

An increase in the number of MC lesions (with or without inflammatory reaction) during the early phase of the resolution 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 NVN1000 Gel or Vehicle Gel with an equal volume of hydrogel thoroughly mixed together by the subject or caregiver and applied to the lesions, 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. Lesions on the labia and penis will not be treated.

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 on the CRF.

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 Weeks 4 and 8 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 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 OTC products including, but not limited to,

Zymaderm and tea tree oil, cimetidine and other histamine H2 receptor antagonists. Surgical procedures (cryotherapy, curettage, other) are prohibited during the study.

8.8 Compliance

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

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

The Investigator will assess subjects at each scheduled study visit for the occurrence of AEs. 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.

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. The date of onset, date ended, seriousness, severity, outcome, relationship to study drug, therapy required, and action taken regarding study drug and study participation will be reported for each AE.

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 9.5.

9.3 Assessment of Causality

Relationship of an AE to study drug will be assessed as follows:

- Definite: There is a clinically plausible time sequence between the onset of the AE and the application of study drug; when the event responds to withdrawal of Study drug and recurs with re-administration of study drug.
- Probable: There is a clinically plausible time sequence between the onset of the AE and the application of study drug; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures.
- Possible: There may or may not be a clinically plausible time sequence between the onset of the AE and the application of study drug and a cause cannot be ruled out.

- Unlikely: There is no reasonable temporal association between the test material and the suspected event and the event could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

- Unrelated: This term should be reserved for those events that cannot be even remotely related to study participation.

9.4 Clinical Laboratory Changes

Any clinically significant changes from Baseline in clinical laboratory values will be documented as an AE.

9.5 Adverse Event Follow-up

9.5.1 Follow-Up of Non-Serious Adverse Events

Non-serious AEs that are not resolved at the time of the last scheduled study visit (Week 12/ET) must be recorded in the study database as ongoing/not recovered/not resolved.

9.5.2 Follow-Up of Post Study Serious Adverse Events

Serious adverse events that are identified on the last scheduled contact (Week 12/ET) must be recorded in the study database and reported to the CRO according to the reporting procedures outlined in Section 10.2. 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 CRO 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.

9.6 Pregnancy

Females 10 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, IUD, hormonal IUD, permanent contraception, same sex partner or partner who has had a vasectomy.

Before enrolling any subject in this clinical trial, the Investigator must review guidelines about study participation with the subject/caregiver, 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.

Cases of pregnancy that occur during maternal exposure to study drug should be reported. During the study, subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The Investigator must immediately notify the 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/ET will be discontinued from the study. The CRO will ask the site to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through the end of the pregnancy as applicable. Protocol-required procedures for the Week 12/ET evaluation must be performed for the subject.

9.7 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.

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 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.

11 STATISTICS

11.1 General Procedures

Prior to the release of unblinded information through Cohort 3, a detailed, finalized Statistical Analysis Plan (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. 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. Although analyses will be descriptive in nature, 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 192 subjects, 2 years of age and older, with a minimum of 3 and a maximum of 70 lesions at baseline will be randomized across a minimum of 3 cohorts. If the third cohort is administered 12% BID, up to an additional 64 subjects will be randomized in a fourth cohort. This Phase 2 study was not powered for formal statistical comparisons. The SB206 active dose groups will be compared to Vehicle gel. No adjustments will be made for multiplicity. No imputations will be utilized for safety or efficacy endpoints

11.3 Analysis Populations

The analysis populations include the following:

The intent-to-treat (ITT) population will consist of all subjects who are randomized.

The modified intent-to-treat (mITT) population will consist of all subjects who are randomized and complete the study treatment (subjects who complete 12 weeks of treatment and subjects who complete treatment due to clearance of all molluscum).

The safety (SAF) population will consist of all patients who take at least one dose of study treatment.

The exposure population will consist of all subjects who receive at least 1 application of active study medication and had a blood a blood sample collected and successfully analyzed for the hMAP3 plasma concentration.

The per-protocol population (PP) will consist of all subjects in the mITT population and have no significant protocol deviations that impact the analyses of the efficacy endpoints.

11.4 Statistical Methods

11.4.1 Demographic and Baseline Characteristics

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

11.4.2 Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects achieving complete clearance of all molluscum contagiosum at Week 12 (subjects who achieved complete clearance before Week 12 need to maintain complete clearance at Week 12) which will be analyzed by a logistic regression model with treatment, number of lesions at Baseline (3-18; 19-70) and atopic dermatitis history (with AD history vs w/o AD history) as factors. The primary analysis will compare each SB206 dose level with the Vehicle using the mITT population.

A sensitivity analysis of the primary endpoint will be repeated using the ITT and per-protocol population. Other sensitivity analyses may be performed and will be specified in the statistical analysis plan.

Secondary endpoints will be analyzed on the mITT and ITT population as follows:

- Proportion of subjects achieving complete clearance of all MC at each visit will be analyzed using the same logistic regression analysis specified in the primary analysis.

- Time to complete clearance of all MC will be analyzed using Kaplan Meier methods.

- Proportion of subjects achieving at least a 75% reduction from baseline in the number of MC at each visit will be analyzed using the same logistic regression analysis specified in the primary analysis.

- Mean change and percent change from baseline in number of MC at each visit will be analyzed using a mixed-model repeated-measures (MMRM) analysis with treatment as the main effect, visit, number of lesions at Baseline (3-18; 19-70) and atopic dermatitis history (with AD history vs w/o AD history) as factors and treatment by visit as an interaction term.

Details of all secondary and exploratory endpoints will be specified in the SAP. Additional exploratory analyses may be conducted, all analyses will be detailed in the SAP, which will be finalized before database lock.

11.4.3 Analysis of Safety

11.4.3.1 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 with an onset on or after the date of the first study drug dose. 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.

11.4.3.2 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.

11.4.3.3 Vital Signs

Blood pressure and pulse will be summarized by treatment group from Baseline through Week 12/ET. Additionally, change from Baseline in vital signs will be summarized at Weeks 1, 2, 4, 8, and 12/ET. Any clinically significant changes from Baseline will be documented as an AE.

11.4.3.4 Laboratory Assessments

Blood chemistry and hematology values will be reported individually at Baseline and day of last dose, which may occur at any time during the study. Therefore, the study day of the last dose will be used to assign the laboratory values to the closest study visit (Week 1, 2, 4, 8, or 12). Laboratory test results will be summarized descriptively at Baseline and each visit. Additionally, shifts from Baseline to each visit in laboratory test results based on normal ranges will be summarized with descriptive statistics. The last laboratory evaluation prior to the first dose of study drug will be used as Baseline for all laboratory analyses. Any clinically significant changes from Baseline will be documented as an AE.

Methemoglobin will be reported as a percentage of hemoglobin. Methemoglobin will be summarized descriptively by treatment group at Baseline and Weeks 1, 2, 4, 8 and 12/ET. Additionally, the change from baseline in methemoglobin will be summarized by treatment group at each post baseline visit.

11.4.3.5 Urine Pregnancy Tests

Urine pregnancy tests results for females 10 years of age and older will be presented in data listings by subject.

11.5 Analysis of hMAP3 Plasma Concentrations

Plasma concentrations of hMAP3, a silicon-containing hydrolyzed monomer of the polymeric NVN1000 drug substance will be determined. Results will be presented in data listings by subject. If quantifiable concentrations are observed, the results will be summarized descriptively.

11.6 Interim Analysis

After all subjects in Cohort 3 have completed their last study visits, the database for all subjects in Cohorts 1-3 will be frozen for purposes of an interim analysis of safety and efficacy data. While this interim analysis is being prepared, the study will complete through Cohort 4 and the final analysis will be based on all subjects in Cohorts 1-4: Cohort 4 (QD dosing of SB206 8% or 12% vs. vehicle). Personnel who are not otherwise involved in the study will prepare the unblinded data and summary tables for the interim analysis. The interim analysis will not impact the final analysis since the study does not involve any formal hypothesis testing.

12 ETHICS AND RESPONSIBILITIES

12.1 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.

12.2 Data Safety Monitoring Board

After 30 subjects randomized in a cohort have completed 2 weeks of treatment, the Data Safety Monitoring Board (DSMB) will review the available unblinded safety and tolerability data. Using predetermined criteria documented in the DSMB charter, the DSMB will determine if the data supports escalating to the next highest dose for the next cohort or if the data shows the dose is not tolerable, decreasing to the next lower dose or frequency for the next cohort. All responsibilities of the DSMB and details of data to be reviewed will be detailed in the DSMB charter.

12.3 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.

12.4 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 Institutional Review Board (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.

12.5 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.

12.6 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 CRF derived from source documents should be consistent with the data recorded on the source documents.

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

12.7 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

13 AUDITING AND MONITORING

13.1 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.

13.2 Monitoring

All aspects of the study will be monitored by the CRO or Novan according to Good Clinical Practices (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.

14 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.

15 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.

16 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.

17 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.

18 REFERENCES

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19 APPENDICES

19.1 APPENDIX I – Names of Study Personnel

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