STUDY TITLE	A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris
PROTOCOL NO.	NI-AC303
SPONSOR	Novan, Inc. 4222 Emperor Blvd., Suite 200 Durham, NC 27703 Tel.: 919-485-8080
VERSION DATE	9 November 2015
VERSION	1.0

The study will be conducted in compliance with the obligations as detailed in this protocol and all applicable regulations and guidelines (e.g., International Conference on Harmonisation, Good Clinical Practices guidelines).

SIGNATURE PAGE

Novan, Inc. or designee commits to conduct the study as outlined herein, in accordance with the current International Conference on Harmonisation Good Clinical Practices and the principles contained in the World Medical Association Declaration of Helsinki, and complying with the obligations and requirements of the sponsor as listed in 21 CFR Part 312.

09 Nov 2015

M. Joyce Rico, MD, MBA
Chief Medical Officer
Novan, Inc.

Date

09 NOV 2015

Carolyn Enloe, MPH
Clinical Program Manager
Novan, Inc.

Date

09 Nov 2015

Melissa Hays
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INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: *"*A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris" and,

I agree that the protocol contains the necessary information required to conduct the study. I also agree to conduct this study as outlined in and according to the obligations of Clinical Investigators and all other pertinent requirements in the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline.

I agree to obtain approval of the protocol and informed consent prior to the start of the study by an Institutional Review Board (IRB).

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all subjects prior to their entry into the study.

I have received and reviewed the Investigator's Brochure including the potential risks and side effects of the product and instructions for use.

I agree to report to Novan, Inc. or designee adverse events that occur during the course of the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in this Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

The Investigator, agreeing to be fully bound, hereby executes this agreement on the date as set forth below.

Investigator Signature

Printed Name **Date**

Address

Phone Number

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Novan, Inc.	
Name of Finished Product: SB204	
Name of Active Ingredient: NVN1000	
Title	A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris
Study Objectives	The primary objective of this study is to evaluate the safety of SB204 4% in subjects with acne vulgaris for up to 40 weeks of treatment.
Treatment Regimens	Eligible subjects at the Baseline visit will be assigned to SB204 QD and treated for up to 40 weeks to acne affected areas including the face, chest, back and upper shoulders.
Formulation	**Investigational Drug:** SB204, containing NVN1000 Gel and hydrogel
Study Period	Subjects will be dosed in the study for up to 40 weeks.
Study Design	This is a multi-center, open label long-term safety (LTS) study to be conducted in approximately 600 subjects with acne vulgaris. Subjects eligible to enroll in this study will have completed one of the Phase 3 pivotal studies with SB204, NI-AC301 or NI-AC302. Subjects who satisfy the entry criteria at the Baseline visit will be enrolled to receive open-label SB204. Investigational drug will be delivered from a double barrel single pump dispenser. The pump dispenses product (NVN1000 Gel and a hydrogel) from two chambers which will be mixed together quickly (about 5 seconds) by the subject and applied to the acne affected areas including the face, chest, back and upper shoulders once daily. No other acne treatments will be permitted during the study. Tolerability and safety assessments include cutaneous tolerability evaluation, adverse event collection, physical exams including blood pressure and pulse rate, and urine pregnancy tests (UPTs). Subjects will return for post-baseline evaluation at Weeks 4, 12, 24, 36 and 40.
Diagnosis and Criteria for Inclusion/Exclusion	Male and female subjects who completed one of the two SB204 Phase 3 pivotal studies will be eligible for participation in the study. The last visit in the Phase 3 pivotal study may serve as the first visit for the long-term safety study. Subjects must enroll in the LTS study within 7 days of completion of NI-AC301 or NI-AC302. Any subject who terminated early from one of these studies for any reason will not be eligible to enroll

	in this long-term safety study. Inclusion criteria: • Have no more than two nodules on the face; • Completed 12 weeks of treatment in NI-AC301 or NI-AC302 Exclusion Criteria: • Terminated early from an SB204 Phase 3 pivotal study for any reason; • Have any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis; • Have an on-going adverse event at the Week 12 visit for NI-AC301 or NI-AC302 that warrants stopping study drug application; • Have facial hair, tattoos or other facial markings that would interfere with efficacy and safety assessments; • Have any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive; • Have used medications or vitamins during the 12 weeks immediately preceding Baseline which are reported to exacerbate acne (e.g. azathioprine, haloperidol, halogens such as iodides or bromides, lithium, anabolic steroids, systemic corticosteroids, phenytoin and phenobarbital). Daily use of a multi-vitamin is acceptable.
Sample Size	Approximately 600 subjects will be entered into the study.
Safety and Tolerability Evaluation	Safety and tolerability assessments will be collected beginning at the Baseline visit for NI-AC303. The subject must enroll in NI-AC303 within 7 days of completion of NI-AC301 or NI-AC302. Demographics and the subject's Week 12 visit values from NI-AC301 or NI-AC302 for blood pressure, pulse, urine pregnancy test, physical exam findings, lesion counts and tolerability will be used as the Baseline values for NI-AC303. Adverse events will be assessed and collected at each evaluation beginning at Baseline. A brief physical exam will be collected at Week 40/Early Termination (ET). Blood pressure and pulse will be collected at each visit through Week 40/ET. Urine pregnancy tests in women of

	child-bearing potential (WOCBP) will be conducted at each visit. Subjects will be assessed at each visit through Week 40 for cutaneous tolerability on the face. Tolerability will be assessed on a scale of 0 to 3 where 0=none, 1=mild, 2=moderate, and 3=severe for erythema, scaling, dryness, pruritus, and burning/stinging. The body surface area (BSA) treated (based on locations) will be collected at each visit for each subject Extent of exposure will be calculated for each subject based on the number of treatments and treatment area. Extent of exposure will also be summarized on a unit day which will be defined as total exposure divided by the total number of days enrolled.
Endpoints	Safety endpoints will include adverse events, changes in physical examination and changes in vital sign measurements. Any clinically significant changes noted during the physical exam as well as from the vital sign measurements will be recorded as adverse events and included in the comparison. Urine pregnancy tests in women of child-bearing potential will be conducted at each visit. Tolerability endpoints will include the investigator's assessment of erythema, scaling, dryness, and the subject's report of pruritus and burning/stinging based on the preceding 24 hours.
Statistical Methods	All statistical processing will be performed using statistical analysis software (SAS®) unless otherwise stated. Safety analyses will be performed using the safety population. **Safety Analyses** <u>Adverse Events</u> All AEs occurring during the study will be recorded and classified on the basis of the Medical Dictionary for Regulatory Authorities (MedDRA) terminology. Descriptions of AEs will include the date of onset, the date the AE ended, the severity of the AE, the relationship to study medication, and the outcome. All reported AEs that occurred on or after the Baseline date will be included in the summaries and analysis. Summaries will be presented to describe the characteristics of the adverse events reported and will include the number and percentage of subjects who report at least one AE and the number of events reported by severity, seriousness, and relationship to study medication. A summary of adverse event system organ class (SOC) and preferred terms (PTs) will also be presented. A subject will be counted only once under

	each SOC and PT. For the summary by severity, subjects will only be counted once for a specific SOC or PT under the worst severity. For the summary by relationship to study medication, subjects will only be counted once for a specific SOC or PT under the highest relationship. If multiple serious adverse events (SAEs) are reported, a table summarizing the SAEs characteristics will be provided. All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim given by the Investigator, preferred term, system organ class, start date, stop date, severity, seriousness, and relationship to study medication. The AE onset will also be shown relative (in number of days) to the day of initial dose of the open label study medication. A summary of adverse events that lead to a subject's discontinuation of study medication usage will also be provided. <u>Physical Examinations</u> Any clinically significant changes from Baseline will be documented as an AE. <u>Vital Signs</u> Blood pressure and pulse will be summarized from Baseline through Week 40. Additionally, change from Baseline in vital signs will be summarized at Weeks 4, 12, 24, 36 and 40. Clinically significant changes from Baseline will be documented as an AE. <u>Urine Pregnancy Tests</u> Urine pregnancy test results for WOCBP will be presented in data listings by subject. **Tolerability Analyses** Cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized with frequency counts and percentages at each evaluation.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
BSA	Body Surface Area
EDC	Electronic Data Capture
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IUD	Intrauterine Device
MedDRA	Medical Dictionary for Regulatory Activities
NOVAN	Novan, Inc.
OTC	Over-the-Counter
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events
UPT	Urine Pregnancy Test
WOCBP	Women of Child-Bearing Potential

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1. INTRODUCTION

1.1 BACKGROUND

Acne vulgaris is a chronic skin disease characterized by open and closed comedones, papules, pustules, and cysts. Current acne therapies include oral and topical antibiotics, topical keratolytics, and oral contraceptives.

Nitric oxide is a free radical gas naturally produced by the human body which has antimicrobial and anti-inflammatory activity. Novan, Inc. has developed a topical gel containing NVN1000, a drug which releases nitric oxide to the skin after topical application. SB204, an admixture of an alcoholic NVN1000 Gel with an aqueous hydrogel, is in development for the treatment of acne vulgaris. In randomized, double-blind, placebo-controlled, 12-week, Phase 2 studies, treatment with SB204 decreased inflammatory and non-inflammatory lesion counts and improved the Investigator Global Assessment (IGA) in subjects with acne and was well tolerated.

To date, approximately 400 subjects have been treated with NVN1000 Gel, including SB204, and approximately 200 subjects have been treated with the Vehicle Gel.

1.2 INVESTIGATIONAL PRODUCT

SB204 is an alcohol-based topical gel containing NVN1000 and the formulation will be dispensed from a dual chamber pump with hydrogel.

Investigational Product	
Name of Active Ingredient	NVN1000
Drug Name/Concentration	SB204 4%
Manufacturer	Ei, LLC
Packaging	Pump designed to deliver 1:1 Hydrogel: NVN1000 Gel to yield final concentration of SB204 4%
Storage Requirements	Refrigerated, 2-8 °C until dispensed.
Appearance Post-Mixing	Opaque white gel
Dosing Schedule	Once daily
Route of Administration	Topical Application

1.3 NONCLINICAL STUDIES WITH NVN1000 GEL

Novan has conducted over 30 nonclinical studies to evaluate the local safety and tolerance of NVN1000 (drug substance and formulated product) following dermal administration to support the acne development program. Repeat dose dermal toxicology studies have included 4-week and 13-week GLP dermal toxicology studies in miniature swine, and a 13-week dermal toxicology study in both rats and mice. A 39-week miniature swine study has completed the in-life portion; data from that study will be available prior to initiation of this long-term safety study. In completed studies in both the miniature swine and mice, doses of NVN1000 far in excess in both concentration and applied surface area of projected clinical doses have not demonstrated any significant toxicological effects. The most relevant and persistent finding has been a transient dermal erythema that is concentration dependent and believed to be a consequence of a vascular dilation, "flushing" effect. Additional safety studies in rabbits and guinea pigs showed no effects on acute dermal irritation or skin sensitization. As expected, due to the alcohol-based formulation, NVN1000 was found to be an ocular irritant. From a genotoxicity perspective, NVN1000 was positive in a standard in vitro AMES assay but negative in three in vivo mutagenicity assays. Additionally, in SEG I and II reproductive toxicology studies in rats and rabbits, oral administration of NVN1000 resulting in high systemic levels of nitrate and hMAP3, a key structural component of NVN1000, showed the requisite maternal toxicological effects upon dose escalation as a complication of high methemoglobin concentrations, but minimal effects on fertility or fetal development.

For additional information refer to the Investigator's Brochure.

1.4 CLINICAL STUDIES WITH NVN1000 GEL

The topical administration of NVN1000 Gel to healthy volunteers or subjects with acne vulgaris has generally been well-tolerated with no safety concerns identified. In nine completed clinical studies, approximately 400 subjects have been treated with NVN1000 Gel or SB204 and approximately 200 subjects have been treated with Vehicle Gel. One unrelated SAE has been reported and the systemic AE profile has been similar in subjects treated with active (NVN1000 Gel or SB204) and vehicle in the acne development program. Asymptomatic, transient erythema has been observed in some subjects. There have been no clinically significant changes in laboratory results including methemoglobin, or changes in physical examinations.

A cross-over pharmacokinetic (PK) study was conducted in 18 subjects with moderate to severe acne. Subjects were randomized to treatment with SB204 8% or Vehicle Gel to the face, chest, upper back, and shoulders (~17% BSA) in two treatment periods. In this study, there was no detectable plasma hMAP3 (LLOQ 5 ng/ml), a component of NVN1000 and no difference in plasma nitrate levels in subjects treated with SB204 versus Vehicle Gel. One subject withdrew during the second dosing period due to contact dermatitis. A 4 period, double-dummy, cross-over study in subjects with moderate to severe acne is ongoing to assess effects of therapeutic and

supratherapeutic doses of SB204 on ECG parameters. The thorough ECG study will be completed prior to dosing in the Phase 3 pivotal program.

In the Phase 2 clinical development program, the topical application of SB204 in subjects with acne vulgaris resulted in significant decreases in inflammatory and non-inflammatory lesion counts and improvement in the Investigator Global Assessment (IGA) when compared to vehicle. Once daily treatment was as effective as twice daily treatment.

A summary of the clinical studies conducted to date in subjects with acne is in the Investigator's Brochure.

1.5 SUMMARY OF BENEFITS AND RISKS

The pathogenesis of acne vulgaris includes several mechanisms which are potential targets for nitric oxide. Nitric oxide has been demonstrated to inhibit several inflammatory pathways relevant in acne, decrease *P. acnes,* and decrease sebum production. In two completed Phase 2 studies, SB204 4% administered in subjects with acne decreased inflammatory and non-inflammatory lesion counts at the end of treatment and improved IGA scores. Once daily treatment was as effective as twice daily treatment. In the studies conducted to date, the systemic AE profile was similar between subjects treated with NVN1000 Gel, SB204, and subjects treated with Vehicle Gel. SB204 4% has been generally well tolerated and has not been associated with a safety or tolerability signal. In PK studies, there was no detectable systemic exposure to the parent compound, NVN1000, or changes in plasma nitrate.

Dermal toxicology studies in mice and minipigs have demonstrated minimal evidence of toxicity with mild-moderate dermal changes most frequently reported. In reproductive toxicology studies, findings were limited to toxicities associated with high methemoglobinemia at supra-therapeutic doses.

Based on the known mechanism of action of nitric oxide, theoretical risks from systemic exposure following topical administration of NVN1000 Gel or SB204 include hypotension and headache. Methemoglobin has been monitored in previous clinical studies with NVN1000 Gel and SB204 and no significant changes in methemoglobin levels have been observed.

Inadvertent administration to the eyes may result in ocular irritation due to the excipients and should be avoided. Should the product be accidently instilled in the eye(s), prompt flushing with copious amount of normal saline or water is recommended.

A transient (approximately 5-10 minutes), asymptomatic erythema has been observed in some subjects shortly after application of NVN1000 Gel or SB204 which is a physiologic response (vasodilation) to local nitric oxide release. Topical application has been associated with local application-site reactions including erythema, scaling, dryness, and burning/stinging. These local

application-site reactions may occur due to the active agent (NVN1000) or the vehicle. In other development programs, local application-site reactions that led to treatment discontinuations were observed following application of alcoholic NVN1000 Gel or Vehicle Gel under occlusion in subjects with psoriasis or to the genital/perianal area in subjects with genital/perianal warts.

Based on available data, Novan anticipates that the risks to subjects enrolling in this Phase 3 study at which the maximum strength of SB204 will be 4% once daily on up to 17% body surface area are minimal, and that appropriate monitoring is in place to assess safety. Some subjects may have a clinical benefit in this long-term, open label study.

2. RATIONALE AND OBJECTIVES

2.1 STUDY RATIONALE

Novan is conducting this study to evaluate the long term safety of SB204 4% administered once daily. Subjects will dose once daily for up to 40 weeks (280 days) with SB204 4% to acne affected areas. Based on the previous human safety data with SB204 at up to 8% and Vehicle Gel as well as the nonclinical safety data including dosing with and without hydrogel, this dose is expected to be safe and well tolerated.

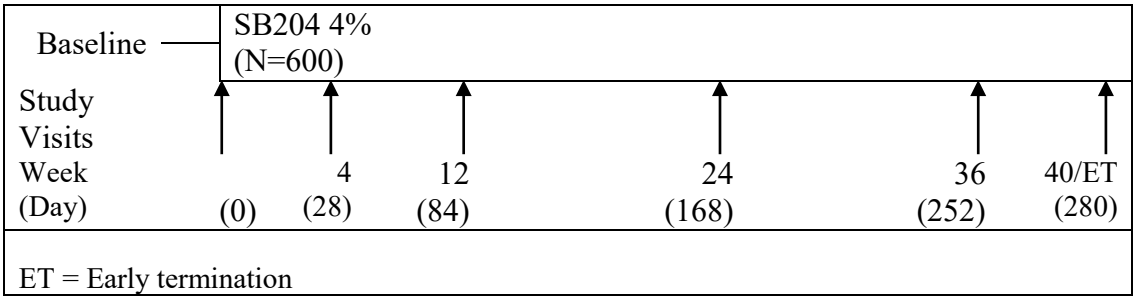
2.2 STUDY OBJECTIVES

The primary objective of this study is to evaluate the long term safety of SB204 4% once daily for up to 40 weeks in subjects with acne vulgaris.

3. STUDY DESIGN

Figure 1 depicts the overall study design for this 40-week, open label study in subjects with acne vulgaris dosed once daily with SB204 4%. Subjects must have completed participation in one of the pivotal acne trials (NI-AC301 or NI-AC302) to be eligible to participate in this long term safety trial. Subjects will be treated chronically or repeatedly as recommended by the Investigator for up to 40 weeks. The Investigator may stop treatment if the subject's acne is in remission and re-initiate treatment if the subject's acne recurs. Any subject who is determined to be clear will remain enrolled in the study until study completion or termination. The total time on study will be counted as the days from enrollment until the subject discontinues or the study terminates.

Figure 1: Study Diagram



3.1 STUDY ENDPOINTS

3.1.1 SAFETY ENDPOINTS

Safety endpoints will include adverse events, changes in physical examination and changes in vital sign measurements. Any clinically significant changes noted during the physical exam as well as from the vital sign measurements will be recorded as adverse events and included in the comparison. Urine pregnancy tests in women of child-bearing potential will be conducted at each visit.

3.1.2 TOLERABILITY ENDPOINTS

The cutaneous tolerability assessments include the investigator's assessment of erythema, scaling, dryness, and the subject's report of pruritus and burning/stinging based on the preceding 24 hours.

3.1.3 EXTENT OF EXPOSURE

Extent of exposure will be calculated based on total number of days of study drug application and the body surface area treated (face, upper back, upper chest/shoulders).

3.1.4 EFFICACY ENDPOINTS

Efficacy endpoints will include change in inflammatory and non-inflammatory lesion counts from baseline at each study visit.

3.2 STRUCTURE

This is a multi-center, open label study. Eligible subjects will have completed either NI-AC301 or NI-AC302, regardless of which treatment arm they were assigned to receive in the original study.

3.3 DURATION

Subjects will be in the study for a maximum of 40 weeks; the Week 12 visit from the pivotal study will serve as the Baseline Visit for this study.

3.4 DOSAGE/DOSE REGIMEN

SB204 will be dispensed from a dual-chamber pump designed to deliver approximately equal amounts of NVN1000 Gel and hydrogel. NVN1000 Gel will be opaque and the hydrogel will be clear. The subject will instantly mix the two substances in the palm of the hand and then immediately massage a thin layer over the acne affected areas once daily after washing. The product should be mixed for about 5 seconds until thoroughly combined with a uniform opaque appearance then applied with the fingertips. Subjects should apply SB204 prior to bedtime.

Up to 2.7 g of SB204 4% will be applied evenly over the acne affected area, including the face, chest, back, and upper shoulders once a day for a period of up to 40 weeks (280 days). The amount of SB204 per application will vary depending on the areas to be treated as shown in Table 1 below. One pump stroke (0.9 g) will be used for the face. Application to the face, upper back and upper chest/shoulders will require up to 2.7 g (three (3) pump strokes).

Table 1: Dosing Amount by Area

Area (BSA)	Number of Pump Strokes	Amount of Product
Face (3%)	1	0.9 g
Upper Back (6%)	1	0.9 g
Upper Chest/Shoulders (8%)	1	0.9 g

3.5 VISIT SCHEDULE

The Week 12 visit for the pivotal studies NI-AC301 or NI-AC302 will serve as the Baseline Visit for this long term safety study. Subjects must have completed the full 12 weeks of treatment in one of the pivotal studies to enroll in the long term safety study. Subjects may enter the long term safety study up to 7 calendar days after their Week 12 visit in the pivotal study. Study visits will take place after the first four weeks then at Weeks 4, 12, 24, 36 and 40.

3.6 STUDY POPULATION

Approximately 600 healthy male and female subjects with acne vulgaris on the face, chest, shoulders or back will be allowed to participate in the study if they have successfully completed 12 weeks in either NI-AC301 or NI-AC302.

A subject whose facial acne cleared during NI-AC301 or NI-AC302 is eligible to enroll if all other inclusion criteria and none of the exclusion criteria are met. If a subject enters the pivotal study at age 40 and is 41 at the time they complete participation in the pivotal study, they are eligible for the long term safety study as long as they meet all other study inclusion criteria and none of the exclusion criteria.

3.7 ELIGIBILITY CRITERIA

3.7.1 INFORMED CONSENT AND AUTHORIZATION TO RELEASE HEALTH INFORMATION

Written informed consent/assent will be obtained from all subjects 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/assent. A subject wishing to participate must give written informed consent/assent prior to any study-related procedures being conducted. 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 Week 12 assessments for the pivotal study NI-AC301 or NI-AC302 should be done prior to consenting the subject for participation in this long term safety study.

The site-specific informed consent and assent forms must be forwarded to Chiltern for approval prior to submission to an Institutional Review Board (IRB) as appropriate. Each subject will sign the consent form that has been approved by the same IRB responsible for protocol approval. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by the 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 consent form(s) must also include a statement that Novan, Chiltern (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 and parent or legal guardian (where applicable) and fully explained by the Investigator (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the study, the IRB approved consent and assent (where applicable) document(s) shall be signed and dated by both the subject and parent or legal guardian (where applicable) and the person obtaining consent (Investigator or designee), and by any other parties required by the IRB or other regulatory authorities. A subject under 18 years of age (or the age of majority in their state) must sign a written informed assent and be accompanied by the parent or legal guardian at the time of consent/assent signing. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at the next study visit to continue study participation. The subject will be given a copy of the signed informed consent 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.

3.7.2 INCLUSION CRITERIA

Each subject must fulfill all of the following inclusion criteria to participate in the study:

1. Have a signed written informed consent form. Subjects less than 18 years of age or the age of majority in their state must sign an assent form for the study and a parent or a legal guardian must sign the informed consent;
2. Have completed the full 12 weeks of treatment in NI-AC301 or NI-AC302;
3. Be in good general health;
4. Have no more than two nodules or cysts on the face;
5. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) prior to enrollment;
6. WOCBP 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;
7. Be willing and able to follow study instructions and likely to complete all study requirements. Subjects under 18 years of age or age of majority must be accompanied by the parent or legal guardian at the time of assent/consent signing.

3.7.3 EXCLUSION CRITERIA

Subjects will not be enrolled if they meet any of the following exclusion criteria:

1. Have any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis;
2. Have any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive;
3. Have an on-going adverse event at the Week 12 visit for NI-AC301 or NI-AC302 that warrants stopping study drug application;
4. Are transgender persons who are taking testosterone (female to male) or estrogen (male to female);
5. Have facial hair, tattoos or other markings that could interfere with assessments or application of study drug;
6. Have a history of experiencing significant burning or stinging when applying any facial treatment (e.g., make-up, soap, masks, washes, sunscreens, etc.) to their face;
7. Female subjects who are pregnant, nursing mothers, or planning to become pregnant during the study;

8. Intend to use a tanning booth or sunbathe during the study;
9. Are members of the same household where a subject is enrolled in NI-AC301, NI-AC302, or NI-AC303;
10. Are immediate family members of study site personnel directly involved in NI-AC301, NI-AC302, or NI-AC303;
11. Have any condition or situation which, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study;
12. Are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
13. Concurrently participating in a different interventional research study.

4. STUDY PROCEDURES AND METHODS

4.1 SUBJECT ENTRY PROCEDURES

Prospective subjects as defined by the eligibility criteria in Sections 3.7.2 and 3.7.3 (Inclusion/Exclusion Criteria) will be considered for entry into this study. Subjects' informed consent/assent must be obtained prior to conducting any procedures for this study and after completion of the Week 12 assessments for NI-AC301 or NI-AC302.

Some baseline procedures (i.e., review of inclusion/exclusion criteria, brief physical exam, blood pressure and pulse rate, lesion counts, cutaneous tolerability, adverse event assessment, concomitant medication review and UPT) must be completed prior to dispensing open label study medication.

WOCBP having a positive UPT at baseline may not be randomized into the study. Women of childbearing potential must agree to use an effective form of contraception during participation in the study and for 30 days after their final study visit. Effective contraception is defined as stabilized on oral contraceptive for at least three months (90 days), intrauterine device (IUD), condom with spermicide, diaphragm with spermicide, implant, NuvaRing®, medroxyprogesterone injection, transdermal patch or abstinence with a documented second acceptable method of birth control should the subject become sexually active. Females taking hormonal contraceptives must have taken the same type for at least three months (90 days) prior to entering the study and must not change type during the study. Subjects who had used hormonal contraception and stopped must have stopped no less than three months prior to the start of the study.

A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for 24 consecutive months), surgically sterilized, or without a uterus and/or both ovaries. Pre-menarchal girls are considered to be of childbearing potential.

After the required procedures are completed and study eligibility is confirmed, study drug will be dispensed to the subject. The subject will be trained on the mixing, application, and storage of the study drug. All study drug applications will be done at home.

Table 2: Schedule of Visits and Procedures

Study visits should occur at approximately the same time of day throughout the study.

PROCEDURES	Visit 1[1] Baseline (Day 0)	Visit 2[3] Week 4 ±5 days (Day 28)	Visit 3 Week 12 ±7 days (Day 84)	Visit 4 Week 24 ±7 days (Day 168)	Visit 5 Week 36 ±7 days (Day 252)	Visit 6[4] Week 40/ET ±7 days (Day 280)
Informed Consent/Assent	X					
Demographics	X[2]					
Medical History	X					
Medication History	X					
Inclusion/ Exclusion Criteria	X					
Brief Physical Examination	X[2]					X
Urine Pregnancy Test (all WOCBP)	X[2]	X	X	X	X	X
Blood Pressure and Pulse	X[2]	X	X	X	X	X
Lesion Counts	X[2]	X	X	X	X	X
Cutaneous Tolerability Evaluation	X[2]	X	X	X	X	X
Instruct on Study Drug Application and Provide Subject Instructions	X					
Record application areas since last visit		X	X	X	X	X
Study Drug Dispensed/Retraining on mixing and application	X	X	X	X	X	
Study Drug Collected		X	X	X	X	X
Subject Study Drug Use Reviewed		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

[1]Data for the Baseline Visit for this study will be the Week 12 data from the Phase 3 pivotal study for completing, eligible subjects.
[2]Demographics and assessments from the Week 12 visit from the preceding Phase 3 study including the physical examination, blood pressure and pulse, UPT, tolerability, and lesion counts do not need to be repeated.
[3]All visit dates are in reference to Baseline, e.g., Visit 2 occurs four weeks (28 days) after Baseline visit.
[4] All Week 40 procedures should be completed for subjects who prematurely discontinue.

4.1.1 BASELINE

The following procedures were performed as Week 12 assessments in NI-AC301 or NI-AC302 and will be used for baseline values for this study:

1. Collect blood pressure and pulse rate after the subject has been sitting quietly for 5 minutes.
2. Perform a brief physical examination.
3. Obtain pregnancy test (WOCBP only) and evaluate results. If pregnancy test is positive, the subject may not participate in the study.
4. Perform Cutaneous Tolerability Evaluation on the face only.
5. Perform lesion counts on the face only. Inflammatory and non-inflammatory lesion counts will be performed on the entire face and reported separately.

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

1. Review study procedures and information regarding the study including the potential risk and benefits of SB204 with the subject and obtain written informed consent/assent.
2. Review subject's concomitant medication information.
3. Verify appropriate contraception being used for WOCBP per Section 6.4.
4. Review prohibited medications, acne treatments, and supplements that should not be used during the trial.
5. Confirm subject meets eligibility criteria.
6. Dispense subject diary and study drug. Instruct subject on dispensing, mixing, and application of study product and diary completion.
7. Collect AEs related to study procedures performed since signing of informed consent.
8. Confirm the study schedule with the subject.

4.1.2 WEEKS 4, 12, 24 AND 36 (DAYS 28, 84, 168, 252)

The following procedures must be performed and recorded at the Weeks 4, 12, 24, and 36 visits:

1. Update concomitant medication information.
2. Update AE information and record any new AEs if applicable.
3. Obtain UPT (WOCBP only) and evaluate results.
4. Collect blood pressure and pulse rate after the subject has been sitting quietly for 5 minutes.

5. Perform cutaneous tolerability evaluation (face only).
6. Perform lesion counts (face only).
7. Record areas treated since last visit (face, upper back, upper chest/shoulders).
8. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
9. Review subject diary for completion.
10. Dispense new study drug and diary.
11. Review and confirm the study schedule with the subject.

4.1.3 WEEK 40/ET (DAY 280)

The following procedures must be performed and recorded at the Week 40/ET visit:

1. Update concomitant medication information.
2. Perform a brief physical exam.
3. Update AE information and record any new AEs.
4. Obtain UPT (WOCBP only) and evaluate results.
5. Collect blood pressure and pulse rate after the subject has been sitting quietly for 5 minutes.
6. Perform cutaneous tolerability evaluation (face only).
7. Perform lesion counts (face only).
8. Record areas treated since last visit (face, upper back, upper chest/shoulders).
9. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
10. Review subject diary for completion.

4.1.4 DISCONTINUATION/WITHDRAWAL PROCEDURES

A subject may voluntarily withdraw from study participation at any time. If the subject 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. If a subject is withdrawn because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, (i.e., prior to Week 40/Day 280 visit) and whenever possible, the subject should be asked to return to the study center to complete the Week 40/ET evaluations. Subjects who withdraw from the study will not be replaced.

If at any time during the study the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator can discontinue a subject at any time if medically necessary. The Investigator may discontinue a subject's participation if the subject 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 discontinuation must be completed.

All subjects who fail to return to the study center for the Week 40/ET visit 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 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 contact the Investigator.

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

- Safety (e.g., severe adverse reactions, pregnancy);
- Lack of efficacy as determined by the Investigator;
- When the requirements of the protocol are not respected (e.g., significant issues with study visit compliance);
- 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 Chiltern, whether the subject is to be withdrawn);
- When a subject is lost to follow-up. The Investigator will try twice to reach the subject by telephone and will send a certified follow-up letter before considering that the subject is lost-to-follow-up. 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.

Refer to Section 6.7 for a discussion of criteria for discontinuation of individual subjects from the study.

All premature discontinuations and their causes must be carefully documented by the Investigator on the subject's study record and in the study database. In no case will a subject who has been assigned a study number and entered into the study be replaced by another.

All Week 40/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 Chiltern.

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

- Completed
- Adverse Event
- Lack of Efficacy
- Withdrawal by Subject
- Physician Decision
- Protocol Violation
- Lost to Follow-Up
- Pregnancy
- Worsening of condition
- Other

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

4.2 TOLERABILITY ASSESSMENTS

The evaluator will assess the subject's face at baseline and each study visit. The cutaneous tolerability scores from Week 12 of NI-AC301 or NI-AC302 will be the subject's baseline tolerability. The cutaneous tolerability assessment should be performed at least 30 minutes after study drug application. Cutaneous tolerability evaluations will include erythema, scaling, dryness, pruritus and burning/stinging. Pruritus and burning/stinging will be based on the subject's report for the previous 24 hours. Cutaneous tolerability endpoints will not be reported as an AE unless they reach severe and/or result in subject's discontinuation from the study. Subjects who develop intolerance to the product as defined by scores of 3 (severe) on two or more categories of tolerability (erythema, scaling, dryness, pruritus, burning/stinging) shall be discontinued from the study. Cutaneous tolerability assessments will be performed according to the following scales:

Erythema

Score	Description
0-None	No evidence of erythema present
1-Mild	Slight pink coloration
2-Moderate	Definite redness
3-Severe	Marked erythema, bright red to dusky dark red in color

Scaling

Score	Description
0-None	No scaling
1-Mild	Fine scales present to limited areas of the face, barely perceptible
2-Moderate	Fine scale generalized to all areas of the face
3-Severe	Scaling and peeling of skin over all areas of the face

Dryness

Score	Description
0-None	No dryness
1-Mild	Slight but definite roughness
2-Moderate	Moderate roughness
3-Severe	Marked roughness

Pruritus

Score	Description
0-None	No itching
1-Mild	Slight itching, not very bothersome
2-Moderate	Moderate amount of itching, somewhat bothersome
3-Severe	Severe amount of itching, definite discomfort and sleep may be disturbed

Burning/Stinging

Score	Description
0-None	No burning/stinging
1-Mild	Slight warm, burning/stinging sensation; not very bothersome
2-Moderate	Definite warm, burning/stinging sensation that is somewhat bothersome
3-Severe	Hot, tingling/sensation that has caused definite discomfort and may have disturbed sleep

4.3 SAFETY ASSESSMENTS

Adverse events will be collected beginning with the Baseline Visit for this study. Adverse events that began during NI-AC301 or NI-AC302 that are ongoing at the conclusion of either study will be reported as AEs at Baseline in this long-term safety study (NI-AC303) and followed. The physical exam, vital signs and pregnancy test results from the Week 12 visit of NI-AC301 or NI-AC302 will be used as the subject's Baseline assessments for this long term safety study and be collected during the study.

4.3.1 ADVERSE EVENTS

AEs will be collected starting after the subject has signed the informed consent and completed any study assessment until the end of the final study visit. The date of onset, date ended, severity,

relationship to study drug, therapy required, and action taken regarding study drug and study participation will be reported for each AE.

See Section 6 for additional information regarding the evaluation of adverse events.

4.3.2 PHYSICAL EXAM

A brief physical exam will be performed at Week 40/ET. If clinically significant changes in the physical examination from Baseline are noted at the Week 40/ET visit, these will be recorded as adverse events.

4.3.3 VITAL SIGNS

Blood pressure and pulse rate will be collected at Weeks 4, 12, 24, 36 and 40/ET. Any clinically significant changes in vital signs from Baseline will be recorded as adverse events whether or not drug related.

4.3.4 PREGNANCY TESTING

All WOCBP must have a UPT at Weeks 4, 12, 24, 36 and 40/ET and if the result is positive, the subject will not be allowed to continue in the study. Refer to Section 6.4 for further information.

4.4 EFFICACY ASSESSMENTS

The same evaluator should perform lesion counting at Weeks 4, 12, 24, 36, and 40/ET. This should be the same evaluator that performed the Week 12 assessments for the NI-AC301 or NI-AC302 study. In the event that this is not possible due to unforeseen circumstances, a different evaluator may evaluate the subject. However, the same evaluator should evaluate subjects at the Baseline and Week 40/ET evaluations. The subject's Week 12 lesion counts from NI-AC301 or NI-AC302 will be considered the Baseline value for this study.

4.4.1 LESION COUNTS

The facial area lesion counts will be taken from the forehead, right and left cheeks, chin and nose. The lesion count groups will be inflammatory and non-inflammatory. Facial inflammatory lesions (pustules, papules, nodules and cysts) will be counted and recorded. Non-inflammatory lesions (open and closed comedones) will be counted and recorded. The following are definitions of each lesion type:

Inflammatory lesions are defined as follows:

Papule –A small, superficial, circumscribed, palpable lesion elevated above the skin surface, less than 10 mm in diameter

Pustule –A superficial elevated lesion that contains yellow fluid (pus) within or beneath the epidermis
Nodule –A firm (indurated) lesion greater than 10 mm in diameter and that is thicker or deeper than the average papule
Cyst - Spherical swelling that contains fluid or semisolid material

Non-inflammatory lesions are defined as follows:

Open comedones (blackhead) –Plugged follicular units with brown/black central debris
Closed comedones (whitehead) –Plugged follicular units with white central debris

4.5 SCREEN FAILURES

A screen failure subject will be a person from whom informed consent is obtained but who does not meet the study eligibility requirements. Subjects will not be allowed to rescreen.

4.6 PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation 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 Chiltern at the earliest possible time by telephone.

5. PROHIBITED THERAPIES AND MEDICATIONS

Concomitant medications are any prescription or over-the-counter (OTC) preparations. Use of concomitant medications will be recorded on the concomitant medications study record and study database beginning at the Baseline Visit until the final evaluation (Week 40/ET).

Subjects will be permitted to apply non-comedogenic moisturizer or sunscreen on an as-needed basis. Moisturizer must not contain antibacterials and the subject must not change moisturizer and/or sunscreen used during the course of the study. If used, moisturizers and sunscreen must be applied at least 30 minutes after study drug application.

Subjects must not have used anti-acne treatments including topical or systemic antibiotics or retinoids as described in Section 3.7.3 prior to Baseline. These medications are also prohibited during the trial. Short term courses of antibiotics (≤ 14 days) for non-acne related illnesses and inhaled or intranasal steroids are permitted during the trial.

Subjects may not be concurrently on drugs associated with exacerbating acne vulgaris (Appendix 16.1). Subjects must not participate in a different interventional research study during the study period.

Any medication/therapy used by the subject following first application of study product will be considered a concomitant medication/therapy (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.

6. EVALUATION OF ADVERSE EVENTS

6.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury or accident) whether or not considered drug related. Any AE that emerges or worsens following administration of the informed consent and until the end of study participation will be collected. A pre-existing condition is one that is present prior to the start of the study and is to be reported as part of the subject's medical history unless it began as an AE in NI-AC301 or NI-AC302. Adverse events that began during NI-AC301 or NI-AC302 that are ongoing at the conclusion of either study will be reported as AEs at Baseline in this long-term safety study (NI-AC303) and followed. Prior conditions should be reported as an AE if the frequency, intensity, or the character of the condition worsens during the study or if the condition persists.

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

A serious adverse event (SAE) includes any event, if in the view of either the investigator or the Medical Monitor results in any of the following outcomes:

- Death
- Life-threatening event (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe)
- Persistent or significant disability/incapacity (i.e., the AE results in a substantial disruption of the subject's ability to carry out normal life functions)
- Requires in-patient hospitalization or prolongs hospitalization (i.e., the AE required at least a 24-hour in-patient hospitalization or prolonged a hospitalization beyond the expected

length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)

- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or investigational product before conception or during pregnancy)
- Does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (i.e., is a significant or important medical event)

6.1.1 ADVERSE EVENT SEVERITY GRADES

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 until there is a return to the subject's baseline condition or until a clinically satisfactory resolution is achieved or the subject is lost to follow-up.

6.1.2 INVESTIGATIONAL PRODUCT CAUSALITY

Relationship of an AE to investigational product will be assessed as follows:

- Definite: There is a clinically plausible time sequence between the onset of the AE and the application of investigational product; when the event responds to withdrawal of investigational product and recurs with re-administration of investigational product.
- Probable: There is a clinically plausible time sequence between the onset of the AE and the application of investigational product; 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 investigational product 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.

6.2 REPORTING ADVERSE EVENTS

For the purpose of AE reporting the trial period is defined as the period after the subject signs the informed consent/assent to the end of subject's last visit.

The Investigator will assess subjects at each scheduled study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "*How have you felt since your last visit?*" 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.

In addition, Chiltern must be notified within 24 hours of the Investigator's knowledge of the event by telephone or email of any immediately reportable events according to the procedure outlined below. Special attention should be paid to recording hospitalizations and concomitant therapies and medications.

6.3 IMMEDIATELY REPORTABLE EVENTS

Serious adverse events (SAEs) are considered immediately reportable events. Any SAE, whether deemed drug-related or not, must be reported to Chiltern telephone, fax, or email as soon as possible after the Investigator or coordinator has become aware of its occurrence. The Investigator/coordinator must complete a Serious Adverse Event (SAE) Form and email it to Chiltern within 24 hours of notification of the event. When appropriate, Novan will notify the appropriate regulatory body of drug related Serious Adverse Events.

Serious Adverse Event (SAE) and Safety Contact Information:

Phone: SAE Hotline: 1-888-SAE CHIL (1-888-723-2445)
Email: GlobalSAEInbox@Chiltern.com
Fax: 1-800-468-2288

If a subject experiences an SAE or pregnancy the Investigator must:

1. Report the SAE or pregnancy by telephone, fax, or email immediately (within 24 hours) after the Investigator becomes aware of the event.
2. Complete an SAE or Pregnancy Notification Form and email, fax, or overnight courier to Chiltern 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 Chiltern 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 investigational product.
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.

6.4 PREGNANCY

Women of child-bearing potential (WOCBP) must use an effective method of birth control during the course of the study and for 30 days following their final study visit. Allowable methods of birth control include stabilized on oral contraceptive for at least three months (90 days), IUD, condom with spermicide, diaphragm with spermicide, implant, NuvaRing®, injection, transdermal patch or abstinence with a documented second acceptable method of birth control should the subject become sexually active. Females taking hormonal contraceptives must have taken the same type for at least three months (90 days) prior to entering the study and must not change type during the study. Those who have used birth control pills or hormonal contraception in the past and stopped must have discontinued usage at least three months (90 days) prior to the start of the study.

A female is considered to be of childbearing potential unless she is post-menopausal (no menses for 24 consecutive months), surgically sterilized, or without a uterus and/or both ovaries. Premenarchal females are considered to be of childbearing potential.

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

- Informed consent document
- Pregnancy prevention information
- Risks to unborn child(ren)
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use

- Guidelines for the follow-up of a reported pregnancy

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

During the study, WOCBP 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 Chiltern of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and email/fax the form to Chiltern. Subjects found to be pregnant prior to Week 40 will be discontinued from the study. Chiltern will ask the site to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Protocol-required procedures for the Week 40/ET evaluation must be performed for the subject.

6.5 FOLLOW-UP OF ADVERSE EVENTS

6.5.1 FOLLOW-UP OF NON-SERIOUS ADVERSE EVENTS

Non-serious AEs that are not resolved at the time of the last scheduled study visit (Week 40/ET) must be recorded in the study database as ongoing/not recovered/not resolved.

6.5.2 FOLLOW-UP OF POST STUDY SERIOUS ADVERSE EVENTS

Serious adverse events that are identified on the last scheduled contact (Week 40/ET) must be recorded in the study database and reported to Chiltern according to the reporting procedures outlined in Sections 6.2 and 6.3. 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 Chiltern 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.

Any new SAEs reported by the subject to the Investigator that occur after the last scheduled contact and are determined by the Investigator to be reasonably associated with the application of investigational product should be reported to Chiltern and the IRB.

6.6 OVERDOSAGE

There is no specific antidote for nitric oxide. In the event of an overdose, best supportive care should be utilized. Methylene blue may be used to treat subjects exhibiting methemoglobinemia.

6.7 DISCONTINUATION OF INDIVIDUAL SUBJECTS FROM THE STUDY

Subjects who develop intolerance to the product as defined by scores of 3 (severe) on 2 or more categories of tolerability (erythema, scaling, dryness, pruritus, burning/stinging) shall be discontinued from the study.

If a subject is determined to be pregnant prior to Week 40, the subject will be discontinued from the study but followed until term.

7. STATISTICAL ANALYSIS

7.1 GENERAL CONSIDERATIONS

All statistical processing will be performed using SAS® unless otherwise stated. A detailed description of the statistical methodology and data reporting for this study will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked and released to Novan. Any deviations from the SAP will be justified in the clinical study report.

7.2 POPULATIONS

7.2.1 SAFETY POPULATION

The safety population will include all subjects that have been dispensed study drug.

7.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics will be summarized. For continuous variables (e.g., age), mean, median, standard deviation, minimum and maximum will be presented. Categorical variables (e.g., ethnicity, race) will be summarized with frequency count and percentage.

7.4 DESCRIPTIVE STATISTICS

Safety data will be summarized as indicated below for the safety population.

Continuous data will be summarized with sample size (N), mean, median, standard deviation, minimum and maximum. Categorical data will be summarized with N, frequency counts, and percentages of N.

7.5 SAFETY

7.5.1 ADVERSE EVENTS

All AEs that occur during the study or continue after enrollment into this study will be recorded and classified on the basis of MedDRA terminology. Treatment-emergent adverse events (TEAEs) are defined as AEs reported on or after the first day of enrollment in this long term safety study.

All information pertaining to an AE noted during the study will be listed by subject, detailing verbatim term given by the PI or designee, preferred term, system organ class (SOC), onset date, resolution date, severity, seriousness, action taken, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to date of first dose in this study.

Treatment-emergent AEs will be summarized by the number of subjects reporting a TEAE, 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.

Adverse events will also be summarized by windows of exposure to study drug. The windows will include but are not limited to: 1) within the first 24 hours of exposure, 2) up to 1 month of exposure, 3) up to 3 months of exposure, 4) up to 6 months of exposure and 5) up to 12 months of exposure.

AEs will also be summarized based on extent of exposure as described in Section 7.7

Serious AEs will be summarized by 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.

7.5.2 PHYSICAL EXAMINATION

Any clinically significant changes from Baseline will be documented as an AE.

7.5.3 VITAL SIGNS

Blood pressure and pulse will be summarized from Baseline through Week 40. Additionally, change from Baseline in vital signs will be summarized at Week 4, 12, 24, 36, and 40. Clinically significant changes from Baseline will be documented as an AE.

7.5.4 URINE PREGNANCY TESTS

Urine pregnancy tests results for WOCBP will be presented in data listings by subject.

7.6 TOLERABILITY

Distribution and shift in cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized from Baseline to Week 40.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be based on days of treatment and the body surface area treated (face, upper back, and/or upper chest/shoulders) as collected at each visit for each subject. AEs will also be summarized by extent of exposure to determine if there is a safety signal due to duration of exposure or total body area exposed.

7.8 EFFICACY ANALYSIS

Lesion counts will be summarized at each evaluation from Baseline through Week 40. Absolute and percent change in lesion counts will be summarized at Weeks 4, 12, 24, 36 and 40.

7.9 SAMPLE SIZE AND POWER CONSIDERATIONS

Approximately 600 subjects who completed treatment in either the NI-AC301 or NI-AC302 will be enrolled into the study from approximately 100 sites in North America. The main objective of this study is to evaluate the long term safety of SB204, therefore, no sample size or power calculations were performed.

8. INVESTIGATIONAL PRODUCT MANAGEMENT

8.1 RECEIPT OF INVESTIGATIONAL PRODUCT

Novan, or designee, will provide all investigational products to the study sites.

8.2 STORAGE OF INVESTIGATIONAL PRODUCT

Upon receipt from Novan, or Novan's designee, a study staff member will place all study supplies in a temperature-controlled area. The pumps should be refrigerated (2-8 °C). 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), the Chiltern CRA or designee 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.

The investigational product will be dispensed at the discretion and by the direction of the Investigator in accordance with the conditions specified in this protocol. It is the Investigator's

responsibility to ensure that accurate records of investigational product issuance and return are maintained.

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

8.3 TREATMENT ASSIGNMENT AND BLINDING

Subjects will receive open label SB204 4%. The evaluator and subject will be not be blinded to the subject's treatment.

8.4 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

A trained study staff member will maintain an inventory of investigational product components. This will include:

- Dates and initials of person designated as responsible for the inventory of the investigational product
- Amount received including date
- Amount currently in refrigerator, 2-8 °C storage
- Pumps dispensed to each subject, identified at a minimum by a unique subject number
- Amount transferred to another location within the study site or destroyed; this should not occur without prior notification to Chiltern
- Non-study disposition (e.g., wasted, broken)
- Amount returned to Novan's designee, if applicable
- Amount destroyed, if applicable

All investigational product accountability forms and treatment logs must be retained in the Investigator's permanent study file. These records must be available for inspection by Novan and Chiltern, their designees, or regulatory agencies at any time.

8.5 RETURNS AND DESTRUCTION

Upon completion or termination of the study, the site will be instructed on return or destruction of clinical supplies.

9. RECORDS MANAGEMENT

9.1 DATA COLLECTION

The full details of procedures for data handling will be documented in the data management plan.

Source study records will be collected for each study subject and a study database will be maintained for all enrolled study subjects. Screen failures will not be entered in the electronic data capture (EDC) system.

Novan requires that the study database be verifiable with the subject's source study record. This requirement necessitates access to all original recordings and other records for each subject. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to the subject's medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to any study procedures being performed.

Before the study database is formally submitted to Novan, the study monitor, Chiltern Medical Monitor or Novan staff may request copies of the subject's source study record for preliminary medical review.

The Investigator must keep written or electronic source documents for every subject participating in the clinical study. These records must include:

- Name Contact information
- Date of birth
- Sex
- Medical history
- Concomitant diseases
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data must be included in the subject's source documents and must include the subject's initials, study number and the date of the evaluation.

The data recorded during the course of the study will be documented in the study database. Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The Investigator will ensure that the study records and any other documents forwarded to Chiltern contain no mention of subject names.

Any amendments and corrections necessary will be undertaken in both the study records and the study database.

Regulatory authorities, Investigational Review Boards, Novan, and Chiltern may request access to all study records and other study documentation for on-site audit or inspection. The Investigator must guarantee direct access to these documents. The original set of study records will be kept by the site or an authorized designee in a secured area. Clinical data will be recorded in an electronic format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by Novan after descriptive and statistical analyses and reports have been generated and are complete.

9.2 FILE MANAGEMENT AT THE STUDY SITE

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.

9.3 RECORDS RETENTION AT THE STUDY SITE

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 or their designees 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.

10. MONITORING, COMPLIANCE, AND QUALITY

All aspects of the study will be monitored by Chiltern according to Good Clinical Practices 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 Chiltern at any time for review and audit to ensure the integrity of the data. The Investigator must notify Chiltern 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 Novan or Chiltern representative will review the protocol and study records with the Investigator(s) and their staff. During the study, the Chiltern 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 SAEs and the recording of safety variables. A reduced source data verification model will be deployed for this study in order to focus on the critical data for analysis and this will be executed per the study specific monitoring plan. 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 Chiltern and the responsible IRB with a study summary shortly after study completion.

10.1 QUALITY ASSURANCE AUDITS AND QUALITY CONTROL

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

11. ETHICS AND RESPONSIBILITY

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 Chiltern 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. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from Novan. Authorized regulatory officials, Novan and Chiltern personnel (or their representatives) will be allowed full access to inspect and copy the records. All study investigational products, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Novan.

Subjects will be identified at a minimum by unique subject numbers in the study database.

13. AMENDMENT POLICY

Only Novan may modify the protocol. Amendments may be approved by all applicable national and local committees including, but not limited to, the government regulatory authorities and/or regional IRB before implementation. The only exception is when an Investigator considers that a subject may be harmed and immediate action is necessary. Under these circumstances, approval of the chairman of the IRB, or an authorized designee must be sought immediately. The Investigator should inform Chiltern and the full IRB no later than five working days after the emergency occurs. Protocol-specified safety reporting requirements must be adhered to independent of any other variables. All amendments that have an impact on subject risk, the study objectives or that require revision of the informed consent document must be approved by the IRB before implementation. Administrative changes to the protocol and/or changes that do not impact subject safety, risk or comfort may be implemented prior to IRB approval if local institutional policy permits. A copy of the written approval of the IRB, which becomes part of the essential study documents file, must be given to the study monitor. Examples of amendments requiring such approval are:

- A significant change in the study design
- An increase in the number of invasive procedures to which subjects are exposed
- An addition or deletion of a test procedure

The Principal Investigator at each study site must sign the Investigator's Agreement page of the amended protocol.

14. USE OF INFORMATION AND PUBLICATION

It is understood by the Investigator that the information generated in this study will be used by Novan in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide Novan with complete test results, all study data and access to all study records.

Investigators may not report the results of this clinical study in any publication, poster or other public forum without express authorization from Novan.

15. REFERENCES

Guideline for Good Clinical Practice. *ICH Harmonised Tripartite Guideline*. **1996**.

Protection of Human Subjects. *Code of Federal Regulation.* **1999.** Part 50, Title 21, Section 20.

Institutional Review Boards. *Code of Federal Regulation.* **1981.** Part 56, Title 21, Section 103.

16. APPENDICES

16.1 APPENDIX 1: LIST OF RESTRICTED MEDICATIONS:

- Anti-acne medications
- Anabolic steroids
- Azathioprine
- Bromides
- Corticosteroids (oral)
- Chloroquine
- Flutamide
- Halides
- Lithium
- Phenobarbital
- Phenytoin
- Vitamin A (> 10,000 IU/day)