STUDY TITLE	A Phase 3 Multi-Center, Randomized, Double-Blinded, Vehicle-Controlled, Parallel Group Study Comparing the Efficacy, Tolerability and Safety of SB204 and Vehicle Gel Once Daily in the Treatment of Acne Vulgaris
PROTOCOL NO.	NI-AC301
SPONSOR	Novan, Inc. 4222 Emperor Blvd., Suite 200 Durham, NC 27703 Tel.: 919-485-8080
AMENDMENT 1	06 January 2016
VERSION	2.0

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.

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

06 Jan 2016
Date

Carolyn Enloe
Carolyn Enloe, MPH
Clinical Program Manager
Novan, Inc.

06 Jan 2016
Date

Melissa Hays
Principal Biostatistician
Chiltern

06 Jan 2016
Date

CONTACT INFORMATION PAGE

Sponsor Contact Information:

Novan, Inc.
4222 Emperor Blvd., Suite 200
Durham, NC 27703
Tel: 919-485-8080
Fax: 919-237-9212

CRO Contact Information:

Chiltern
4000 CentreGreen Way
Suite 300
Cary, NC 27513
Tel: 919-462-8867

PROJECT MANAGER:
Jamie Palmer
Tel: 423-990-0276
Mobile: 423-943-6163
Fax: 423-968-3567
E-mail: Jamie.Palmer@chiltern.com

MEDICAL MONITOR:
William R Welder, MD, MPH
Tel: 423-990-0471
Fax: 888-833-6865
E-mail: Bill.Welder@Chiltern.com

Serious Adverse Event (SAE) and Safety Contact Information:

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

PROTOCOL AMENDMENT

RATIONALE FOR AMENDMENT

This protocol amendment is required to update the inclusion and exclusion criteria and the definition of subjects in the safety population. Eligible subjects are those age 9 and older. Subjects with severe recalcitrant nodulocystic acne are excluded. The term "principal investigator (PI)" has been added to the list of abbreviations. The safety population will be comprised of all randomized subjects that received at least one dose of study medication**.** Edits to the clinical and non-clinical background sections update results from completed studies. Analysis specifics have been moved to the statistical analysis plan (SAP). Minor edits have been made to the document to ensure consistency.

IDENTIFICATION OF CHANGES

Any changes to the original protocol are identified below and 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: SYNOPSIS: Key Inclusion Criteria

Be male or female, 9 ~~to 40~~ years of age **and older**~~, inclusive~~ and in good general health;

Change 2: SYNOPSIS: Key Inclusion Criteria

Have a minimum of 20 but no**t** more than 40 inflammatory lesions (papules, pustules, **nodules, and cysts)** on the face;

Change 3: SYNOPSIS: Key Exclusion Criteria

Have any dermatological conditions on the face that could interfere with clinical evaluations such as **severe recalcitrant nodulocystic acne,** acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis

Change 4: SYNOPSIS: Primary Efficacy Analysis

All three co-primary outcomes must show superiority over vehicle (p-value≤0.05) in order for efficacy to be demonstrated; therefore no adjustments for multiplicity will be made.

~~The analysis of treatment differences in the absolute change in non-inflammatory lesion counts will be conducted using a repeated measures analysis of covariance with factors for treatment, site, sex, age, visit and treatment by visit interaction. The Baseline lesion count will be included as the covariate and subject nested within site will be the random repeated measure at each visit to adjust for the variability due to repeated visits. Change from Baseline lesion counts at each visit will be the dependent variable. Only the estimate of treatment differences at Week 12/ET will be evaluated for efficacy.~~

~~The analysis of the absolute change in inflammatory lesion counts will use the same method as the analysis of the non-inflammatory lesions.~~

~~Subjects will be considered an IGA success if their IGA score is clear (0) or almost clear (1) at and is decreased by ≥ 2 grades from Baseline.~~

~~Analysis of treatment differences in IGA success at Week 12/ET will be conducted using a logistic general linear covariance model with factors for treatment, site, sex and age, and with Baseline IGA score as a covariate.~~

Change 5: SYNOPSIS: Secondary Efficacy Analysis

Secondary efficacy outcomes include the percent change in inflammatory and non-inflammatory lesion counts at Week 12/ET, the median time to 35% improvement in inflammatory lesions, and the median time to a two or more grade improvement in IGA. ~~The percent change in lesions will be analyzed for treatment differences using the same models as described in the co-primary efficacy analyses. Survival analysis methods will be used to sequentially estimate the treatment differences in the median time to 35% improvement in inflammatory lesions and the median time to a two or more grade improvement in the IGA. A subject will be censored if the endpoint is not realized.~~

Change 6: LIST OF ABBREVIATIONS

Added PI (Principal Investigator) to List of Abbreviations and Definitions

Change 7: PROTOCOL BODY: Section 3.6, Study Population, Paragraph 1

Approximately 1300 male and female subjects ~~between the ages of~~ 9 **years of age and older** ~~40 (inclusive)~~ with moderate to severe acne vulgaris on the face will be randomized to participate in the study.

Change 8: PROTOCOL BODY: Section 1.1

To date, approximately ~~400~~ **500** subjects have been treated with NVN1000 Gel, including SB204, and approximately ~~200~~ **275** subjects have been treated with the vehicle gel.

Change 9: PROTOCOL BODY: Section 1.1, Background

NVN1000 demonstrated mutagenicity in an Ames assay, but was not mutagenic in two in vivo genotoxicity tests in two tissue types (bone marrow via intraperitoneal (IP) administration and skin via topical administration) **and in a human lymphocyte chromosome aberration assay.**

Change 10: PROTOCOL BODY: Section 3.6, Study Population

Approximately 1300 male and female subjects ~~between the ages of~~ 9 ~~and 40 (inclusive)~~ **years of age and older** with moderate to severe acne vulgaris on the face will be randomized to participate in the study. Eligible subjects will have: **at least 25 but no more than 70 non-inflammatory lesions (open and closed comedones);** at least 20 but no more than 40 inflammatory lesions (papules, pustules, **nodules, and cysts**); ~~at least 25 but no more than 70 non-inflammatory lesions (open and closed comedones);~~ no more than two nodules or cysts; and an IGA of 3 (moderate) or 4 (severe) on a 5-point IGA scale (Appendix 16.2).

Change 11: PROTOCOL BODY: Section 3.7.2, Inclusion Criteria 2

Be male or female, 9 ~~to 40~~ years of age **and older**~~, inclusive~~ at Baseline and in good general health;

Change 12: PROTOCOL BODY: Section 3.7.2, Inclusion Criteria 5

Have a minimum of 20 but not more than 40 inflammatory lesions (papules, pustules, **nodules, and cysts**) on the face at Baseline;

Change 13: PROTOCOL BODY: Section 3.7.3, Exclusion Criteria 1

Have any dermatological conditions on the face that could interfere with clinical evaluations such as **severe recalcitrant nodulocystic acne,** acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis;

Change 14: PROTOCOL BODY: Section 7.2.2, Safety Population

The safety (SAF) population will include all ~~study~~ **randomized** subjects **that received at least one dose of study medication.** ~~who were and dispensed study medication and grouped by the treatment they were actually dispensed~~. All safety and tolerability analyses will be performed on the safety analysis population (SAF) population **based on the treatments the subjects actually applied.**

Change 15: PROTOCOL BODY: Section 7.4.1, Primary Efficacy Analysis

All three co-primary outcomes must show superiority over vehicle (p-value ≤0.05) in order for efficacy to be demonstrated; **therefore no multiplicity adjustments will be made to the co-primary outcome analyses.**

~~The analysis of treatment differences in the absolute change in non-inflammatory lesion counts will be conducted using a repeated measures analysis of covariance with factors for treatment, site, sex, age, visit and treatment by visit interaction. The Baseline lesion count will be included as the covariate and subject nested within site will be the random repeated measure at each visit to adjust for the variability due to repeated visits. Change from Baseline lesion counts at each visit will be the dependent variable. However, only the estimate of treatment differences at Week 12/ET will be evaluated for efficacy.~~

~~The analysis of the absolute change in inflammatory lesion counts will use the same method as the analysis of the non-inflammatory lesions.~~

~~Subjects will be considered an IGA success if their IGA score is clear (0) or almost clear (1) and is decreased by ≥ 2 grades from Baseline.~~

~~Analysis of treatment differences in IGA success at Week 12/ET will be conducted using a logistic general linear covariance model with factors for treatment, site, sex and age, and with Baseline IGA score as a covariate.~~

Prior to analysis of co-primary outcomes, missing post-Baseline **lesion counts and IGA scores** results at each visit will be imputed using a **Markov chain Monte Carlo (MCMC)** multiple imputation methodology. ~~Missing lesion counts and missing IGA scores will be assumed to be missing at random at each visit (MAR). Therefore a Markov chain Monte Carlo (MCMC) imputation method will be employed to impute all missing lesion counts and IGA scores for all~~

~~visits.~~ Separate multiple imputation (MI) procedures will be used for each outcome, using Statistical Analysis Software (SAS) procedure MI. Details of PROC MI and options used in the imputation procedures will be provided in a statistical analysis plan. ITT subjects with only Baseline assessments will have the Baseline value carried forward across all visits.

The primary analyses of the co-primary efficacy endpoints will be performed in the ITT population where missing data have been imputed as described above. Additional analyses of the co-primary outcomes will be performed using the PP population. To access the sensitivity of the primary efficacy results to imputation methods, each co-primary outcome will be analyzed as described above, but with missing data imputed by last observation carried forward (LOCF) and Baseline observation carried forward (BOCF) on the ITT population.

Change 16: PROTOCOL BODY: Section 7.4.2, Secondary Efficacy Analyses

Secondary efficacy outcomes include the percent change in inflammatory and non-inflammatory lesion counts at Week 12/ET, the median time to 35% improvement in inflammatory lesions and the time to a two or more grade improvement in the IGA. ~~The percent change in lesions will be analyzed for treatment differences using the same models as described in the co-primary efficacy analyses. Survival analysis methods will be used to sequentially estimate the treatment differences in the median time to 35% improvement in inflammatory lesions and the median time to a two or more grade improvement in the IGA. A subject will be censored if the endpoint is not realized.~~

Change 17: PROTOCOL BODY: Section 7.8, Sample Size and Power Consideration

Approximately 1300 subjects will be randomized into the study in a 1:1 ratio (650 in each ~~active~~ arm) at approximately 50 sites in North America.

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "A Phase 3 Multi-Center, Randomized, Double-Blinded, Vehicle-Controlled, Parallel Group Study Comparing the Efficacy, Tolerability and Safety of SB204 and Vehicle Gel 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, Randomized, Double-Blinded, Vehicle-Controlled, Parallel Group Study Comparing the Efficacy, Tolerability and Safety of SB204 and Vehicle Gel Once Daily in the Treatment of Acne Vulgaris
Study Objectives	The objectives of this study are to compare efficacy, safety, and tolerability of SB204 and Vehicle Gel in subjects with acne vulgaris for 12 weeks.
Treatment Regimens	Eligible subjects at the Baseline visit will be randomized 1:1 to SB204 4% QD or Vehicle Gel QD and treated for up to 12 weeks (84 days).
Formulation	**Investigational Drug:** SB204 4% Dosing: Approximately 900 mg of SB204 Gel once daily to the face Duration of Treatment: 12 weeks **Comparator Drug**: Vehicle Gel Dosing: Approximately 900 mg of Vehicle Gel once daily to the face Duration of Treatment: 12 weeks
Study Period	Subjects will be dosed in the study for up to 12 weeks.
Study Design	This is a multi-center, double-blinded, randomized, vehicle-controlled, parallel group, study to be conducted in approximately 1300 subjects with acne vulgaris. Subjects who satisfy the entry criteria will be randomized to SB204 4% QD or Vehicle Gel QD in a 1:1 ratio. Investigational drug will be delivered from a double barrel single pump dispenser. The pump dispenses product from two chambers (NVN1000 Gel and a hydrogel or Vehicle Gel and a hydrogel) which will be mixed together in the palm for approximately 5 seconds by the subject and applied to the entire face once daily after washing. Efficacy assessments will include Investigator Global Assessments (IGA) and inflammatory and non-inflammatory lesion counts. Tolerability and safety assessments include cutaneous tolerability evaluation (erythema, scaling, dryness, pruritus, burning/stinging), adverse event collection, physical exams, blood pressure, pulse rate, and urine pregnancy tests (UPTs). Subjects will return for post-Baseline evaluation at Weeks 2, 4, 8, and 12/Early Termination (ET).
Main Inclusion / Exclusion Criteria	Key Inclusion Criteria: • Be male or female, 9 years of age and older and in good general health; • Have Baseline IGA score of 3 (moderate) or 4 (severe); • Have a minimum of 25 but not more than 70 non-inflammatory lesions (open and closed comedones) on the face;

	• Have a minimum of 20 but not more than 40 inflammatory lesions (papules, pustules, nodules, and cysts) on the face; • Have no more than two nodules or cysts on the face. Key Exclusion Criteria: • Have any dermatological conditions on the face that could interfere with clinical evaluations such as severe recalcitrant nodulocystic acne, acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis; • 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 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; • Have used medications or vitamins which are reported to exacerbate acne during the 12 weeks immediately preceding Baseline (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. • Have had a severe acne flare during the 12 weeks preceding Baseline. • 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.
Sample Size	Approximately 1300 subjects will be randomized into the study in a 1:1 ratio (~650 in each arm).
Efficacy Evaluation	The same blinded evaluator should perform Investigator Global Assessments (IGA) and lesion counting at Screening, Baseline, and Weeks 2, 4, 8, and 12/ET. In the event that this is not possible due to unforeseen circumstances, a different blinded evaluator may evaluate the subject. However, the same evaluator should evaluate subjects at the Baseline and Week 12/ET evaluations. <u>Investigator Global Assessment (IGA)</u> The IGA score will be determined based on the evaluation of the overall signs and symptoms of acne vulgaris. IGA evaluations will be performed prior to the lesions counts, approximately three feet from the subject, and scored on a scale of 0 (clear) to 4 (severe). <u>Lesion Counts</u> At Screening, Baseline, and Weeks 2, 4, 8 and 12/ET, the evaluator will count the total number of non-inflammatory and inflammatory lesions on the subject's face including the forehead, right and left cheeks, chin and nose. Non-inflammatory lesion count will include the number of open and closed comedones. Inflammatory lesion count will include the number of papules and

	pustules. The number of nodules and cysts will be recorded separately and included with the inflammatory lesion count.
Tolerability Evaluation	Subjects will be assessed at each visit from Baseline through Week 12/ET for cutaneous tolerability. 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.
Safety Evaluation	Adverse events will be assessed and collected at each evaluation beginning at Screening. A brief physical exam will be collected at Screening, Baseline and Week 12/ET. Blood pressure and pulse will be collected at Screening, Baseline and each visit through Week 12/ET. Any clinically significant changes noted during the physical exam or vital sign measurements will be recorded as adverse events. Urine pregnancy tests in women of child-bearing potential will be conducted at Screening, Baseline, and Weeks 4, 8 and 12/ET.
Additional Evaluations	Photographs will be collected at Baseline, Week 4, Week 8, and Week 12/ET at a subset of sites.
Endpoints	Primary Efficacy Endpoints The co-primary efficacy endpoints are: • The absolute change in inflammatory lesion count from Baseline to Week 12/ET; • The absolute change in non-inflammatory lesion count from Baseline to Week 12/ET; • The proportion of subjects with IGA success at Week 12/ET. A subject will be considered a success if the IGA score is clear (0) or almost clear (1) and ≥2 grades less than Baseline. Secondary Efficacy Endpoints The secondary endpoints include the following: 1. The percent change in inflammatory lesion count from Baseline to Week 12/ET; 2. The percent change in non-inflammatory lesion count from Baseline to Week 12/ET; 3. The median time to a 35% reduction in the inflammatory lesion count; 4. The median time to a two (2) or more grade improvement in IGA.
Statistical Methods	All statistical processing will be performed using SAS® unless otherwise stated. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of ≤ 0.05 unless stated otherwise. Inferential testing will compare the active treatment group to the vehicle treatment group. Efficacy analyses will be performed using the intent-to-treat (ITT) and per-protocol (PP) populations with the ITT population considered as primary. Safety analyses will be performed using the safety (SAF) population. Descriptive Statistics Descriptive statistics will be presented for the efficacy data at each evaluation visit. 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. Descriptive

	statistics will be presented for the active treatment group and vehicle treatment group. Summaries over both treatment groups will be presented for demographic and Baseline characteristics. **Efficacy Analysis** Efficacy of SB204 4% will be based on statistical superiority over vehicle for change from Baseline in lesion counts and IGA score improvement at Week 12/ET. <u>Primary Efficacy Analysis</u> There are three co-primary efficacy outcomes: • change in inflammatory lesions counts at Week 12/ET • change in non-inflammatory lesions counts at Week 12/ET and • IGA success at Week 12/ET which is defined as an IGA score of clear (0) or almost clear (1) and ≥2 grades less than Baseline. All three co-primary outcomes must show superiority over vehicle (p-value≤0.05) in order for efficacy to be demonstrated; therefore no adjustments for multiplicity will be made. <u>Secondary Efficacy Analyses</u> Secondary efficacy outcomes include the percent change in inflammatory and non-inflammatory lesion counts at Week 12/ET, the median time to 35% improvement in inflammatory lesions, and the median time to a two or more grade improvement in IGA. Analysis of the secondary efficacy outcomes will be adjusted for multiplicity using a hierarchical step-down procedure. These endpoints will be tested in the specified order with the rule that once a p-value exceeds 0.05, endpoints further down in the order are not statistically significant. **Tolerability Analyses** Cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized from Baseline to Week 12/ET. Additionally, change from Baseline in tolerability assessments will be summarized at Weeks 2, 4, 8, and 12/ET. **Safety Analyses** <u>Adverse Events</u> 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. Adverse events noted prior to the first study drug administration that worsen after Baseline will also be reported as AEs and included in the summaries.

	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 (PT), 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. Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, SOC, preferred term, severity, relationship to study drug (causality), and seriousness. Serious 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. <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 by treatment group from Baseline through Week 12/ET. Additionally, change from Baseline in vital signs will be summarized at Weeks 2, 4, 8, and 12/ET. Any clinically significant changes from Baseline will be documented as an AE. <u>Urine Pregnancy Tests</u> Urine pregnancy test results for women of child-bearing potential (WOCBP) will be presented in data listings by subject.

LIST OF ABBREVIATIONS

	Definition
AE	Adverse Event
BSA	Body Surface Area
BOCF	Baseline Observation Carried Forward
CFR	Code of Federal Regulations
CRF	Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent to Treat population
ITT	Intent to Treat population
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NOVAN	Novan, Inc.
OTC	Over-the-Counter
PI	Principal Investigator

PP	Per-Protocol population
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Population
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

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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, for topical application. SB204, an admixture of an alcoholic NVN1000 Gel with an aqueous hydrogel, is in development for the treatment of acne vulgaris. In a randomized, double-blind, placebo-controlled, 12-week, Phase 2 study, SB204 decreased inflammatory and non-inflammatory lesion counts in subjects with acne and was well tolerated.

To date, approximately 500 subjects have been treated with NVN1000 Gel, including SB204, and approximately 275 subjects have been treated with the vehicle gel.

1.2 INVESTIGATIONAL PRODUCT

NVN1000 has been developed to deliver controlled release of nitric oxide from micron sized polysiloxane macromolecules. The active agent is formulated into an alcohol-based topical gel and the formulation will be dispensed from a dual chamber pump.

	Investigational Products	
Name of Active Ingredient	NVN1000	None
Drug Name/ Concentration	SB204 4%	Vehicle Gel
Manufacturer	Ei, LLC	Ei, LLC
Packaging	Pump designed to deliver 1:1 Hydrogel: NVN1000 Gel to yield final concentration of SB204 4%	Pump designed to deliver 1:1 Hydrogel: Vehicle Gel
Storage Requirements	Refrigerated until dispensing, 2-8 °C	Refrigerated until dispensing, 2-8 °C
Appearance Post-Mixing	Opaque white gel	Opaque white gel
Dosing Schedule	Once daily	Once daily
Route of Administration	Topical Application	Topical Application

1.3 NONCLINICAL STUDIES WITH NVN1000

Novan has completed over 30 nonclinical studies with NVN1000 to assess pharmacology, pharmacokinetics (ADME), and toxicology. In mini-pig and mouse studies, doses of SB204 far in excess both in 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. Oral administration of NVN1000 drug substance in a SEG I reproductive toxicology study in rats showed no adverse effects on fertility and mating behavior. Oral administration of NVN1000 drug substance in SEG II reproductive toxicology studies in rats and rabbits showed minor effects on fetal development at the highest doses. Dermal application has been safe and resulted in minimal exposure to nitrate or systemic silica when applied topically at supratherapeutic doses. In a 13-week GLP dermal toxicology study with SB204 in mini-pigs at doses of 48-fold (mg/kg) and 14-fold (mg/cm^2) in excess of current maximum human dose, there was no increase in plasma nitrate concentrations, minimal systemic exposure (5-22 ng/mL) to the parent compound as measured by hMAP3, and no significant toxicologic findings (Study 14-NC-001). Cumulatively, these nonclinical data demonstrate that systemic absorption of NVN1000 after dermal administration at supratherapeutic doses is minimal, with no major systemic organ toxicity.

NVN1000 demonstrated mutagenicity in an Ames assay, but was not mutagenic in two in vivo genotoxicity tests in two tissue types (bone marrow via intraperitoneal (IP) administration and skin via topical administration) and in a human lymphocyte chromosome aberration assay.

In nonclinical pharmacology studies conducted by Novan and outside laboratories, NVN1000 or related compounds demonstrated:

- Bactericidal activity against *P. acnes* in vitro;
- Anti-inflammatory activity in an allergic contact dermatitis ear swelling model;
- Inhibition of lipogenesis by immortalized sebaceous cells.

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

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 serious adverse event (SAE) has been reported in the acne development program. The Adverse Event (AE profile has been similar in subjects treated with active (SB204) or Vehicle Gel. An asymptomatic, transient erythema has been observed in some subjects treated with SB204. There have been no clinically significant changes in laboratory results including methemoglobin, or in physical examinations.

In a maximum use cross-over pharmacokinetic (PK) study conducted in 18 subjects with moderate to severe acne, there was no detectable exposure to the NVN1000 polysiloxane backbone assessed by measuring plasma concentrations of hydrolyzed *N*-Methylaminopropyl-trimethoxysilane (hMAP3) and no increase in plasma nitrate levels following topical administration of SB204. 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 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.

Additional details regarding completed clinical studies are 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 in vitro to decrease *P. acnes,* inhibit several inflammatory pathways relevant in acne, and to decrease sebum production. In two completed Phase 2 studies, subjects with acne treated with SB204 had lower inflammatory and non-inflammatory lesion counts with greater 'success' on the dichotomized IGA score ('clear/almost clear' and at least a two grade change from Baseline) at the end of treatment when compared to subjects treated with Vehicle Gel. Once daily dosing was as effective as twice daily dosing. In the studies conducted to date, the systemic AE profile was similar between subjects treated with SB204 and subjects treated with Vehicle Gel. SB204 4% has been generally well tolerated and was not associated with a safety or tolerability signal.

In the maximum use pharmacokinetic study, there was no observed hMAP3 in plasma and no change in nitrate levels after topical application of SB204 8% twice daily to approximately 17% body surface area (BSA).

A transient (approximately 5-10 minutes), asymptomatic erythema has been observed in some subjects shortly after application of SB204 which is a physiologic response (vasodilation) to local nitric oxide release. In the most recently completed study, local application-site reactions were reported in approximately 5% of subjects treated with SB204. These local application-site reactions resolved after discontinuation of the product and by the end of the study. Topical application has been generally well-tolerated as assessed by scores for erythema, peeling, pruritus, and burning/stinging. Tolerability will be assessed during the planned study, and discontinuation criteria for intolerance by individual subjects is described in Section 6.7.

Both SB204 and Vehicle Gel contain alcohol; inadvertent administration to the eyes may result in ocular irritation 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.

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. The rate of headache has been comparable in subjects treated with NVN1000 or SB204 and Vehicle Gel. Neither hypotension nor methemoglobinemia have been observed in nine completed studies that have enrolled over 400 subjects treated with NVN1000 Gel or SB204.

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 to approximately 3% body surface area are minimal, and that appropriate monitoring is in place to assess safety. Subjects randomized to treatment with SB204 4% once daily may have a clinical benefit from study participation.

2. RATIONALE AND OBJECTIVES

2.1 STUDY RATIONALE

Novan is conducting this study to evaluate the efficacy, cutaneous tolerability and safety of SB204 4% and Vehicle Gel administered once daily to the face.

Subjects will dose once daily for up to 12 weeks (84 days) with SB204 4% or Vehicle Gel. Approximately 900 mg of gel (one pump stroke) will be applied evenly over the face (3% BSA). Based on the previous human safety data with SB204 and Vehicle Gel as well as the nonclinical safety data, this dose is expected to be safe and well tolerated.

2.2 STUDY OBJECTIVES

The primary objective of this study is to compare the efficacy, tolerability and safety of SB204 4% and Vehicle Gel once daily for 12 weeks in subjects with acne vulgaris.

3. STUDY DESIGN

Figure 1 depicts the overall study design for this 12-week, two arm, randomized, double-blinded study in subjects with moderate to severe acne vulgaris dosed once daily with SB204 or Vehicle Gel. Subjects receiving current treatment for acne vulgaris at the time of the Screening Visit may enter a wash out period of up to 35 days prior to randomization.

Figure 1: Study Diagram

Visits	Randomization				
		SB204 4% QD (N=650)			
		Vehicle Gel QD (N=650)			
Screening Day -35 to Day 0	Baseline (Day)	(14)	(28)	(56)	(84)
	Study Week	2	4	8	12/ET
	ET = Early termination				

3.1 STUDY ENDPOINTS

3.1.1 Efficacy Endpoints

Primary Efficacy Endpoints
The co-primary efficacy endpoints are:

- The absolute change in inflammatory lesion count from Baseline to Week 12/ET;
- The absolute change in non-inflammatory lesion count from Baseline to Week 12/ET;
- The proportion of subjects with IGA success at Week 12/ET. A subject will be considered a success if the IGA score is clear (0) or almost clear (1) and ≥2 grades less than Baseline

Secondary Efficacy Endpoints
The secondary efficacy endpoints include the following:

- The percent change in inflammatory lesion count from Baseline to Week 12/ET;
- The percent change in non-inflammatory lesion count from Baseline to Week 12/ET;
- The median time to a 35% reduction in inflammatory lesion counts;
- The median time to a two (2) or more grade improvement in IGA.

3.1.2 Tolerability Endpoints

The cutaneous tolerability assessments include the evaluator'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 Safety Endpoints

Safety endpoints will include the change from Baseline in vital sign measurements. Any clinically significant changes on physical exam or vital sign measurements will be recorded as AEs and included in the comparison.

3.2 STRUCTURE

This is a multi-center, randomized, double-blinded, vehicle-controlled, two arm study.

3.3 DURATION

Subjects will be in the study for a maximum of 17 weeks including up to 35 days for screening followed by up to 84 days of treatment. Subjects who do not require washout from any current treatment may be screened and randomized on the same day.

3.4 DOSAGE/DOSE REGIMEN

Approximately 900 mg (1 ml) of SB204 4% or Vehicle Gel will be applied evenly over the entire face once a day for a period of up to 84 days. The product will be dispensed from a dual-chamber pump designed to deliver approximately equal amounts of NVN1000 Gel and hydrogel or Vehicle Gel and hydrogel. The NVN1000 Gel and Vehicle 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 entire face 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. Application of study drug should occur prior to bedtime.

3.5 VISIT SCHEDULE

The screening period will last up to 35 days. At the end of the screening period, subjects will have their Baseline Visit. Study visits will take place approximately every two weeks for the first four weeks, then every four weeks for the next eight weeks.

3.6 STUDY POPULATION

Approximately 1300 male and female subjects 9 years of age and older with moderate to severe acne vulgaris on the face will be randomized to participate in the study. Eligible subjects will have: at least 25 but no more than 70 non-inflammatory lesions (open and closed comedones); 20 but no more than 40 inflammatory lesions (papules, pustules, nodules, and cysts); no more than two nodules or cysts; and an IGA of 3 (moderate) or 4 (severe) on a 5-point IGA scale (Appendix 16.2).

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, 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 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 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 and 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 (ICF). 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. Be male or female, 9 years of age and older at Baseline and in good general health;
3. Have a Baseline IGA score of (3) moderate or (4) severe;
4. Have a minimum of 25 but not more than 70 non-inflammatory lesions (open and closed comedones) on the face at Baseline;
5. Have a minimum of 20 but not more than 40 inflammatory lesions (papules, pustules, nodules, and cysts) on the face at Baseline;
6. Have no more than two nodules or cysts on the face at Baseline;
7. WOCBP must have a negative urine pregnancy test (UPT) prior to randomization;
8. 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; 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 hormonal contraceptives in the past and stopped must have discontinued usage at least three months prior to the start of the study; and
9. 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 severe recalcitrant nodulocystic acne, 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 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;
4. Female subjects who are pregnant, nursing mothers, or planning to become pregnant during the study;
5. Female subjects with known polycystic ovarian disease;
6. Have used estrogens (e.g., Depogen, Depo-Testadiol, Gynogen, Valergen, etc.) or oral contraceptives for less than 3 months (90 days) immediately preceding Baseline, discontinued use of estrogens or oral contraceptives less than 3 months (90 days) prior to Baseline, or planning to begin or discontinue use of this therapy during the treatment period;
7. Are transgender persons who are taking testosterone (female to male) or estrogen (male to female);
8. Have facial hair, tattoos or other markings that could interfere with assessments or application of study drug;
9. Have used medications or vitamins which are reported to exacerbate acne during the 12 weeks immediately preceding Baseline (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;
10. Have had a severe acne flare in the 12 weeks preceding Baseline;
11. Have a history of hypersensitivity or allergic reactions to any of the ingredients in the SB204 or Vehicle Gel as described in the Investigator's Brochure;
12. Have used the following <u>topical</u> preparations on the face within the time specified prior to Baseline or require the concurrent use of any of the following topical agents on the face:

Topical astringents/abrasives	1 week
Other topical anti-acne medications*	2 weeks
Antibiotics	2 weeks
Moisturizers or sunscreens containing antibacterials	2 weeks
Anti-inflammatory products or corticosteroids	4 weeks
Topical corticosteroids	4 weeks

* Includes benzoyl peroxide, salicylic acid, dapsone, alpha-hydroxy acid, glycolic acids, retinoids, or retinol-containing products

13. Have used the following systemic medications within the time specified prior to Baseline or require the concurrent use of any of the following systemic medications:

Systemic antibiotics+	4 weeks
Other systemic acne treatments	4 weeks
Corticosteroids	12 weeks
Systemic retinoids	24 weeks
Therapeutic Vitamin A Supplements > 10,000 IU/day	24 weeks

+Short courses (≤ approximately 14 days) of antibiotics are allowed if needed during the treatment phase of the study for non-acne related illnesses.
*Intranasal and inhaled corticosteroids may be used throughout the trial if the subject is on a stable dose.

14. Have had the following procedures on the face within the time specified prior to Baseline:

Cryodestruction/Chemo-destruction	4 weeks
Dermabrasion	4 weeks
Photo / Photodynamic Therapy	4 weeks
Acne Surgery	4 weeks
Intralesional Corticosteroids	4 weeks
X-ray, Laser Therapy, or Other Device	4 weeks

15. Intend to use a tanning booth or sunbathe during the study;
16. 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;
17. Are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
18. Have used an investigational drug or device within 30 days of Baseline or concurrent participation in a different interventional research study;
19. Are members of the same household where a subject is enrolled in NI-AC301, NI-AC302, or NI-AC303;
20. Are immediate family members of study site personnel directly involved in NI-AC301, NI-AC302, or NI-AC303;
21. Have participated in a previous study with SB204 or NVN1000 Gel.

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.

Some Baseline procedures (i.e., review of inclusion/exclusion criteria, brief physical exam, blood pressure and pulse rate, IGA, lesion counts, cutaneous tolerability, 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.

WOCBP having a positive UPT at Screening or 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 3 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.

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 pump to 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 1: Schedule of Visits and Procedures

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

PROCEDURES	Screening (Day -35 to Day 0) [1]	Baseline (Day 0)	Week 2[2] ±3 days (Day 14)	Week 4 ±5 days (Day 28)	Week 8 ±5 days (Day 56)	Week 12/ET[3] ±7 days (Day 84)
Informed Consent/Assent	X					
Demographics	X					
Medical History	X	X				
Medication History	X	X				
Inclusion/Exclusion Criteria	X	X				
Brief Physical Examination	X	X[4]				X
Urine Pregnancy Test (all WOCBP)	X	X[4]		X	X	X
Blood Pressure and Pulse	X	X	X	X	X	X
IGA	X	X	X	X	X	X
Lesion Counts	X	X	X	X	X	X
Cutaneous Tolerability Evaluation		X	X	X	X	X
Instruct on Study Drug Application and Provide Subject Instructions		X				
Study Drug and Diary Dispensed		X		X	X	
Study Drug and Diary Collected				X	X	X
Subject Compliance Reviewed			X	X	X	X
Photography[5]		X		X	X	X
Concomitant Medications		X	X	X	X	X
Adverse Events	X	X	X	X	X	X

[1]Subjects who meet all eligibility criteria at Screening and do not require a medication wash-out may complete all Baseline assessments and be randomized on the same day as the Screening visit.
[2]All visit dates are in reference to Baseline, e.g., Visit 2 occurs two weeks (14 days) after Baseline visit.
[3]All Week 12 procedures should be completed for subjects who prematurely discontinue.
[4]If the Baseline Visit is within 7 calendar days of the Screening visit, Physical Examination and UPT do not need to be repeated.
[5]Photography will be done at a subset of sites.

4.1.1 Screening (Day -35 to Day 0)

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 SB204 with the subject and obtain written informed consent/assent.
2. Obtain demographic information.
3. Obtain subject's medical history and medication history.
4. Verify appropriate contraception being used for WOCBP per Section 6.4.
5. Collect blood pressure and pulse rate after the subject has been sitting quietly for 5 minutes.
6. Perform a brief physical examination.
7. Obtain pregnancy test (WOCBP only) and evaluate results. If pregnancy test is positive, the subject may not participate in the study.
8. Perform Investigator's Global Assessment (IGA).
9. Perform lesion counts. Inflammatory and non-inflammatory lesion counts will be performed on the entire face.
10. Confirm subject meets eligibility criteria.
11. Review prohibited medications, acne treatments, and supplements that should not be used prior to Baseline and during the trial.
12. Collect AEs related to study procedures performed since signing of informed consent.
13. Confirm the study schedule with the subject.

4.1.2 Baseline (Day 0)

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

1. Update medication history and record concomitant medication information.
2. Perform a brief physical examination. If the Baseline visit occurs within 7 calendar days of the Screening visit, the physical examination does not need to be repeated.
3. Obtain pregnancy test (WOBCP only) and evaluate results. If pregnancy test is positive, the subject may not participate in the study. If the Baseline visit occurs within 7 calendar days of the Screening visit, the pregnancy test does not need to be repeated.
4. Collect blood pressure and pulse rate after the subject has been sitting quietly for 5 minutes.
5. Perform cutaneous tolerability assessment.
6. Perform IGA.
7. Perform lesion counts.

8. Have subject wash face and dry with lint free towel in preparation for photographs (if applicable).
9. Collect photographs (if applicable).
10. Confirm eligibility and randomize subject.
11. Dispense subject diary and study drug. Instruct subject on dispensing, mixing, and application of study product and diary completion.
12. Update AE information for AEs reported at Screening and record any new AEs (e.g., AEs related to washout, AEs related to study procedures performed at visit, etc.).
13. Confirm the study schedule with the subject.

4.1.3 Week 2 (Day 14)

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

1. Update concomitant medication information.
2. Update AE information and record any new AEs if applicable.
3. Collect blood pressure and pulse rate after the subject has been sitting quietly for 5 minutes.
4. Perform cutaneous tolerability evaluation.
5. Perform IGA.
6. Perform lesion counts.
7. Review diary completion and study drug compliance with subject.
8. Review and confirm the study schedule with the subject.

4.1.4 Weeks 4 and 8 (Days 28 and 56)

The following procedures must be performed and recorded at the Week 4 and Week 8 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.
6. Perform IGA.
7. Perform lesion counts.

8. Have subject wash face and dry with lint free towel in preparation for photographs (if applicable).
9. Collect photographs (if applicable).
10. Collect returned study drug and diary, perform accountability, and review diary completion and study drug compliance with subject.
11. Dispense new study drug and diary.
12. Review and confirm the study schedule with the subject.

4.1.5 Week 12/ET (Day 84)

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. 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.
7. Perform IGA.
8. Perform lesion counts.
9. Have subject wash face and dry with lint free towel in preparation for photographs (if applicable).
10. Collect photographs (if applicable).
11. Collect returned study drug and diary, perform accountability, and review diary completion and study drug compliance with subject.

4.1.6 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 12/Day 84 visit) and whenever possible, the subject should be asked to return to the study center to complete the Week 12/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 12/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 dosing 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 randomized into the study be replaced by another using the same randomization number or treatment assignment.

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 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 as determined by the Investigator
- 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 EFFICACY ASSESSMENTS

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

4.2.1 Investigator Global Assessment

The Investigator's Global Assessment Score will be a static assessment that is independent of the Baseline score. The evaluator will make the assessment without referring to the Baseline value and prior to performing lesion counts. The assessment should be made approximately three feet from the subject. The same evaluator should perform each study assessment for each study subject whenever possible, for consistency in evaluations.

Subjects are eligible to participate in the study if they have a Baseline IGA score of 3 (moderate) or 4 (severe).

The following scores will be used to assign IGA scores:

Grade	Description
0	Clear: Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost clear: Rare non-inflammatory lesions with rare papules (papules may be resolving and hyperpigmented, though not pink-red).
2	Mild: Some non-inflammatory lesions with no more than a few inflammatory lesions.
3	Moderate: Up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one nodulocystic lesion.
4	Severe: Up to many non-inflammatory and inflammatory lesions, but no more than a few nodulocystic lesions

4.2.2 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

4.3 TOLERABILITY ASSESSMENTS

The evaluator will assess the subject's face at Baseline and each study visit. The cutaneous tolerability assessment for visits other than Baseline 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 be reported as an AE if 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

4.4 SAFETY ASSESSMENTS

4.4.1 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.

4.4.2 Physical Exam

A brief physical exam will be performed at Screening, Baseline (Day 0) and Week 12/ET. If clinically significant changes in the physical examination from Baseline are noted at the Week 12/ET visit, these will be recorded as adverse events.

4.4.3 Vital Signs

Blood pressure and pulse rate will be collected at Screening, Baseline, and at Weeks 2, 4, 8, and 12/ET. Any clinically significant changes in vital signs from Baseline will be recorded as adverse events whether or not drug related.

4.4.4 Pregnancy Testing

All WOCBP must have a UPT at Screening and Baseline and if the result is positive, the subject will not be allowed to participate in the study. Refer to Section 6.4 for further information.

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 subjects will be considered to be of childbearing potential for this study.

Pregnancy tests will also be performed at Weeks 4, 8, and 12/ET. If a subject is determined to be pregnant prior to Week 12, the subject will be discontinued from the study but followed until term.

4.5 ADDITIONAL ASSESSMENTS

4.5.1 Photography

Photographs of the face will be taken at Baseline and Weeks 4, 8, and 12/ET at a subset of sites. Baseline photographs may be reviewed by the sponsor or members of the study team to confirm appropriateness of enrolled subjects.

4.6 SCREEN FAILURES

A subject is considered screened once they have signed the ICF and completed one screening assessment. A screen failure subject will be any screened subject who does not meet the study eligibility requirements. Subjects will not be allowed to rescreen. Screen failures will not be recorded in the case report form (CRF).

4.7 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. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and Chiltern.

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 12/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 should not change moisturizer and/or sunscreen used during the course of the study. If used, moisturizers and sunscreen should be applied at least 30 minutes after study drug application.

Subjects must not have used anti-acne treatments including topical agents to the face, systemic antibiotics or procedures that may impact acne (as described in Section 3.7.3) prior to Baseline. These medications and procedures are also prohibited during the trial. Topical anti-acne agents may be used to treat acne on the chest, back or upper shoulders in this study.

Subjects may not be concurrently on drugs associated with exacerbating acne vulgaris. (Appendix 16.1). Subjects who have used an investigational drug or device within 30 days of Baseline should not be enrolled. Subjects must not participate in a different interventional research study during the study period. Any subject who has participated in a previous study with SB204 or NVN1000 Gel must not participate.

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.

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. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during the study.

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 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 and completed one study assessment 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 by telephone, email, or fax 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 fax/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 fax/email 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, 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 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.

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 the form to Chiltern. Subjects found to be pregnant prior to Week 12 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 12/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 12/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 12/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 12, 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. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of ≤ 0.05 unless stated otherwise.

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, based on N. Data will be presented for the active treatment group and vehicle treatment group. Demographic and Baseline data will also be presented over both treatment groups.

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 Intent to Treat (ITT) Population

The intent to treat (ITT) population will include all study subjects who were randomized and dispensed study medication and grouped by the treatment to which they were assigned at randomization. All efficacy analyses will be performed on the ITT population.

7.2.2 Safety Population

The safety (SAF) population will include all randomized subjects who received at least one dose of study medication. All safety and tolerability analyses will be performed on the safety analysis population (SAF) population based on the treatments the subjects actually applied.

7.2.3 Per-Protocol Population

The per protocol (PP) population will include subjects who complete the Week 12 evaluation without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise

evaluation of treatment efficacy). The PP population will include subjects in the SAF population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications;
- Did not attend the Week 12 visit;
- Have not been compliant with the dosing regimen;
- Out of visit window at the Week 12 visit by ±7 days.

Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations. To determine dosing non-compliance criteria, the data will be reviewed in a blinded manner and a cut-point will be determined.

7.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographic and Baseline characteristics will be summarized by treatment group and overall for the ITT, PP and SAF populations. 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 by treatment group. Age will also be categorized and summarized as proportion of adults (age≥18) and juvenile (age<18).

7.4 EFFICACY ANALYSIS

Efficacy of SB204 4% will be based on statistical superiority over vehicle for change from Baseline in lesion counts and improvement in IGA score at Week 12/ET.

7.4.1 Primary Efficacy Analyses

There are three co-primary efficacy outcomes:

- change in inflammatory lesions counts at Week 12/ET
- change in non-inflammatory lesions counts at Week 12/ET and
- IGA success at Week 12/ET which is defined as an IGA score of clear (0) or almost clear (1) and ≥2 grades less than Baseline

All three co-primary outcomes must show superiority over vehicle (p-value ≤0.05) in order for efficacy to be demonstrated; therefore no multiplicity adjustments will be made to the co-primary outcome analyses..

Prior to analysis of co-primary outcomes, missing post-Baseline lesion counts and IGA scores results at each visit will be imputed using a Markov chain Monte Carlo (MCMC) multiple imputation methodology. Separate multiple imputation (MI) procedures will be used for each outcome, using Statistical Analysis Software (SAS) procedure MI. Details of PROC MI and options used in the imputation procedures will be provided in a statistical analysis plan. ITT

subjects with only Baseline assessments will have the Baseline value carried forward across all visits.

The primary analyses of the co-primary efficacy endpoints will be performed in the ITT population where missing data have been imputed as described above. Additional analyses of the co-primary outcomes will be performed using the PP population. To access the sensitivity of the primary efficacy results to imputation methods, each co-primary outcome will be analyzed as described above, but with missing data imputed by last observation carried forward (LOCF) and Baseline observation carried forward (BOCF) on the ITT population.

7.4.2 Secondary Efficacy Analyses

Secondary efficacy outcomes include the percent change in inflammatory and non-inflammatory lesion counts at Week 12/ET, the median time to 35% improvement in inflammatory lesions and the time to a two or more grade improvement in the IGA.

Analysis of the secondary efficacy outcomes will be adjusted for multiplicity using a hierarchical step-down procedure. These endpoints will be tested in the specified order with the rule that once a p-value exceeds 0.05, endpoints further down in the order are not statistically significant. The order will be as follows:

1) Percent change in inflammatory lesions at Week 12/ET

2) Percent change in non-inflammatory lesions at Week 12/ET

3) Median time to achieve 35% reduction in inflammatory lesions

4) Median time to a two or more grade improvement in the IGA.

7.5 DRUG EXPOSURE AND COMPLIANCE

Drug exposure and compliance will be performed on Safety Population. The number of days that study drug was taken and study drug compliance will be summarized by treatment group.

Duration of exposure will be defined as:

(Date of Last Drug Administration – Date of First Drug Administration + 1 day) / 7 days, rounded down to an integer.

The percent compliance for SB204 will be calculated as follows and presented as follows:

% Compliance = (Number of Doses Expected– Number of Doses Missed)/(Number of Doses Expected)*100

Where the number of doses expected is the defined as the number of days from Baseline to the Week 12/ET visit. Subject's diaries will be reviewed at each visit to report the number of doses that were missed.

Percent compliance will be summarized by frequency count and percentage of subjects with compliance as defined in the SAP. Percent compliance will also be summarized as a continuous variable using descriptive statistics.

7.6 TOLERABILITY

Cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized by visit from Baseline to Week 12/ET by treatment group. The proportion of subjects in each treatment group who shift scores from Baseline at each visit will also be summarized.

7.7 SAFETY

7.7.1 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. Adverse events noted prior to the first study drug administration that worsen after Baseline will also be reported as TEAEs and included in the summaries.

All information pertaining to an AE noted during the study will be listed by subject, detailing verbatim term given by the Investigator or designee, preferred term, 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.

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

7.7.2 Physical Examination

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

7.7.3 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 Week 2, 4, 8, and 12/ET. Any clinically significant changes from Baseline will be documented as an AE.

7.7.4 Urine Pregnancy Tests

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

7.8 SAMPLE SIZE AND POWER CONSIDERATIONS

Approximately 1300 subjects will be randomized into the study in a 1:1 ratio (650 in each arm) at approximately 50 sites in North America. In the previous phase 2 study, the pooled vehicle IGA 'success' rate was 7.1% and the pooled SB204 IGA success rate was 13.4%. Using NQuery Advisor v7 (Statistical Solutions, Ltd) to estimate sample size and statistical power, based on a vehicle IGA success rate of 7% and a 6% difference for the SB204 arm, a sample size of 1294 was estimated to have at least 95% power for a two-sided test at the alpha=0.05 level using the continuity corrected chi-square test.

The statistical power for detecting treatment differences in inflammatory or non-inflammatory lesions exceeds 99% once at least 256 subjects are treated in each group. This is based on the following assumptions:

- For inflammatory lesions: vehicle mean change = -7.6, SB204 mean change = -14.1, and a common standard deviation = 17.1

- For non-inflammatory lesions: vehicle mean change = -5.8, SB204 mean change = -11.3, and common standard deviation = 11.8

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) until dispensed to a subject. 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 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 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 be randomized to SB204 4% or Vehicle Gel on a 1:1 basis through utilization of the IWRS. The evaluator and subject will be blinded to the subject's treatment.

8.4 UNBLINDING OF TREATMENT ASSIGNMENT

In the event that a subject should experience an adverse event for which it is medically required to break the blind in order to determine appropriate treatment, unblinding can be achieved by using the IWRS. A study subject for whom the blind is broken will be discontinued from the study. Although not required, the Investigator should contact the Chiltern Medical Monitor prior to breaking the blind.

8.5 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 or 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 by regulatory agencies at any time.

8.6 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 randomized study subjects.

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, the Chiltern Medical Monitor or other 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 at a minimum 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 or their designees, 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, 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 (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 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 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 primary efficacy and 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 CRO 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, Chiltern, and Novan 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 only 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 Regulations.* **1999**.Part 50, Title 21, Section 20.

Institutional Review Boards. *Code of Federal Regulations.* **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)

16.2 APPENDIX 2: DEFINITIONS FOR IGA SCORE

Grade	Description
0	Clear: Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost clear: Rare non-inflammatory lesions with rare papules (papules may be resolving and hyperpigmented, though not pink-red).
2	Mild: Some non-inflammatory lesions with no more than a few inflammatory lesions.
3	Moderate: Up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one nodulocystic lesion.
4	Severe: Up to many non-inflammatory and inflammatory lesions, but no more than a few nodulocystic lesions