STUDY TITLE	A Phase 2, Multi-Center, Randomized, Evaluator-Blinded, Vehicle-Controlled Study Comparing the Efficacy, Tolerability, and Safety of SB204 Gel and Vehicle Gel Once or Twice Daily in the Treatment of Acne Vulgaris
PROTOCOL NO.	NI-AC202
SPONSOR	Novan, Inc. 4222 Emperor Blvd., Suite 200 Durham, NC 27703 Tel.: 919-485-8080
AMENDMENT 1	16 Oct 2014
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.

16 Oct 2014

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

Date

16 Oct 2014

Carolyn Enloe, MPH
Clinical Study Manager
Novan, Inc.

Date

16 OCT 2014

John N. Quiring, Ph.D.
Statistician
QST Consultations, Ltd.

Date

SPONSOR INFORMATION PAGE

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PROTOCOL AMENDMENT

RATIONALE FOR AMENDMENT

This protocol amendment is required due to a change in the calibration of the device employed in methemoglobin readings and increases the upper limit of methemoglobin for study enrollment from > 2.0% to > 3.0% and changes the criterion for subject discontinuation in the study due to elevated methemoglobin from > 3.0% to > 5.0%. The change in methemoglobin levels permissible for study enrollment and continuation reflect this change in the calibration of the device. The amendment also increases the screening period from 28 days to 35 days to accommodate the washout period. The protocol was edited to ensure consistency across sections.

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.

Change 1: SYNOPSIS: Diagnosis and Criteria for Inclusion, Exclusion Criterion # 12

Have a methemoglobin value of **> 3.0%** at Screening or Baseline.

Change 2: PROTOCOL BODY: Section 1.5, Summary of Benefits and Risks, Paragraph 3

Tolerability will be assessed during the planned study, and discontinuation criteria for intolerance by subjects is described in Section **6.7.**

Change 3: PROTOCOL BODY: Section 1.5, Summary of Benefits and Risks, Paragraph 4

Methemoglobin will be monitored during the study and treatment stopped in any subject with a measured methemoglobin **> 5.0%.**

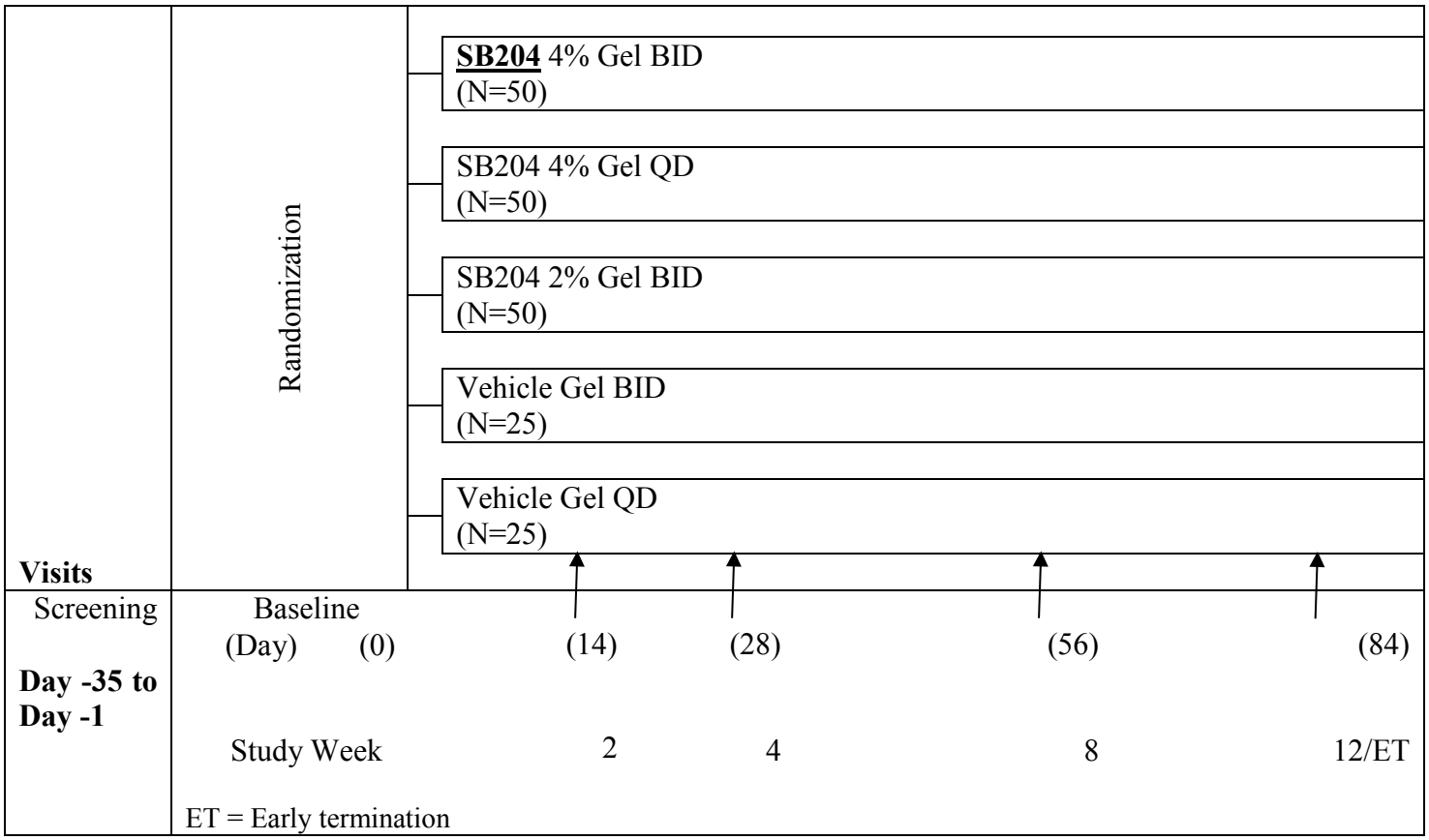
Change 4: PROTOCOL BODY: Section 2.1, Study Rationale, Paragraph 1

Novan is conducting this study to evaluate the efficacy, cutaneous tolerability and safety of **SB204 2% Gel,** SB204 4% Gel and Vehicle Gel administered once or twice daily to the face.

Change 5: PROTOCOL BODY: Section 3, Study Design, Paragraph 1

Subjects receiving current treatment for acne vulgaris may enter a wash out period after screening of up to **35 days** prior to randomization.

Change 6: PROTOCOL BODY, Figure 1, Study Diagram



Change 7: PROTOCOL BODY: Section 3.3, Duration, Paragraph 1

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.

Change 8: PROTOCOL BODY: Section 3.5, Visit Schedule, Paragraph 1

The screening period will last up to **35 days.**

Change 9: PROTOCOL BODY: Section 3.7.3, Exclusion Critieria, Exclusion Critierion # 12

Have a methemoglobin value of **> 3.0%** at Screening or Baseline.

Change 10: PROTOCOL BODY: Section 4.1, Subject Entry Criteria, Paragraph 2

Subjects with clinically significant anemia as determined by the Investigator or methemoglobin values **> 3.0%** will not be randomized.

Change 11: PROTOCOL BODY: Table 2, Schedule of Visits and Procedures

PROCEDURES	Screening **(Day -35 to Day -1)**	Baseline (Day 0)	Week 2[1] ±3 days (Day 14)	Week 4 ±3 days (Day 28)	Week 8 ±5 days (Day 56)	Week 12/ET[2] ±5 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[3]				X
Chemistry, Hematology, PT/PTT	X	X[3]				X
Urine Pregnancy Test (all WOCBP)	X	X[3]		X	X	X
Methemoglobin	X	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	X	
Study Drug and Diary Collected			X	X	X	X
Subject Compliance Reviewed			X	X	X	X
Photography		X				X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

[1] All visit dates are in reference to Baseline, e.g., Visit 2 occurs two weeks (14 days) after Baseline visit

[2] All Week 12 procedures should be completed for subjects who prematurely discontinue.

[3] If the Baseline Visit is within **3 calendar days** of the Screening visit, Physical Examination, Chemistry, Hematology, PT/PTT, and UPT do not need to be repeated.

Change 12: PROTOCOL BODY: Header for Section 4.1.1, Screening **(Day -35 to Day -1)**

Change 13: PROTOCOL BODY: Section 4.1.2, Baseline (Day 0)

~~This visit can be combined with Screening.~~ The following procedures must be performed and recorded at the Baseline visit:

1. ~~Obtain any updated concomitant medication information.~~
2. ~~Update medical history.~~

1. Update medication history and concomitant medication information.
2. Perform a brief physical examination.

Change 14: PROTOCOL BODY: Section 4.1.3, Week 2 (Day 14)

9. Review subject diary for completion.
10. Dispense new study drug and diary **(if needed)**.

Change 15: PROTOCOL BODY: Section 4.1.7, Discontinuation/Withdrawal Procedures, Paragraph 5

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

Change 16: PROTOCOL BODY: Section 4.1.7, Discontinuation /Withdrawal Procedures, Paragraph 7

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

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

- **Worsening of condition**
- Other

Change 17: PROTOCOL BODY: Section 4.4.5, Methemoglobin, Paragraph 2

Subjects with methemoglobin values of **≥ 3.0%** at Screening or Baseline will not be eligible to participate in the study.

Change 18: PROTOCOL BODY: Section 4.4.6, Pregnancy Testing, Paragraph 2

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.**

Change 19: PROTOCOL BODY: Section 6.7, Discontinuation of Individual Subjects from the Study, Paragraph 2

Subjects with **≥ 5.0%** methemoglobin at any post-baseline visit will 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.

Change 20: PROTOCOL BODY: Section 9.1, Data Collection, Paragraph 2

Only **status of informed consent and assent signature,** gender, date of birth, **ethnicity, race,** and reason for failure will be entered in the electronic data capture (EDC) system for screen failures.

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "A Phase 2, Multi-Center, Randomized, Evaluator-Blinded, Vehicle-Controlled Study Comparing the Efficacy, Tolerability, and Safety of SB204 Gel and Vehicle Gel Once or Twice 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		Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Title	A Phase 2, Multi-Center, Randomized, Evaluator-Blinded, Vehicle-Controlled Study Comparing the Efficacy, Tolerability, and Safety of SB204 Gel and Vehicle Gel Once or Twice Daily in the Treatment of Acne Vulgaris		
Study Objectives	The primary objective of this study is to compare the efficacy, tolerability, and safety of two concentrations of SB204 Gel and Vehicle Gel once or twice daily for 12 weeks in subjects with moderate to severe acne vulgaris on the face.		
Treatment Regimens	Eligible subjects at the Baseline visit will be randomized 2:2:2:1:1 to SB204 4% Gel BID, SB204 4% Gel QD, SB204 2% Gel BID, Vehicle Gel BID, or Vehicle Gel QD and treated for 12 weeks (84 days).		
Formulation	**Investigational Drug:** SB204 4% Gel **Investigational Drug:** SB204 2% Gel **Comparator Drug**: Vehicle Gel		
Study Period	Subjects will be dosed in the study for up to 12 weeks.		
Study Design	This is a multi-center, evaluator-blinded, randomized, vehicle-controlled, parallel-group study to be conducted in approximately 200 subjects with acne vulgaris. Subjects who satisfy the entry criteria will be randomized to SB204 4% Gel BID, SB204 4% Gel QD, SB204 2% Gel BID, Vehicle Gel BID, or Vehicle Gel QD in a 2:2:2:1:1 ratio. The SB204 Gel and Vehicle Gel 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 5-10 seconds by the subject and applied to the entire face once or twice 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 and pulse rate, laboratory assessments including chemistry, hematology, methemoglobin, PT/ PTT measurements, and urine pregnancy tests (UPTs). Subjects will return for post-baseline evaluation at Weeks 2, 4, 8, and 12.		

Name of Sponsor/Company: Novan, Inc. **Name of Finished Product:** SB204 **Name of Active Ingredient:** NVN1000	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*

Diagnosis and Criteria for Inclusion	Male and female subjects between the ages of 12 and 40 (inclusive at Baseline) with acne vulgaris on the face, and at least 20 but no more than 40 inflammatory lesions (papules and pustules), 25 to 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 will be eligible for participation in the study. Inclusion criteria: 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, 12 to 40 years of age, inclusive and in good general health; 3. Have a Baseline IGA score of moderate (3) or severe (4); 4. Have a minimum of 25 but not more than 70 non-inflammatory lesions (open and closed comedones) on the face; 5. Have a minimum of 20 but no more than 40 inflammatory lesions (papules and pustules) on the face; 6. Have no more than two nodules or cysts on the face; 7. Women of childbearing potential (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. Males must agree to avoid fathering a child during the study and for 60 days after the last dose of the study drug by ensuring one of the acceptable methods of contraception listed is used and not donating sperm; and 10. 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.

Name of Sponsor/Company: Novan, Inc. **Name of Finished Product:** SB204 **Name of Active Ingredient:** NVN1000	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*

Exclusion Criteria:

1. Have any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis;
2. Have any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive;
3. Have 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. Have used estrogens (e.g., Depogen, Depo-Testadiol, Gynogen, Valergen, etc.) or oral contraceptives for less than 12 weeks immediately preceding Baseline, discontinued use of estrogens or oral contraceptives less than 12 weeks prior to Baseline, or planning to begin or discontinue use of this therapy during the treatment period;
6. Have used medications or vitamins which are reported to exacerbate acne during the 12 weeks immediately preceding Baseline (e.g. azothioprine, haloperidol, halogens such as iodides or bromides, lithium, anabolic steroids, systemic corticosteroids, phenytoin and phenobarbital). The subject must not have had a severe acne flare for at least 12 weeks preceding Baseline. Daily use of a multi-vitamin is acceptable.
7. Have a history of hypersensitivity or allergic reactions to any of the ingredients in the SB204 Gel or Vehicle Gel as described in the Investigator's Brochure;
8. Subjects using or requiring short- or long-acting nitrates, nitric oxide donor drugs or supplements (eg; arginine, citrulline) or drugs associated with methemoglobinemia;
9. Have used the following topical preparations within the time specified prior to Baseline or require the concurrent use of any of the following topical agents:

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	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 Retinoids or retinol-containing products or corticosteroids 4 weeks * Includes benzoyl peroxide, salicylic acid, dapsone, alpha-hydroxy acid, or glycolic acids 10. Have used the following <u>systemic</u> 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 (≤10 days) of antibiotics if needed during the treatment phase of the study for non-acne related illnesses are allowed. * Intranasal and inhaled corticosteroids may be used throughout the trial if the subject is on a stable dose. 11. Have had the following procedures on the face, including treatment area within the time specified prior to Baseline: Cryodestruction/Chemo-destruction 4 weeks Dermabrasion 4 weeks Photodynamic Therapy 4 weeks Acne Surgery 4 weeks Intralesional Corticosteroids 4 weeks X-ray, Laser Therapy, or Other Device 4 weeks

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	12. Have a methemoglobin value of > 3.0% at Screening or Baseline; 13. Have clinically significant anemia at Screening as determined by the Investigator; 14. Intend to use a tanning booth or sunbathe during the study; 15. 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. Subjects scheduled for endoscopy with use of topical anesthetics should not be enrolled. 16. Are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function; 17. Have used an investigational drug or device within 30 days of Baseline or concurrent participation in a different research study; 18. Have participated in a previous study with SB204 Gel or NVN1000 Gel.		
Sample Size	Approximately 200 subjects will be randomized into the study in a 2:2:2:1:1 ratio (~50 in each active arm and 25 in each vehicle arm).		
Efficacy Evaluation	The same blinded evaluator will perform Investigator Global Assessments and lesion counting at Screening, Baseline, and Weeks 2, 4, 8, and 12. In the event that this is not possible due to unforeseen circumstances, a different blinded evaluator will evaluate the subject. However, the same evaluator should evaluate subjects at the Baseline and Week 12 evaluations. <u>Investigator Global Assessment (IGA)</u> The IGA score will be determined based on the Investigator evaluation of the overall signs and symptoms of acne vulgaris. IGA evaluations will be performed prior to the lesion counts, approximately 3 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, the Investigator 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, which will be recorded separately.		

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	Inflammatory lesion count will include the number of papules and pustules, which will be recorded separately. The number of nodules and cysts will be reported separately and included with the inflammatory lesion counts.
Tolerability Evaluation	Subjects will be assessed at each visit from Baseline through Week 12 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 performed at Screening, Baseline, and Week 12/Early Termination (ET). Blood pressure and pulse will be measured at Screening, Baseline, and each visit through Week 12/ET. Any clinically significant changes noted during the physical exam as well as from the change in vital sign measurements or safety laboratory assessments will be recorded as adverse events. Methemoglobin will be measured with a pulse co-oximeter and recorded at Screening, Baseline, and Weeks 2 and 12/ET. Chemistry, hematology, and PT/PTT will be assessed at Screening, Baseline, and Week 12. Urine pregnancy tests in women of child-bearing potential will be performed at Screening, Baseline, and Weeks 4, 8, and 12/ET.
Additional Evaluations	Photographs of the face will be taken at Baseline and Week 12/ET.

Name of Sponsor/Company: Novan, Inc. **Name of Finished Product:** SB204 **Name of Active Ingredient:** NVN1000		Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Endpoints	Primary Efficacy Endpoints The co-primary efficacy endpoints are: a. The absolute change in inflammatory lesion count from Baseline to Week 12; b. The absolute change in non-inflammatory lesion count from Baseline to Week 12; c. The proportion of success according to the dichotomized IGA. A subject will be considered a success if the IGA at Week 12 is clear or almost clear and is at least 2 grades less than Baseline. Secondary Efficacy Endpoints The secondary endpoints include the following: a. The percent change in inflammatory lesion count from Baseline to Week 12; b. The percent change in non-inflammatory lesion count from Baseline to Week 12; c. The median time to improvement.		
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 each active treatment group to the combined Vehicle treatment group. Comparisons will not be performed between active treatments. 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 population. For the dichotomized IGA, subjects will be considered a success if their IGA score is clear or almost clear and at least two grades less than Baseline. For those subjects for whom no Week 12 assessments are available, the last observation will be carried forward (LOCF) in order to provide a value for efficacy parameters that are missing, primarily due to missed visits. Additionally, a sensitivity analysis to estimate missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) independently for each treatment group. All hypotheses will be two-sided at an alpha level of 0.05. Descriptive Statistics Descriptive statistics will be presented for the efficacy data at each evaluation for the ITT and PP populations. Safety data will be summarized as indicated below for the safety population. Continuous		

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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. Descriptive statistics will be presented for the active treatment groups, each vehicle treatment group, and the vehicle treatment groups combined.

Efficacy Analysis
Lesion counts will be summarized at each evaluation from Baseline through Week 12. Absolute and percent change in lesion counts will be summarized at Weeks 2, 4, 8, and 12. IGA scores will be summarized from baseline through Week 12. The dichotomized IGA scores will be summarized at Weeks 2, 4, 8, and 12.

Primary Efficacy Analysis
The analysis of the absolute change in non-inflammatory lesion counts at Week 12 will be conducted using an analysis of covariance with factor of treatment and baseline lesion count as the covariate. The analysis of the absolute change in inflammatory lesion counts at Week 12 will use the same method as the analysis of the non-inflammatory lesions.

The analysis of the dichotomized IGA scores at Week 12 will be analyzed with a Cochran-Mantel-Haenszel test.

Pairwise comparisons of each active treatment group to the combined vehicle treatment group will be computed without concern for controlling for multiplicity.

Secondary Efficacy Analyses
The analyses of percent change in inflammatory and non-inflammatory lesion counts at Week 12 will use the same method as the analysis of the non-inflammatory lesions.

The time to improvement will be compared between each of the active treatment groups and the combined Vehicle treatment group using the Kaplan-Meier method. An observation will be censored if improvement is not achieved by Week 12 (inclusive). The log-rank test will be used to compare time to response between each active treatment group and the combined Vehicle treatment group.

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Tolerability Analyses
Cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized from Baseline to Week 12. Additionally, change from Baseline in tolerability assessments will be summarized at Weeks 2, 4, 8, and 12.

Safety Analyses
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 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, 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.

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

Vital Signs
Blood pressure and pulse will be summarized by treatment group from

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Baseline through Week 12. Additionally, change from Baseline in vital signs will be summarized at Weeks 2, 4, 8, and 12.

Laboratory Assessments

Blood chemistry, hematology, and PT/PTT values will be reported individually at Screening, Baseline, and Week 12. Laboratory test results will be summarized descriptively at Baseline and Week 12. Additionally, shifts from Baseline to Week 12 in laboratory test results based on normal ranges will be summarized with descriptive statistics. The last laboratory evaluation prior to the first dose of study drug will be used as Baseline for all laboratory analyses.

Methemoglobin

Methemoglobin will be reported as a percentage of hemoglobin. Methemoglobin will be summarized at Baseline and Weeks 2 and 12/ET. Additionally, the change from Baseline in methemoglobin at Weeks 2 and 12/ET will be summarized.

Urine Pregnancy Tests

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
ANOVA	Analysis of Variance
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
IUD	Intrauterine Device
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Regulatory Activities
NOVAN	Novan, Inc.
OTC	Over-the-Counter
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating Procedure
TBSA	Total Body Surface Area
TEAE	Treatment Emergent Adverse Events
UPT	Urine Pregnancy Test
US	United States
WOCBP	Women of Child-Bearing Potential

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1. INTRODUCTION

1.1 BACKGROUND

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

Nitric oxide is a free radical gas naturally produced by the human body which has antimicrobial and anti-inflammatory activity. Novan, Inc. has developed a topical gel containing NVN1000, a drug which releases nitric oxide to the skin after topical application. SB204, comprising 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 240 subjects have been treated with NVN1000 Gel, including SB204, and 150 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% Gel or SB204 2% Gel	Vehicle Gel
Manufacturer	Novan, Inc.	Novan, Inc.
Packaging	Pump designed to deliver 1:1 Hydrogel: NVN1000 Gel to yield final concentration of SB204 4% Gel or SB204 2% Gel	Pump designed to deliver 1:1 Hydrogel: Vehicle Gel
Storage Requirements	Refrigerated, 2-8 °C	Refrigerated, 2-8 °C
Appearance Post-Mixing	Opaque white gel	Opaque white gel
Dosing Schedule	Once or twice daily	Once or twice daily
Route of Administration	Topical Application	Topical Application

1.3 NONCLINICAL STUDIES WITH NVN1000 GEL

The development program for NVN1000 Gel includes over 25 non-clinical studies to assess safety following topical application. Studies performed to date with NVN1000 demonstrated the safety of the inert carrier silica particles and the lack of systemic silica particle bioavailability when applied topically. Following daily topical administration of NVN1000 Gel to rats (at doses of 6, 12, and 20%) for five days or to miniature pigs (at doses of 6, 12, and 20%) for 28 days (10% TBSA), systemic exposure (blood levels) of nitrate and silicon were not statistically different from background levels. The in-life portion of a 13-week dermal toxicity study in mini-pigs has been completed; no significant findings have been noted to date. In a 13-week dermal toxicity study in rats, local application events led to unscheduled study termination of all dose groups in a time-dependent manner.

Pharmacokinetic studies to date in rats with the NVN1000 Gel have led to no appreciable systemic bioavailability (<2%) of NVN1000 or related compounds following repeated topical administration as assessed by nitrate as a marker for nitric oxide exposure and silicon as a marker for the polysiloxane backbone of NVN1000. Silicon and nitrate were detected in blood only sporadically and at the same frequency and levels found in pre-dose blood samples. Co-administration of NVN1000 Gel with hydrogel did not impact the pharmacokinetics.

NVN1000 Gel demonstrated mutagenicity in an Ames assay, but was not mutagenic in two in vivo genotoxicity tests in two tissue types: bone marrow via IP administration and skin via topical administration.

For additional information refer to the Investigator's Brochure.

1.4 CLINICAL STUDIES WITH NVN1000 GEL

The topical administration of NVN1000 Gel to healthy volunteers or subjects with acne vulgaris has generally been well-tolerated with no safety concerns identified. In seven completed clinical studies, approximately 240 subjects have been treated with NVN1000 Gel or SB204 Gel and approximately 150 subjects have been treated with Vehicle Gel. No SAEs have been reported and the AE profile has been similar in subjects treated with active (NVN1000 or SB204 Gel) and vehicle. Asymptomatic, transient erythema has been observed in some subjects treated with higher concentrations of NVN1000. There have been no clinically significant changes in laboratory results including methemoglobin, or changes in physical examinations. A cross-over pharmacokinetic (PK) study was conducted in 18 subjects with moderate to severe acne. Subjects received nine applications of SB204 8% Gel or Vehicle Gel to the face, chest, upper back, and shoulders (~17% TBSA) over five days, had a nine day washout, then crossed over to the other treatment for nine applications over five days. PK analysis of samples for nitrate and silicon is pending. One subject withdrew during the second dosing period due to contact dermatitis. In a psoriasis microplaque assay, local application-site reactions following application of alcoholic

NVN1000 Gel or Vehicle Gel under occlusion were observed in some treated subjects that led to treatment discontinuations.

Table 1 provides a listing of the clinical studies conducted to date in subjects with acne. Additional details regarding these studies are in the Investigator's Brochure.

Table 1: Clinical Studies Conducted to Date in Subjects with Acne

Study Number	Study Title	Population	Number Enrolled	Treatment Groups	Frequency / Duration of Treatment
Phase 1					
NI-AC002 [KGL 7563]	A Phase I, Multiple-Dose, Single-Center, Observer-Blind, Randomized, Parallel-Group Study Evaluating the Safety and Cutaneous Tolerability of NVN1000 Topical Gel in Healthy Volunteers	Healthy volunteers ≥ 18 years of age with elevated *P. acnes* counts	60	NVN1000 2 % Gel NVN1000 4 % Gel NVN1000 8 % Gel Vehicle Gel	Once daily for 4 weeks (28 days) over entire face
NI-AC004 [KGL 7603]	A Phase 1, 3-Day Study of Safety and Tolerability of NVN1000 Topical Gel in Healthy Volunteers	Healthy volunteers ≥ 18 years of age with elevated P. *acnes* counts	15	NVN1000 8% Gel NVN1000 Gel 8% and moisturizer Vehicle Gel	Once daily for 3 days on forehead
NI-AC006 [KGL 7666]	A Phase 1, Multiple-Dose, Evaluator-Blind, Randomized, Parallel-Group Study Evaluating the Safety and Cutaneous Tolerability of SB204 (NVN1000 Gel with Hydrogel) in Healthy Volunteers	Healthy volunteers ≥ 18 years of age with elevated *P. acnes* counts	30	SB204 4% (NVN1000 Gel with Hydrogel) Vehicle Gel with Hydrogel	Twice daily for 14 days to face
NI-AC101	A Phase 1, Single-center, Double-Blind, Randomized, Cross-over Pharmacokinetic, Safety, and Tolerability Study of SB204 8% (NVN1000 Gel) and Vehicle Gel	Subjects ≥ 18 years of age with moderate or severe acne vulgaris	18	SB204 8% Gel Vehicle Gel	Twice daily for 4 days and once on the 5th day to upper back, upper chest, shoulders and face for two dosing periods
Phase 2					
NI-AC001	A Single-Center, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Comparison, POC Study Comparing the Tolerability, Safety and Efficacy of NVN1000 Topical Gel and Gel Vehicle in the Treatment of Moderate to Severe Acne Vulgaris	Subjects 12-40 years of age with moderate to severe acne vulgaris	70	NVN1000 2% Gel Vehicle Gel	Once daily at bedtime for 8 weeks (56 days) over entire face
NI-AC201	A Multi-Center, Randomized, Evaluator-Blinded, Vehicle Controlled, Parallel Group, 3-arm Study Comparing the Efficacy, Tolerability, and Safety of 2 Concentrations of SB204 (NVN1000 Gel and Vehicle Gel with Hydrogel) Twice Daily in the Treatment of Acne Vulgaris	Subjects 12-40 years of age with mild to severe acne vulgaris	153	SB204 4% Gel ; SB204 1% Gel ; Vehicle Gel with Hydrogel	Twice daily for 12 weeks to face

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 sebum production, decrease *P. acnes,* alter keratinocyte differentiation, and inhibit inflammasome activation. In a recently completed Phase 2 study, SB204 4% Gel administered twice daily in subjects with acne decreased inflammatory and non-inflammatory lesion counts at the end of treatment. In the studies conducted to date, the AE profile was similar between subjects treated with NVN1000 Gel, SB204 Gel, and subjects treated with Vehicle Gel. NVN1000 Gel at 2%, 4%, and 8% concentrations was well tolerated and was not associated with a safety or tolerability signal.

Nitric oxide released from NVN1000 is anticipated to be pharmacologically active in the skin. Any nitric oxide absorbed through the skin would be extremely short-lived (milliseconds) with rapid auto-oxidation to nitrite and nitrate. Systemic bioavailability of NVN1000 or related compounds following repeated topical administration of NVN1000 Gel was < 2% in non-clinical pharmacokinetic studies conducted to date both with and without hydrogel.

Dermal toxicology studies have demonstrated minimal evidence of toxicity in a 28 day miniature pig study dosed with 20% NVN1000 Gel across 10% TBSA, low dermal irritation in rabbits, and no dermal sensitization in guinea pigs. A 13-week dermal toxicology study in mini-pigs with NVN1000 2%, 4%, and 8% Gel (10% TBSA) has completed the in-life period with no significant observed effects; histopathology and toxicokinetics data will be available prior to enrollment in the current study. Local application site events in a 13 week dermal toxicology study in rats with NVN1000 2%, 4%, and 8% Gel (10% TBSA) led to premature discontinuation of all dose groups in a time-dependent manner. These local adverse effects seen in the rat study are species specific and monitorable. Tolerability will be assessed during the planned study, and discontinuation criteria for intolerance by subjects is described in Section 6.7.

Based on the known mechanism of action of nitric oxide, theoretical risks from systemic exposure following topical administration of NVN1000 Gel or SB204 Gel include hypotension and headache. Methemoglobinemia has been reported in patients treated with inhaled nitric oxide. Methemoglobin will be monitored during the study and treatment stopped in any subject with a measured methemoglobin > 5.0%.

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.

A transient (approximately 5-10 minutes), asymptomatic erythema has been observed in some subjects shortly after application of NVN1000 Gel or SB204 Gel which is a physiologic response

(vasodilation) to local nitric oxide release. Topical application has been associated with local application-site reactions including erythema, peeling, desquamation, or burning/stinging. These local application-site reactions may occur due to the active agent (NVN1000) or the vehicle. Local application-site events including erosions and contact dermatitis were reported in subjects with psoriasis treated with NVN1000 Gel and Vehicle Gel under occlusion. These local application-site reactions resolved after discontinuation of the product and by the end of the study.

Based on available data, Novan anticipates that the risks to subjects enrolling in this Phase 2 study at which the maximum strength of SB204 Gel will be 4% twice daily to approximately 4 percent total body surface area are minimal, and that appropriate monitoring is in place to assess safety. At this stage of development, it is unknown if a clinical benefit will be observed in subjects with acne vulgaris following treatment for 12 weeks.

2. RATIONALE AND OBJECTIVES

2.1 STUDY RATIONALE

Novan is conducting this study to evaluate the efficacy, cutaneous tolerability and safety of SB 204 2% Gel, SB204 4% Gel and Vehicle Gel administered once or twice daily to the face.

Subjects will dose once (in the evening) or twice daily (morning and evening) for up to 12 weeks (84 days) with SB204 4% Gel, twice daily with SB204 2% Gel, or once or twice daily with Vehicle Gel. Approximately 0.9 g of gel (three (3) pump strokes) will be applied evenly over the face (4% TBSA). Based on the previous human safety data with SB204 Gel at up to 8% and Vehicle Gel as well as the nonclinical safety data including dosing with and without hydrogel, this dose is expected to be safe and well tolerated.

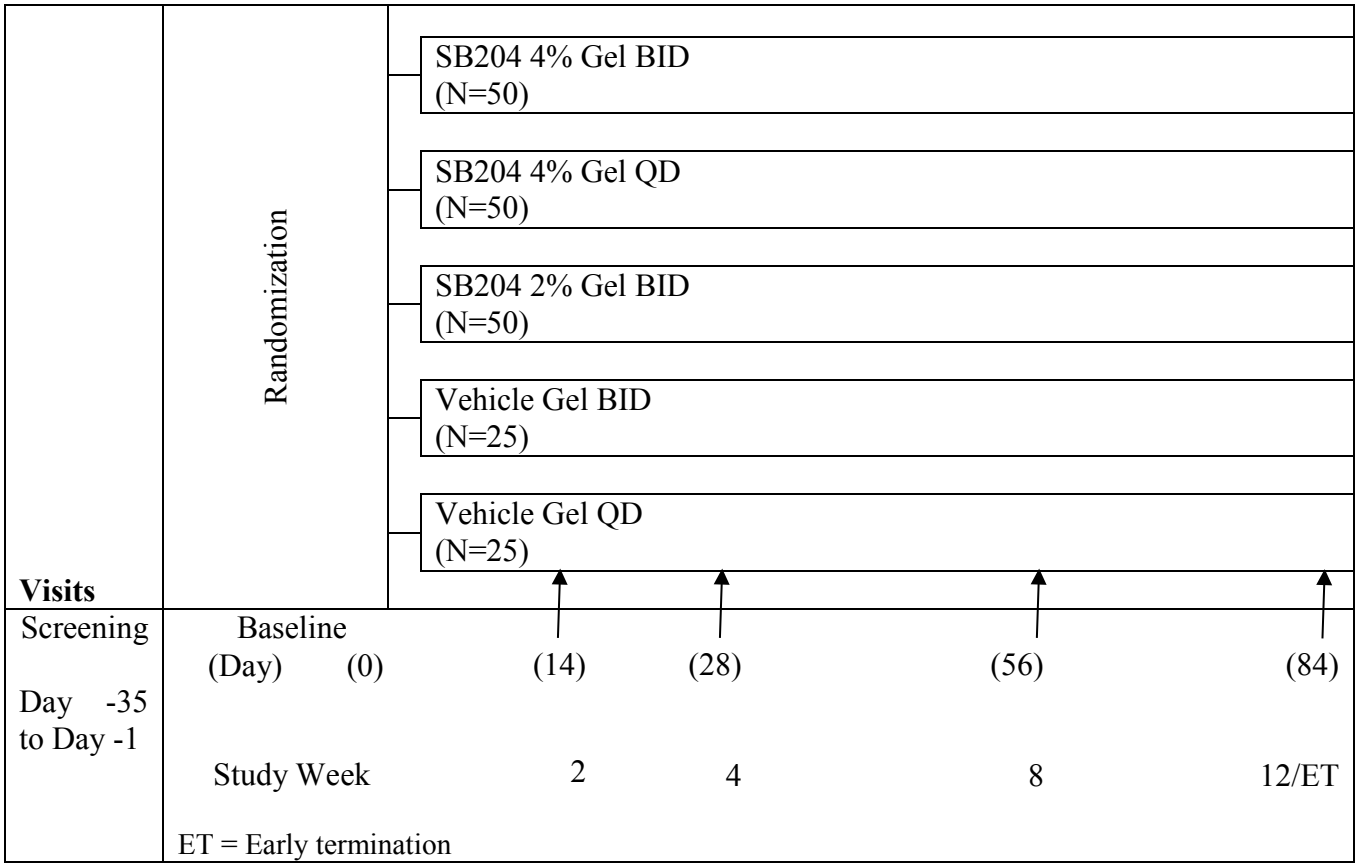
2.2 STUDY OBJECTIVES

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

3. STUDY DESIGN

Figure 1 depicts the overall study design for this 12 week, 5 arm, randomized, evaluator blinded study in subjects with moderate to severe acne vulgaris dosed once or twice daily with SB204 and Gel Vehicle. Subjects receiving current treatment for acne vulgaris may enter a wash out period after screening of up to 35 days prior to randomization.

Figure 1: Study Diagram



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;
- The absolute change in non-inflammatory lesion count from Baseline to Week 12;
- The proportion of success according to the dichotomized IGA. A subject will be considered a success if the IGA at Week 12 is clear or almost clear and is at least 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;
- The percent change in non-inflammatory lesion count from Baseline to Week 12;
- The median time to improvement.

3.1.2 TOLERABILITY ENDPOINTS

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

3.1.3 SAFETY ENDPOINTS

Safety endpoints will include the change from baseline in percent methemoglobin, change from baseline vital sign measurements and in chemistry, hematology, and PT/PTT values, and the comparison of adverse events between groups. Any clinically significant changes noted during the physical exam as well as from the vital sign measurements, or safety laboratory assessments will be recorded as adverse events and included in the comparison.

3.2 STRUCTURE

This is a multi-center, randomized, evaluator-blinded, vehicle-controlled, 5-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.

3.4 DOSAGE/DOSE REGIMEN

Approximately 0.9 g of SB204 2% Gel, SB204 4% Gel, or Vehicle Gel will be applied evenly over the entire face once or twice 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 or twice daily after washing. The product should be mixed for 5-10 seconds until thoroughly combined with a uniform opaque appearance then applied with the fingertips (Appendix 2). Subjects assigned to once daily dosing should apply their dose at 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 200 healthy male and female subjects between the ages of 12 and 40 (inclusive) with moderate to severe acne vulgaris on the face will be randomized to participate in the study.

Eligible subjects will have: at least 20 but no more than 40 inflammatory lesions (papules and pustules); 25 to 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 3).

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 QST Consultations (QST) 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 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, 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, 12 to 40 years of age, inclusive and in good general health;
3. Have a baseline IGA score of moderate (3) or severe (4);
4. Have a minimum of 25 but not more than 70 non-inflammatory lesions (open and closed comedones) on the face;
5. Have a minimum of 20 but no more than 40 inflammatory lesions (papules and pustules) on the face;
6. Have no more than two nodules or cysts on the face;
7. Women of childbearing potential (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;
9. Males must agree to avoid fathering a child during the study and for 60 days after the last dose of the study drug by ensuring one of the acceptable methods of contraception listed is used and not donating sperm; and
10. Be willing and able to follow study instructions and likely to complete all study requirements. Subjects under 18 years of age or age of majority must be accompanied by the parent or legal guardian at the time of assent/consent signing.

3.7.3 EXCLUSION CRITERIA

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

1. Have any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, acne secondary to medications or other medical conditions, perioral dermatitis, clinically significant rosacea, or gram-negative folliculitis;
2. Have any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive;

3. Have 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. Have used estrogens (e.g., Depogen, Depo-Testadiol, Gynogen, Valergen, etc.) or oral contraceptives for less than 12 weeks immediately preceding Baseline, discontinued use of estrogens or oral contraceptives less than 12 weeks prior to Baseline, or planning to begin or discontinue use of this therapy during the treatment period;
6. Have used medications or vitamins which are reported to exacerbate acne during the 12 weeks immediately preceding Baseline (e.g. azothioprine, haloperidol, halogens such as iodides or bromides, lithium, anabolic steroids, systemic corticosteroids, phenytoin and phenobarbital). The subject must not have had a severe acne flare for at least 12 weeks preceding Baseline. Daily use of a multi-vitamin is acceptable.
7. Have a history of hypersensitivity or allergic reactions to any of the ingredients in the SB204 Gel or Vehicle Gel as described in the Investigator's Brochure;
8. Subjects using or requiring short- or long-acting nitrates, nitric oxide donor drugs or supplements (eg; arginine, citrulline) or drugs associated with methemoglobinemia;
9. Have used the following <u>topical</u> preparations within the time specified prior to Baseline or require the concurrent use of any of the following topical agents:

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
Retinoids or retinol-containing products or corticosteroids	4 weeks

* Includes benzoyl peroxide, salicylic acid, dapsone, alpha-hydroxy acid, or glycolic acids

10. Have used the following <u>systemic</u> 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 (≤10 days) of antibiotics if needed during the treatment phase of the study for non-acne related illnesses are allowed.

* Intranasal and inhaled corticosteroids may be used throughout the trial if the subject is on a stable dose.

11. Have had the following procedures on the face, including treatment area within the time specified prior to Baseline:

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

12. Have a methemoglobin value of > 3.0% at Screening or Baseline;

13. Have clinically significant anemia at Screening as determined by the Investigator;

14. Intend to use a tanning booth or sunbathe during the study;

15. 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. Subjects scheduled for endoscopy with use of topical anesthetics should not be enrolled.

16. Are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;

17. Have used an investigational drug or device within 30 days of Baseline or concurrent participation in a different research study;

18. Have participated in a previous study with SB204 Gel 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, methemoglobin assessment, 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 with clinically significant anemia as determined by the Investigator or methemoglobin values >3.0% will not be randomized.

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, 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. Male subjects must agree to avoid fathering a child during the study and for 60 days after the last dose of the study drug by ensuring one of the acceptable methods of contraception is used and not donating sperm.

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 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 2: 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 -1)	Baseline (Day 0)	Week 2[1] ±3 days (Day 14)	Week 4 ±3 days (Day 28)	Week 8 ±5 days (Day 56)	Week 12/ET[2] ±5 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[3]				X
Chemistry, Hematology, PT/PTT	X	X[3]				X
Urine Pregnancy Test (all WOCBP)	X	X[3]		X	X	X
Methemoglobin	X	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	X	
Study Drug and Diary Collected			X	X	X	X
Subject Compliance Reviewed			X	X	X	X
Photography		X				X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

[1] All visit dates are in reference to Baseline, e.g., Visit 2 occurs two weeks (14 days) after Baseline visit

[2] All Week 12 procedures should be completed for subjects who prematurely discontinue.

[3] If the Baseline Visit is within 3 calendar days of the Screening visit, Physical Examination, Chemistry, Hematology, PT/PTT, and UPT do not need to be repeated.

4.1.1 SCREENING (DAY -35 TO DAY – 1)

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

1. Review study procedures and information regarding the study including the potential risk and benefits of SB204 with the subject and obtain written informed consent/assent.
2. Obtain demographic information.
3. Obtain subject's medical history, medication history, and concomitant medication information.
4. Verify appropriate contraception being used for WOCBP and male subjects per Section 6.4.
5. Measure percent methemoglobin.
6. Collect blood pressure and pulse rate.
7. Perform a brief physical examination.
8. Obtain pregnancy test (WOCBP only) and evaluate results. If pregnancy test is positive, the subject may not participate in the study.
9. Perform Investigator's Global Assessment (IGA).
10. Perform lesion counts. Inflammatory and non-inflammatory lesion counts will be performed on the entire face.
11. Collect chemistry, hematology, and PT/PTT.
12. Confirm subjects meet eligibility criteria.
13. Review prohibited medications, acne treatments, and supplements that should not be used prior to Baseline and during the trial.
14. Collect AEs related to study procedures performed since signing of informed consent.
15. 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 concomitant medication information.
2. Perform a brief physical examination.
3. Obtain pregnancy test (WOBCP only) and evaluate results. If pregnancy test is positive, the subject may not participate in the study.
4. Measure percent methemoglobin.
5. Collect blood pressure and pulse rate.

6. Collect chemistry, hematology, and PT/PTT.
7. Perform IGA.
8. Perform lesion counts.
9. Perform cutaneous tolerability assessment.
10. Have subject wash face and dry with lint free towel.
11. Collect photographs.
12. Confirm eligibility and randomize subject.
13. Dispense subject diary and study drug. Instruct subject on dispensing, mixing, and application of study product and diary completion.
14. 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.).
15. 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. Measure percent methemoglobin.
4. Collect blood pressure and pulse rate.
5. Perform IGA.
6. Perform lesion counts.
7. Perform cutaneous tolerability evaluation.
8. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
9. Review subject diary for completion.
10. Dispense new study drug and diary if needed.
11. Review and confirm the study schedule with the subject.

4.1.4 WEEK 4 (DAY 28)

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

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.
5. Perform IGA.
6. Perform lesion counts.
7. Perform cutaneous tolerability evaluation.
8. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
9. Review subject diary for completion.
10. Dispense new study drug and diary.
11. Review and confirm the study schedule with the subject.

4.1.5 WEEK 8 (DAY 56)

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

1. Update concomitant medication information.
2. Update AE information and record any new AEs.
3. Obtain UPT (WOCBP only) and evaluate results.
4. Collect blood pressure and pulse rate.
5. Perform IGA.
6. Perform lesion counts.
7. Perform cutaneous tolerability evaluation.
8. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
9. Review subject diary for completion.
10. Dispense new supply of study drug and diary.
11. Review and confirm the study schedule with the subject.

4.1.6 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. Measure percent methemoglobin.
6. Collect blood pressure and pulse rate.
7. Collect chemistry, hematology, and PT/PTT.
8. Perform IGA.
9. Perform lesion counts.
10. Perform cutaneous tolerability evaluation.
11. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
12. Review subject diary for completion.
13. Have subject wash face and dry with a lint-free towel.
14. Collect photographs.

4.1.7 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 QST, 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.

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 QST and Novan.

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

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

- Other

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

4.2 EFFICACY ASSESSMENTS

The same blinded evaluator will perform Investigator Global Assessments and lesion counting at Screening, Baseline and Weeks 2, 4, 8, and 12. In the event that this is not possible due to unforeseen circumstances, a different blinded evaluator will evaluate the subject. However, the same evaluator should evaluate subjects at the Baseline and Week 12 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 Investigator 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 investigator will perform each study assessment for each study subject, 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: Few non-inflammatory lesions with no more than 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 nodular lesion.
4	Severe: Up to many non-inflammatory and inflammatory lesions, including nodular 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

separately. Non-inflammatory lesions (open and closed comedones) will be counted and recorded separately. 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

4.3.1 CUTANEOUS TOLERABILITY EVALUATIONS

The Investigator will evaluate the subject's face prior to the first application of investigational product in addition to evaluating at 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 not be reported as an AE unless they reach severe and/or result in subject's discontinuation 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. Any clinically significant changes in vital signs from Baseline will be recorded as adverse events whether or not drug related.

4.4.4 LABORATORY ASSESSMENTS

Chemistry, hematology, and PT/PTT will be collected at Screening, Baseline, and Week 12/ET. If clinically significant changes in lab results from Baseline are noted at the Week 12/ET visit, these will be recorded as adverse events. Subjects with clinically significant anemia at Screening as determined by the Investigator will not be eligible to participate.

4.4.5 METHEMOGLOBIN

Methemoglobin will be measured at Screening, Baseline, Week 2 and Week 12/ET using a Masimo Rainbow® SET® Rad-57™ pulse co-oximeter that analyzes methemoglobin levels. The percent methemoglobin will be displayed on the pulse co-oximeter and recorded in the subject's study record and in the study database.

Subjects with methemoglobin values of > 3.0% at Screening or Baseline will not be eligible to participate in the study.

Clinically significant changes in methemoglobin will be recorded as adverse events. The adverse event term should reflect the underlying diagnosis or symptoms and not the pulse co-oximeter result itself.

Clinical symptoms and signs of methemoglobinemia in relation to the level of methemoglobin are listed in Table 3.

Table 3: Clinical Symptoms and Signs of Methemoglobinemia in Relation to the Level of Methemoglobin

Level of Methemoglobin	Clinical Symptoms and Signs
<10%	Frequently asymptomatic, occasionally grayish skin
10%-20%	Skin changes such as cyanosis
20%-30%	Dyspnea, headache, anxiety
30%-50%	Dizziness, palpitations, confusion, tachypnea
50%-70%	Seizures, cardiac arrhythmias, metabolic acidosis, coma
>70%	Death

Source: (Boylston, 2002)

4.4.6 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.

Pregnancy tests will also be performed at Weeks 4, 8, and 12. 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 Week 12/ET. Baseline photographs may be reviewed by the sponsor or member of the study team to confirm appropriateness of enrolled subjects.

4.6 SCREEN FAILURES

A screen failure subject will be a person from whom informed consent is obtained and is documented in writing (i.e., subject signs an informed consent form) but who does not meet the study eligibility requirements. Subjects will not be allowed to rescreen.

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 QST at the earliest possible time by telephone. QST will contact Novan for confirmation on subject discontinuation decision prior to informing the site. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and QST.

5. PROHIBITED THERAPIES AND MEDICATIONS

Concomitant medications are any prescription or OTC preparations. Use of concomitant medications will be recorded on the concomitant medications study record and study database beginning at the Screening 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 must not change moisturizer and/or sunscreen used during the course of the study. If used, moisturizers and sunscreen must be applied at least 30 minutes after study drug application. Use of facial cleanser, moisturizers, and sunscreen will be considered concomitant medications; but these products will be recorded on a specific study record for facial cleansers, moisturizers and sunscreen.

Subjects must not have used anti-acne treatments including topical or systemic antibiotics or retinoids as described in Section 3.7.3 prior to Baseline. These medications are also prohibited during the trial.

Subjects may not be concurrently on nitroglycerin, drugs associated with methemoglobinemia, drugs associated with exacerbating acne vulgaris, or drugs/supplements that are nitric oxide releasers (Appendix 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 research study during the study period. Any subject who has participated in a previous study with SB204 Gel/NVN1000 Gel must not participate.

Any medication/therapy used by the subject following first application of study product will be considered a concomitant medication/therapy (e.g., aspirin, acetaminophen, birth control pills, vitamins, soap, moisturizer, sunscreen, 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 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 QST Medical Monitor results in any of the following outcomes:

- Death
- Life-threatening event (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe.)
- Persistent or significant disability/incapacity (i.e., the AE results in a substantial disruption of the subject's ability to carry out normal life functions)
- Requires in-patient hospitalization or prolongs hospitalization (i.e., the AE required at least a 24-hour in-patient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or investigational product before conception or during pregnancy)
- Does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (i.e., is a significant or important medical event)

6.1.1 ADVERSE EVENT SEVERITY GRADES

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

- Mild: Event may be noticeable to subject; does not influence daily activities; usually does not require intervention
- Moderate: Event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- Severe: Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed

The Investigator will follow all subjects who experience AEs until there is a return to the subject's baseline condition or until a clinically satisfactory resolution is achieved or the subject is lost to follow-up.

6.1.2 INVESTIGATIONAL PRODUCT CAUSALITY

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

- Definite: There is a clinically plausible time sequence between the onset of the AE and the application of investigational product; when the event responds to withdrawal of investigational product and recurs with re-administration of investigational product.
- Probable: There is a clinically plausible time sequence between the onset of the AE and the application of investigational product; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures.
- Possible: There may or may not be a clinically plausible time sequence between the onset of the AE and the application of investigational product and a cause cannot be ruled out.
- Unlikely: There is no reasonable temporal association between the test material and the suspected event and the event could have been produced by the subject's clinical state or other modes of therapy administered to the Subject.
- Unrelated: This term should be reserved for those events that cannot be even remotely related to study participation.

6.2 REPORTING ADVERSE EVENTS

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

The Investigator will assess subjects at each scheduled study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "*How have you felt since your last visit?*" All AEs (serious and non-serious) reported by the subject must be recorded on the subject's study record and entered into the study database.

In addition, QST 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 QST by telephone or email as soon as possible after the investigator or coordinator has become aware of its occurrence. The

investigator/coordinator must complete a Serious Adverse Event (SAE) Form and email it to QST along with the subject's Adverse Events Log and Concomitant Medications Log 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:

Email: safety@qstconsultations.com

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

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

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.

Male subjects must agree to avoid fathering a child during the study and for 60 days after the last dose of study drug by ensuring one of the acceptable methods of contraception listed is used and by not donating sperm.

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). Male subjects should be instructed to contact the investigator if their female partner becomes pregnant during the time the subject is enrolled through in the study through 60 days after the final visit. The Investigator must immediately notify QST of any female subject or the female partner of a male subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and email the form to QST. Subjects found to be pregnant prior to Week 12 will be discontinued from the study. QST 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 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 QST 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 QST 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 QST 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 (Boylston, 2002).

6.7 DISCONTINUATION OF INDIVIDUAL SUBJECTS FROM THE STUDY

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

Subjects with > 5.0% methemoglobin at any post-baseline visit will 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® version 9.3 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 each active treatment group to the combined Vehicle treatment group. Comparisons will not be performed between active treatments. Efficacy analyses will be performed for the intent-to-treat (ITT) and per-protocol (PP) populations. Safety analyses will be performed using the safety population.

For the dichotomized IGA, subjects will be considered a success if their IGA score is clear or almost clear and at least two grades less than Baseline.

For those subjects for whom no Week 12 assessments are available, the last observation will be carried forward (LOCF) in order to provide a value for efficacy parameters that are missing, primarily due to missed visits. Additionally, a sensitivity analysis to estimate missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) independently for each treatment group. All hypotheses will be two-sided at an alpha level of 0.05.

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 ITT population will include all study subjects who were randomized and dispensed study medication.

7.2.2 SAFETY POPULATION

The safety population will include all randomized subjects with documented use of study medication (at least one application) and at least one post-baseline safety assessment.

7.2.3 PER-PROTOCOL POPULATION

The 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 safety 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, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect;
- Have missed more than one interim study visit;
- Have not been compliant with the dosing regimen (i.e. subjects must apply 80-120% of the expected applications of study medication during participation in the study);

- Out of visit window at the Week 12 visit by ±5 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.

7.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics will be summarized by treatment group for the ITT, PP and safety 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.

7.4 DESCRIPTIVE STATISTICS

Descriptive statistics will be presented for the efficacy data at each evaluation for the ITT and PP populations. Safety data will be summarized as indicated below for the safety population.

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

Descriptive statistics will be presented for the active treatment groups, each vehicle treatment group, and the vehicle treatment groups combined.

7.5 EFFICACY ANALYSIS

Lesion counts will be summarized at each evaluation from Baseline through Week 12. Absolute and percent change in lesion counts will be summarized at Weeks 2, 4, 8, and 12. IGA scores will be summarized from Baseline through Week 12. The dichotomized IGA scores will be summarized at Weeks 2, 4, 8, and 12.

Primary Efficacy Analysis
The analysis of the absolute change in non-inflammatory lesion counts at Week 12 will be conducted using an analysis of covariance with factor of treatment and baseline lesion count as the covariate.

The analysis of the absolute change in inflammatory lesion counts at Week 12 will use the same method as the analysis of the non-inflammatory lesions.

The analysis of the dichotomized IGA scores at Week 12 will be analyzed with a Cochran-Mantel-Haenszel test.

Pairwise comparisons of each active treatment group to the combined vehicle treatment group will be computed without concern for controlling for multiplicity.

Secondary Efficacy Analyses
The analyses of percent change in inflammatory and non-inflammatory lesion counts at Week 12 will use the same method as the analysis of the non-inflammatory lesions.

The time to improvement will be compared between each of the active treatment groups and the combined Vehicle treatment group using the Kaplan-Meier method. An observation will be censored if improvement is not achieved by Week 12 (inclusive). The log-rank test will be used to compare time to response between each active treatment group and the combined Vehicle treatment group.

7.5.1 SENSITIVITY EFFICACY ANALYSES

A sensitivity analysis will use the method of Markov Chain Monte Carlo (MCMC) multiple imputation to impute missing data for the non-inflammatory and inflammatory lesion counts and IGA at Week 12. This method does not rely on the assumption of data missing at random. Additionally, the pattern of missing observations in each treatment group cannot influence the missing value estimation in the other because the imputation is being conducted independently for each treatment group.

Lesion Counts
Multiple imputation and subsequent analysis will involve four distinct phases with these principal tasks:

1. Calculate the number of missing values to be estimated by MCMC (nmiss) for 12 week value.
2. Create a data set of subjects, one for each treatment group, with observed values and those needing estimation by MCMC. The missing lesion count values in each data set will be filled in using the MCMC method '5 x nmiss' times to generate '5 x nmiss' data sets. The resulting data sets for each treatment group will be combined into one complete data set for each imputation.

   Syntax:

```
proc mi data=datain out=dataout seed=&seed. nimpute=5xnmiss;
   where trtpn=(1, 2,, 3, 4, or 5);
   mcmc chain=multiple;
   var lescnt2-lescnt5;
run;
```

3. For each complete data set, the absolute change in non-inflammatory lesion counts and absolute change in inflammatory lesion counts for baseline minus the 12 week value will be computed. Each complete data set will be analyzed as specified for the particular analysis.

The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

IGA
The sensitivity analysis for the IGA multiple imputation will involve four principal tasks:

1. Calculate the number of missing values, by treatment group, for IGA (total from Weeks 2, 4, 8, and 12).
2. Missing values will be filled in `5 x nmiss` times to generate `5 x nmiss` complete data sets, where nmiss is the maximum number of missing values of both treatment groups. The resulting imputed datasets for each treatment group will be combined into one complete dataset by imputation number.

   Syntax:

```
proc mi data=datain out=dataout seed=&seed. nimpute=5 x nmiss;
   where trtpn=(1, 2, 3, 4, or 5);
   mcmc chain=multiple;
   var IGA1 IGA2 IGA4 IGA8 IGA12;
run;
```

3. For each complete dataset, dichotomous endpoints (defined as IGA = 0 or 1 and at least a two-grade reduction from Baseline) will be computed. The imputed IGA values will be rounded to the nearest integer value prior to computing the dichotomized endpoints. Each complete data set will be analyzed with a Cochran-Mantel-Haenszel test.

Results from these analyses will be combined into a single inference using SAS® PROC MIANALYZE.

7.6 TOLERABILITY

7.6.1 CUTANEOUS TOLERABILITY

Cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized from Baseline to Week 12 by treatment group.

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 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, 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. 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. Additionally, change from Baseline in vital signs will be summarized at Week 2, 4, 8, and 12.

7.7.4 LABORATORY ASSESSMENTS

Blood chemistry, hematology, and PT/PTT values will be reported individually at Screening, Baseline, and Week 12. Laboratory test results will be summarized descriptively at Baseline and Week 12. Additionally, shifts from Baseline to Week 12 in laboratory test results based on normal ranges will be summarized with descriptive statistics. The last laboratory evaluation prior to the first dose of study drug will be used as Baseline for all laboratory analyses.

7.7.5 METHEMOGLOBIN

Methemoglobin will be reported as a percentage of hemoglobin. Methemoglobin will be summarized descriptively by treatment group at Baseline and Weeks 2 and 12. Additionally, the change from baseline in methemoglobin will be summarized by treatment group at Weeks 2 and 12.

7.7.6 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 200 subjects will be randomized into the study in a 2:2:2:1:1 ratio (~ 50 in each active arm and ~25 in each vehicle arm) at approximately 20 sites in North America. The main objective of this study is to evaluate the efficacy, tolerability and safety of SB204 with respect to vehicle.

8. INVESTIGATIONAL PRODUCT MANAGEMENT

8.1 RECEIPT OF INVESTIGATIONAL PRODUCT

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

8.2 STORAGE OF INVESTIGATIONAL PRODUCT

Upon receipt from Novan, or Novan's designee, a study staff member will place all study supplies in a temperature-controlled area. The pumps should be refrigerated (2-8 °C). Access to study supplies should be strictly limited to the study staff. Neither the Investigator nor any member of the study staff will distribute any of the study supplies to any person not participating in this study.

If a study staff member becomes aware that the study supplies have not been properly handled (i.e., supply arrives and was not placed in refrigerator upon receipt), Novan must be contacted immediately. In such an event, study supplies should 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 QST personnel. Other supplies will be stored at room temperature.

8.3 TREATMENT ASSIGNMENT AND BLINDING

Subjects will be randomized to SB204 4% Gel, SB204 2% Gel, or Vehicle Gel on a 2:2:2:1:1 through utilization of the IWRS. The evaluator 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 contacting the QST Medical Monitor who will arrange for the treatment assignment to be sent to the site by the unblinded IWRS administrator. A study subject for whom the blind is broken will discontinue study product and will be scheduled for a follow up safety visit and be encouraged to stay in the study until the AE is resolved or stabilized.

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 and lot number
- Amount currently in refrigerator, 2-8 °C storage
- Pumps dispensed to each subject, identified by subject initials and a unique subject number
- Amount transferred to another location within the study site or destroyed — this should not occur without prior notification to Novan
- 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, QST, or 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 study subjects. Only status of informed consent and assent signature, gender, date of birth, ethnicity, race, and reason for failure will be entered in the electronic data capture (EDC) system for screen failures.

Novan and QST require 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, QST Medical Monitor or Novan may request copies of the subject's source study record for preliminary medical review.

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

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

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

The data recorded during the course of the study will be documented in the study database. Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The Investigator will ensure that the study records forwarded to QST, Novan or their designees, and any other documents, 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, QST or Novan 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 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 QST or Novan according to Good Clinical Practices (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (i.e., informed consent regulations, (21 C.F.R. § 50.20, 1999), and Institutional Review Board regulations, (21 C.F.R. § 56.103, 1981)). Access to all records, both during the trial and after trial completion, should be made available to QST and Novan at any time for review and audit to ensure the integrity of the data. The Investigator must notify QST 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 QST or Novan representative will review the protocol and study records with the Investigator(s) and their staff. During the study, the study monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries into the study database, the adherence to the protocol and to GCP, the progress of enrollment, to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the investigational product is being stored, dispensed and accounted for according to specifications. The Investigator and key trial personnel must be available to assist the monitor during these visits.

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

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

The Investigator must provide QST 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 QST 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 QST 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, QST 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 by initials and 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 QST 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 QST and 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

Boylston, M.; Beer, D. Methemoglobinemia: A case study. Crit. Care Nurse, **2002**. *22*, 50-55.

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

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

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

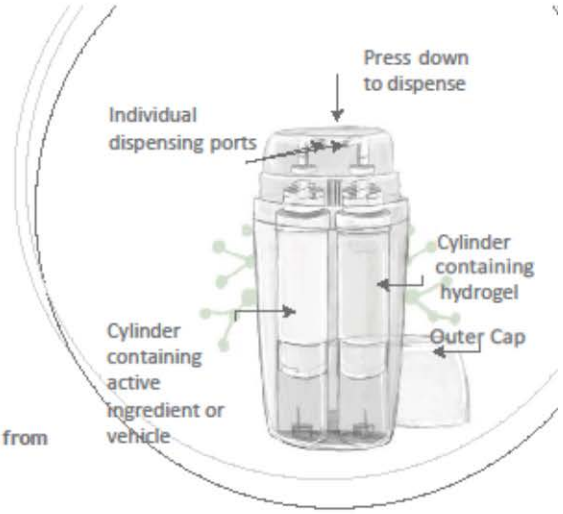
16. APPENDICES

16.1 APPENDIX 1: LIST OF RESTRICTED MEDICATIONS AND SUPPLEMENTS:

- Anti-acne medications
- Anabolic steroids
- Azathioprine
- Benzocaine & Cetacaine sprays
- Bromides
- Corticosteroids (oral)
- Dapsone
- EMLA Creams
- Chloroquine
- Flutamide
- Halides
- L-arginine
- L-citrulline
- Lidocaine
- Lithium
- Nitric oxide supplements
- Nitrates
- Nitric oxide
- Nitroglycerin
- Nitroprusside
- Nitrous oxide
- Phenobarbital
- Phenytoin
- Vitamin A (> 10,000 IU/day)

16.2 APPENDIX 2: SUBJECT INSTRUCTIONS FOR APPLICATION OF STUDY DRUG

NI-AC202 Subject Instructions for Application of Study Drug



Step 1: Before applying study drug

- Wash your hands and face gently using warm water with a mild cleanser and pat dry.

Step 2: Remove cap from the top of pump.

Step 3: Dispense study drug into the palm of your hand then mix together.

- The study drug comes in a pump dispenser. Place the pump dispenser about 1-3 inches from the palm of your opposite hand.
- By depressing the pump you simultaneously release a small amount of active ingredient or vehicle and hydrogel into the palm of your hand. After depressing the pump 3 times, put the pump down.
- With your free hand mix the active ingredient or vehicle and hydrogel together. Mix for 5-10 seconds until thoroughly combined.

Step 4: Immediately upon completing the mixing of the gels in your hand apply and massage into your entire face with your fingertips.

- Apply as if you were gently washing the area.
- Allow the study drug to dry. Do not rinse the area.

Avoid application to the eyes, lips and mucous membranes.

Store study drug in your refrigerator.

16.3 APPENDIX 3: DEFINITIONS FOR IGA SCORE

Grade	Description
0	Clear: Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost clear: Few non-inflammatory lesions with no more than 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 nodular lesion.
4	Severe: Up to many non-inflammatory and inflammatory lesions, including nodular lesions