STUDY TITLE	A Phase 2 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Ascending Dose Study Assessing Tolerability, Safety, and Efficacy of Topical NVN1000 in Subjects with External Genital Warts and Perianal Warts
PROTOCOL NO.	NI-WA201
SPONSOR	Novan, Inc. 4222 Emperor Blvd., Suite 200 Durham, NC 27703 Tel: 919-485-8080
AMENDMENT 3	22 Mar 2016
VERSION	4.0

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.

23 March 2016

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

Date

for Jason Scoggin.

22 Mar 2016

Jason P. Scoggin, MA, CCRA
Clinical Study Manager, Clinical Operations
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SAEs are to be reported in the Medidata RAVE database. If the database is not available then a paper SAE report form will be faxed to PPD at 1-888-529-3580.

Safety Hotline number- 1-888-483-7729
Safety Fax number-1-888-529-3580

PROTOCOL AMENDMENT

RATIONALE FOR AMENDMENT

This protocol amendment is being implemented to add a potential interim analysis for Cohorts 1 and 2. Results of the interim analysis will be used internally to facilitate planning of additional studies. The amendment will also serve to provide clarification regarding females of childbearing potential.

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 and minor formatting changes have been incorporated and not defined below.

Change 1: PROTOCOL BODY: Section 4.1, Study Procedures and Methods, Subject Entry Procedures, Paragraph 4

A female is considered to be of childbearing potential **if she is sexually active with a non-sterilized male partner** UNLESS she is post-menopausal (no menses for 24 consecutive months), surgically sterilized, or without a uterus and/or both ovaries.

Change 2: PROTOCOL BODY: Section 7.1, Statistical Analysis, General Considerations, Paragraph 2

An interim analysis may be conducted upon completion of Cohorts 1 and 2. A detailed description of the statistical methodology and data reporting for **the interim and complete analysis for** this study will be provided in the Statistical Analysis Plan (SAP).

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "A Phase 2 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Ascending Dose Study Assessing Tolerability, Safety, and Efficacy of Topical NVN1000 in Subjects with External Genital Warts and Perianal Warts" 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: NVN1000	
Title	A Phase 2 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Ascending Dose Study Assessing Tolerability, Safety, and Efficacy of Topical NVN1000 in Subjects with External Genital Warts and Perianal Warts
Study Objectives	The objectives of this study are to assess tolerability, safety and efficacy of NVN1000 Gel in the treatment of external genital warts (EGW) and perianal warts (PAW).
Study Population	Approximately 120 male and female subjects, age 18 -50 years, with a minimum of 2 and a maximum of 20 warts at screening.
Treatment Regimens	Topical application of NVN1000 Gel mixed with an equal volume of hydrogel applied to warts for up to 12 weeks.
Formulation	**Investigational Products:** NVN1000 Gel: 8%, 16%, and 24% Vehicle Gel NVN1000 and Vehicle Gel will be co-administered with an equal volume of a phosphate buffered carboxymethyl cellulose based hydrogel to be dispensed and mixed prior to application.
Study Design	This is a phase 2, multi-center, double-blind, randomized, vehicle-controlled, variable dose study to be conducted in approximately 120 non-immunocompromised adult subjects with EGW/PAW. After obtaining informed consent, subjects will be randomized 3:1 to active and vehicle treatment. After 12 subjects enrolled in each cohort have completed 2 weeks of treatment, the DSMB will review the available safety and tolerability data. Using predetermined criteria documented in the DSMB charter, the DSMB will determine if the data supports escalating to the next highest dose. Alternatively, other recommendations may be made based on safety/tolerability review, such as continued dosing at the same or lower dose frequency for subsequent cohort(s). A cohort will include all subjects dosed with the same dose/dose frequency. The standard operating procedures of the DSMB will be documented in the DSMB charter, including the board's accountability to Novan. NVN1000 Gel and Vehicle Gel will be co-administered with an equal volume of a cellulose based hydrogel provided to the subjects. The subjects will dispense a pea-sized amount (approximately 250 mg) of the NVN1000 Gel or Vehicle Gel and a pea-sized amount (approximately 250 mg) of the hydrogel and mix the two gels together prior to application of the mixed gel to their warts.

	Subjects will apply the study drug (NVN1000 Gel or Vehicle Gel) for up to 12 weeks, to all warts identified at baseline and new warts that arise during treatment. Warts that clear during the treatment period will not continue to be treated. Safety and tolerability assessments will include: adverse events, laboratory assessments (including chemistry, hematology, coagulation times, and measurement of methemoglobin by pulse co-oximetry), and local application assessments. The primary efficacy endpoint will be the proportion of subjects with complete clearance of baseline warts at or before Week 12. Secondary endpoints will include the time to clearance, the decrease in overall wart burden (complete or partial clearance), and the total number of warts at Week 12.
Main Inclusion / Exclusion Criteria	**Inclusion Criteria:** • Be male or female, 18-50 years old, and in good general health; • Have between 2 and 20 external genital warts/perianal warts, with a maximum total wart surface area less than the area of the subject's palm (approximately 1% BSA); • Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) prior to randomization; • 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; • Be willing and able to follow study instructions and likely to complete all study requirements; **Exclusion Criteria:** • History of neoplasia including cervical intraepithelial neoplasiaon 2/3, invasive cervical carcinoma, or other HPV associated malignancies within 5 years or current neoplasia (with the exception of non-melanoma skin cancer on non-genitals); • Any recent (< 6 months) history of other genital infections, or other genital diseases including Bowens disease, Lichen Sclerosis et Atrophicus, Bowenoid papulosis, erythroplasia of Querat, verrucous carcinoma, lichen planus, and psoriasis that requires use of interfering topical or systemic therapy or makes evaluations and wart counting inconclusive; • Have active HSV infection of the genitals as defined by initial outbreak within the 2 weeks prior to screening or during the screening period or frequent recurrences (more than 4 events within one year prior to screening) if not receiving HSV suppressive therapy; • Have received treatment for EGW/PAW during the 28 days prior to

	baseline including podophyllotoxin, imiquimod, sinecatechins, or surgical procedures (cryotherapy, laser surgery, cold steel, electorfulgeration); • Have a confirmed methemoglobin level of > 3.0% at Screening or Baseline per handheld pulse co-oximeter device; • Have hemoglobin at Screening < 10 g/dL.
Sample Size	Approximately 120 subjects will be randomized into the study in a 3:1 ratio of active:vehicle in 4 different cohorts.
Safety/Tolerability Assessments	Adverse events reported from the time of informed consent through end of the final study visit will be collected. Methemoglobin will be measured at Baseline, Week 2, and Week 12/early termination (ET). Vital signs (blood pressure and pulse) will be measured at Baseline, Weeks 2, 4, 8 and 12/ET. Clinical laboratory tests (hematology, chemistry, and coagulation times) will be collected at Screening, Baseline and Week 12/ET. Tolerability will be assessed by the Investigator at Baseline and Weeks 2, 4, 8, and 12/ET.
Endpoints	**Tolerability Endpoint**: Tolerability of NVN1000 Gel and Vehicle Gel will be collected using a 4 point tolerability scale to assess erythema, erosions/ulcers, edema and stinging/burning. **Safety Endpoints:** Safety endpoints will include adverse events, changes in physical examination including vital signs and changes in laboratory examination including methemoglobin. Any clinically significant changes noted during the physical exam as well as from the vital sign measurements or laboratory examinations will be recorded as adverse events and included in the comparison. **Efficacy Endpoints:** For all efficacy analyses, unless otherwise specified, efficacy will be based on warts which are present at baseline. Selected summaries will be presented for total warts. Total wart summaries will be based on any wart(s) observed at the given visit, including warts that were not present at baseline. <u>Primary</u> • Proportion of subjects with complete clearance of baseline EGW/PAW at or before Week 12 <u>Secondary</u> • Proportion of subjects with complete clearance of total EGW/PAW at or before Week 12 • Proportion of subjects with a complete or partial clearance of baseline EGW/PAW at or before Week 12. A partial clearance is defined as a reduction in the number of baseline warts

	• Proportion of subjects with complete clearance of baseline EGW/PAW at Weeks 2, 4, 8 and 12 • Proportion of subjects with complete clearance of total EGW/PAW at Weeks 2, 4, 8 and 12 • Proportion of subjects with a complete or partial clearance of baseline EGW/PAW at Weeks 2, 4, 8 and 12 • Percent reduction in baseline EGW/PAW wart counts at Weeks 2, 4, 8 and 12 • Count of baseline warts and count of total warts at Weeks 2, 4, 8 and 12 • Time to complete clearance of baseline warts • Recurrence of baseline warts cleared prior to Week 12

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
BSA	Body Surface Area
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ET	Early Termination
EGW	External Genital Warts
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine Device
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LOCF	Last Observation Carry Forward
MedDRA	Medical Dictionary for Regulatory Activities
NOVAN	Novan, Inc.
OTC	Over-the-Counter
PAW	Perianal Warts
PP	Per-Protocol
PPD PVG	PPD Pharmacovigilance
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

External genital warts (EGW) and perianal warts (PAW) are a common sexually transmitted disease due to infection with human papillomavirus (HPV). Current EGW/PAW treatments include local destructive procedures and topical treatments. These treatments are associated with local application site adverse reactions and wart recurrence rates of 10-30%.

Nitric oxide is a free radical gas naturally produced by the human body which has anti-virucidal and anti-inflammatory activity. Novan, Inc. has developed a topical gel containing NVN1000, a drug which releases nitric oxide to the skin after application. In an animal model of skin papillomas, topical NVN1000 gel prevented wart growth in a dose responsive fashion.

NVN1000 is also in development for the treatment of acne vulgaris. To date, approximately 400 subjects have been treated with topical NVN1000, and 200 subjects have been treated with the Vehicle Gel. In the completed studies for acne vulgaris, NVN1000 has been generally safe and well tolerated.

Novan is conducting this Phase 2, variable dose, randomized, double-blind study to assess tolerability, safety and efficacy of topical NVN1000 in subjects with EGW/PAW.

1.2 INVESTIGATIONAL PRODUCT

NVN1000 delivers nitric oxide from micron sized polysiloxane macromolecules in the presence of water. The active agent, NVN1000, is formulated in an alcohol-based topical gel and will be dispensed in multi-use 15-gram tubes. In the proposed study, the NVN1000 Gel will be the same as in the acne vulgaris trials; the hydrogel co-administered with NVN1000 Gel will have a different chemical composition.

Table 1: Characteristics of Investigational Product

	Investigational Products	
Name of Active Ingredient	NVN1000	None
Drug Name/ Concentration	NVN1000 8% Gel, NVN1000 16% Gel, or NVN1000 24% Gel	Vehicle Gel
Manufacturer	Novan, Inc.	Novan, Inc.
Packaging	15g aluminum tubes	15g aluminum tubes
Storage Requirements	Refrigerated, 2-8 °C prior to dispensing to subject; store at room temperature after dispensing.	Refrigerated, 2-8 °C prior to dispensing to subject; store at room temperature after dispensing.
Appearance Post-Mixing	Opaque white gel	Opaque white gel
Dosing Schedule	Twice daily, Once daily, or Once Daily 3 Times per Week on Non-Consecutive Days	Twice daily, Once Daily, or Once Daily 3 Times per Week on Non-Consecutive Days
Route of Administration	Topical Application	Topical Application

Subjects in this study will dispense a pea-sized (approximately 250 mg) of NVN1000 Gel per application to be mixed with an equal volume of hydrogel. The mixed product will be applied to each EGW/PAW identified by the investigator and to approximately 1 cm of surrounding skin. The maximal dose of NVN1000 per application is depicted in the table below.

Table 2: NVN1000 Dosing Calculations

NVN1000 Gel Dose	Amount NVN1000 (mg) per application	Amount NVN1000 per treatment area (mg/cm^2) per application
8%	20	0.114
16%	40	0.227
24%	60	0.341

1.3 NONCLINICAL STUDIES WITH NVN1000

The development program for NVN1000 includes 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 miniature pigs (at NVN1000 Gel doses of 4, 8, and 16% which corresponds to SB204 doses of 2, 4, and 8%, respectively) for 13 weeks (10% TBSA), systemic exposure (blood levels) of nitrate and silicon were not statistically different from background levels and there were no significant toxicologic findings in treated animals. 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 and minipigs with the NVN1000 Gel have led to no systemic exposure to NVN1000 or related compounds following repeated topical administration.

NVN1000 Gel will be co-administered with a carboxymethyl cellulose hydrogel in this Phase 2 study in EGW/PAW. A 28-day bridging study in minipigs with NVN1000 Gel 8% and 16% coadministered with the carboxymethyl cellulose hydrogel has completed the in-life portion with no significant local application site events. Histologic analysis and toxicokinetic analysis will be completed prior to first dosing of subjects with EGW/PAW.

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 intraperitoneal (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 eight completed clinical studies, approximately 250 subjects have been treated with NVN1000 Gel or SB204 Gel and approximately 150 subjects have been treated with Vehicle Gel. No treatment related SAEs have been reported and the AE profile has been similar in subjects treated with active (NVN1000 or SB204 Gel) and Vehicle Gel. 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 in physical examinations.

A cross-over pharmacokinetic (PK) study (NI-AC101) was conducted in 18 subjects with moderate to severe acne. Subjects received nine applications of SB204 8% Gel (containing NVN1000 Gel 16%) 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. There was no systemic exposure to hydrolyzed MAP3, a marker for exposure to the parent compound, NVN1000, and no difference in serum nitrate levels on Day 1 or Day 5 in subjects treated with NVN1000 Gel 8% twice daily. Subjects treated in the PK study (NI-AC101) received 288 mg of NVN1000/application. Subjects in the NI-WA201 study will receive a maximum amount of NVN1000 per application of 20 mg twice daily (Cohort 1); 20 mg once daily (Cohort 2); 40 mg (16%) once daily (Cohort 3); or 60 mg (24%) once daily (Cohort 4).

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

Table 3: Completed Clinical Studies in the Acne Development Program

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 HealthyVolunteers	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 inHealthy Volunteers	Healthy volunteers ≥ 18 years of age with elevated P. *acnes* counts	15	NVN1000 8% Gel NVN1000 8% Gel 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 17% BSA 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

External warts (EGW) and perianal warts (PAW) are sexually transmitted diseases caused by infection with papillomaviruses. In the Shope Cottontail rabbit animal model, topical application of NVN1000 Gel inhibited growth of wild type and mutant papillomavirus (Coggan, 2014).

Nitric oxide released from NVN1000 is anticipated to be pharmacologically active in the skin with no systemic exposure to NVN1000 or nitric oxide. In a 5-day cross-over pharmacokinetic study in adults with moderate to severe acne in which NVN1000 Gel at a final concentration of 8% (SB204) was applied to 17% BSA, there was no systemic exposure to NVN1000 and no difference in serum nitrate levels following repeated topical administration.

Dermal toxicology studies have demonstrated minimal evidence of toxicity in a 13-week miniature pig study, low dermal irritation in rabbits, and no dermal sensitization in guinea pigs. Local application site events in a 13-week dermal toxicology study in rats 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.

The independent DSMB will monitor safety and tolerability.

Topical application has been associated with local application-site reactions including erythema, peeling, scaling, 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 and in two subjects in the first cohort dosed in this study with NVN1000 Gel 8% or Vehicle Gel. Within 2 weeks of dosing, these subjects developed severe erythema, burning or erosions leading to treatment discontinuation. At the time of this protocol amendment, it is unknown which treatment these subjects received.

Based on the known mechanism of action of nitric oxide, theoretical risks from systemic exposure following topical administration of NVN1000 Gel include hypotension and headache. There have been no reports of hypotension or clinically significant changes in vital signs in subjects treated with NVN1000. Reports of headache in the NVN1000 Gel development program are the same in NVN1000 Gel and Vehicle Gel treated subjects.

Methemoglobinemia has been reported in patients treated with inhaled nitric oxide. In the NVN1000 development program, there have been no clinically significant changes in methemoglobin following topical NVN1000 application in over 250 subjects treated in 8 clinical trials. Methemoglobin will be monitored during the study via a hand-held co-oximeter and treatment stopped in any subject with a confirmed methemoglobin > 5.0%. A confirmed

methemoglobin is defined as at least two readings within 0.5% of each other taken within a 30 minute period.

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, application site 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.

Based on available data, Novan anticipates that the risks to subjects enrolling in this escalating dose Phase 2 study in subjects with EGW/PAW 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 EGW/PAW following treatment with NVN1000 for 12 weeks; there is no anticipated benefit for subjects randomized to Vehicle Gel.

2. RATIONALE AND OBJECTIVES

2.1 STUDY RATIONALE

Novan is conducting this study to evaluate the tolerability, safety and efficacy of variable doses of NVN1000 8% Gel, NVN1000 16% Gel, NVN1000 24% Gel and Vehicle Gel administered to EGW/PAW.

Subjects will dose for up to 12 weeks (84 days $\pm$ 5) with NVN1000 Gel or Vehicle Gel co-administered with an equal volume of a carboxymethyl cellulose hydrogel. Approximately 250 mg (a pea-sized amount) of NVN1000 Gel or Vehicle Gel and an equal volume of hydrogel will be dispensed per application. The subjects will mix the two gels together and then apply to the surface of the warts and approximately 1 cm of surrounding skin (maximum of 1% TBSA to be treated). Subjects will be randomized 3:1 to active:vehicle in four dose cohorts initiated at NVN1000 8% Gel. Based on the previous human safety data with NVN1000 Gel at up to 16% as well as the nonclinical safety data, this dose is expected to be safe and well tolerated. The safety/tolerability of each cohort will be assessed by an independent DSMB after the first 12 subjects of each cohort complete two weeks of dosing.

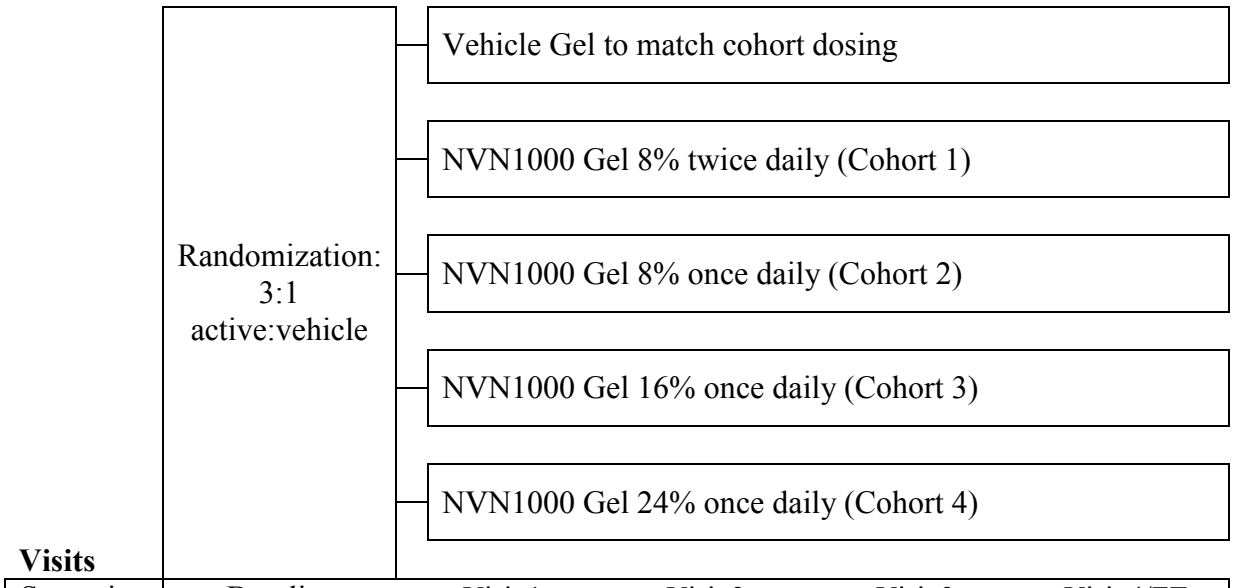
2.2 STUDY OBJECTIVES

The objectives of this study are to assess tolerability, safety and efficacy of topical NVN1000 Gel and Vehicle Gel for up to 12 weeks in subjects with EGW/PAW.

3. STUDY DESIGN

Figure 1 depicts the study design for each cohort in this 12-week, variable dose, randomized, double blind study in subjects with EGW/PAW dosed with NVN1000 Gel or Vehicle Gel. Subjects receiving current treatment for EGW/PAW may enter a wash out period after screening of up to 35 days prior to randomization.

Figure 1: Study Diagram (For Each Cohort)



Visits					
Screening	Baseline	Visit 1	Visit 2	Visit 3	Visit 4/ET
Day -35 to Day -1	Day 0	Day 14	Day 28	Day 56	Day 84
	Study Week	2	4	8	12

3.1 STUDY ENDPOINTS

3.1.1 EFFICACY ENDPOINTS

For the primary efficacy analyses, efficacy will be based on warts which are present at baseline.

Selected summaries will be presented for total warts counts, including warts present at baseline and warts that arise during the treatment period. Total wart counts will be based on any wart(s) observed at the given visit, including warts that were not present at baseline.

3.1.1.1 PrimaryEndpoint

The primary endpoint is the proportion of subjects with complete clearance of baseline EGW/PAW at or before Week 12

3.1.1.2 Secondary Endpoints

Secondary endpoints include:

- Proportion of subjects with complete clearance of total EGW/PAW at or before Week 12
- Proportion of subjects with a complete or partial clearance of baseline EGW/PAW at or before Week 12. A partial clearance is defined as a reduction in the number of baseline warts
- Proportion of subjects with complete clearance of baseline EGW/PAW at Weeks 2, 4, 8 and 12
- Proportion of subjects with complete clearance of total EGW/PAW at Weeks 2, 4, 8 and 12
- Proportion of subjects with a complete or partial clearance of baseline EGW/PAW at Weeks 2, 4, 8 and 12
- Percent reduction in baseline EGW/PAW wart counts at Weeks 2, 4, 8 and 12
- Count of baseline warts and count of total warts at Weeks 2, 4, 8 and 12
- Time to complete clearance of baseline warts
- Recurrence of baseline warts cleared prior to Week 12

3.1.2 TOLERABILITY ENDPOINTS

The tolerability assessments include the Investigator's assessment of erythema, edema, erosions/ulcers, and the subject's report of burning/stinging based on the preceding 24 hours on a 4-point (0-3) scale (Section 4.3).

3.1.3 SAFETY ENDPOINTS

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

3.2 STRUCTURE

This is a variable dose, double-blind, multi-center, randomized, vehicle-controlled, 4-arm study. Dosing initiated at NVN1000 8% Gel twice daily. Amendement 1 modified Cohort 2 dosing to NVN1000 8% once daily based on local intolerability observed in two subjects randomized in Cohort 1. Cohort 3 will be dosed with NVN1000 16% once daily and Cohort 4 will be dosed with NVN1000 24% once daily. An independent Data Safety Monitoring Board (DSMB) will review

tolerability and safety data approximately 2 weeks after randomization of the 12th subject in each cohort to determine whether dosing shall change. Subjects will continue to enroll and accrue in the open dosing cohort pending the DSMB review. Upon completion of the DSMB review, the recommendations of the DSMB regarding dosing will be implemented.

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 (±5) days of treatment.

3.4 DOSAGE/DOSE REGIMEN

Approximately 250 mg of NVN1000 8% Gel, NVN1000 16% Gel, NVN1000 24% Gel, or Vehicle Gel will be mixed with an equal volume of hydrogel at each application. The mixed gel will be applied to the surface of all external genital and perianal warts identified by the Investigator and to approximately 1 cm of surrounding normal skin, for a period of up to 84 (± 5) days. Subjects in Cohort 1 dosed twice daily. The dose frequency for Cohort 2 and Cohort 3 is once daily. Cohort 4 will be implemented after review by the DSMB of safety and tolerability of Cohort 3. If dosing is well tolerated in Cohort 3, the DSMB may recommend increasing the strength of NVN1000 to 24%. After reviewing the safety and tolerability results for Cohort 3, the DSMB may also recommend extending enrollment in Cohort 3 or decreasing the dose to Cohort 2. A similar data review will occur after enrollment of 12 subjects in Cohort 4 (NVN1000 24% vs Vehicle).

The test product and the hydrogel will be dispensed from 15 g aluminum tubes and stored by the subject at room temperature. The NVN1000 Gel and Vehicle Gel will be opaque and the hydrogel will be clear. The product should be mixed for 5-10 seconds until thoroughly combined with a uniform opaque appearance then applied.

NVN1000 Gel and Vehicle Gel are similar in appearance, have similar mixing characteristics, and can not be differentiated by gross inspection.

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 120 otherwise healthy, non-immunocompromised male and female subjects between the ages of 18 and 50 (inclusive) with EGW/PAW will be randomized to participate in the study. Eligible subjects will have at least 2 but no more than 20 EGW/PAW.

3.7 ELIGIBILITY CRITERIA

3.7.1 INFORMED CONSENT AND AUTHORIZATION TO RELEASE HEALTH INFORMATION

Written informed consent 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. A subject willing to participate must give written informed consent 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 must be forwarded to PPD for approval prior to submission to an Institutional Review Board (IRB) as appropriate. An IRB approved informed consent form specific for this study will be provided to each subject to read and sign. 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 legal representative (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 document(s) shall be signed and dated by both the subject and legal representative (where applicable) and the person obtaining consent (Investigator or designee), and by any other parties required by the IRB or other regulatory authorities. 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);
2. Be male or female, 18 to 50 years of age, inclusive and in good general health;
3. Have a minimum of two but not more than 20 EGW/PAW with a maximum total wart surface area less than the area of the subject's palm (approximately 1% BSA);

4. If currently receiving treatment for EGW/PAW at the time of screening, be willing to discontinue treatment for 28 days prior to randomization and during the study;
5. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) prior to randomization;
6. WOCBP must agree to use an effective method of birth control during the course of the study and for 30 days after their final study visit;
7. Be willing and able to follow study instructions and likely to complete all study requirements.

3.7.3 EXCLUSION CRITERIA

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

1. History of neoplasia including cervical intraepithelial neoplasia 2/3, invasive cervical carcinoma, or other HPV associated malignancies within 5 years or current neoplasia (with the exception of non-melanoma skin cancer on non-genitals);
2. Any recent (< 6 months) history of other genital infections, or other genital diseases including Bowens disease, Lichen Sclerosis et Atrophicus, Bowenoid papulosis, erythroplasia of Querat, verrucous carcinoma, lichen planus, and psoriasis thatrequires use of interfering topical or systemic therapy or makes evaluations and wart counting inconclusive;
3. Have active HSV infection of the genitals as defined by initial outbreak within the 2 weeks prior to screening or during the screening period or frequent recurrences (more than 4 events within one year prior to screening), if not receiving HSV suppressive therapy;
4. Presence of broken or non-intact skin near the wart site;
5. Have received treatment for EGW/PAW during the 28 days prior to baseline including podophyllotoxin, imiquimod, sinecatechins, or surgical procedures (cryotherapy, laser surgery, cold steel, electorfulgeration);
6. Subjects using or requiring short- or long-acting nitrates, nitric oxide donor drugs or supplements (e.g., arginine, citrulline) or drugs associated with methemoglobinemia;
7. Immunocompromised subjects including those who are known HIV positive or receiving current immunosuppressive treatment, including radiation therapy, non-inhaled corticosteroids (inhaled corticosteroid ≤ 1000 ug daily dose is acceptable), or chemotherapy;
8. Treatment within 30 days or during the study with any immunosuppressant agents including corticosteroids or biologics that target the immune system;
9. Have a history of hypersensitivity or allergic reactions to any of the ingredients in the NVN1000 Gel or Vehicle Gel as described in the Investigator's Brochure;

10. Have a confirmed methemoglobin level of > 3.0% at Screening or Baseline per handheld pulse co-oximeter device;
11. Have hemoglobin at Screening < 10 g/dL;
12. Subjects with warts solely involving the urethral meatus; peri-meatal warts will not be treated or counted;
13. Subjects with known internal (vaginal, cervical, urethral, rectal) warts;
14. Female subjects who are pregnant, nursing mothers, or planning to become pregnant during the study;
15. Subjects scheduled to undergo endoscopy with use of topical anesthetics;
16. Have any condition or situation which, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study including clinically significant chronic medical or psychiatric conditions, or a recent (within two years) history of alcohol or substance abuse;
17. Are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
18. Have used an investigational drug or device within 30 days of Baseline or concurrent participation in a different interventional research study;
19. Have participated in a previous study with NVN1000 Gel or SB204 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 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, wart counts, adverse event assessment, concomitant medication review and UPT) must be completed prior to randomization. Subjects with hemoglobin < 10 g/dL 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 includes oral contraceptives, IUD, implant, NuvaRing®, medroxyprogesterone injection, transdermal patch or abstinence with a documented second method of birth control should the subject become sexually active.

A female is considered to be of childbearing potential if she is sexually active with a non-sterilized partner UNLESS she is post-menopausal (no menses for 24 consecutive months), surgically sterilized, or without a uterus and/or both ovaries.

After the required procedures are completed and study eligibility is confirmed, the subject will be randomized to treatment utilizing an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) which will identify the study kit 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.

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

Table 4: Schedule of Visits and Procedures

SCHEDULE OF EVENTS

PROCEDURES	Screening (Day -35 – Day -1)	Visit 1 Baseline (Day 0)	Visit 2[1] Week 2 ±3 days (Day 14)	Visit 3 Week 4 ±5 days (Day 28)	Visit 4 Week 8 ±5 days (Day 56)	Visit 5 Week 12/ET[2] ±5 days (Day 84)
Informed Consent	X					
Demographics/Smoking	X					
Medical History	X	X				
Medication History	X	X				
Inclusion/Exclusion	X	X				
Brief Physical Examination	X	X[3]				X
Chemistry, Hematology, PT/PTT	X	X[3]				X
Urine Pregnancy Test	X	X[3]		X	X	X
Methemoglobin[4]	X	X	X			X
Blood Pressure and Pulse	X	X	X	X	X	X
Wart Counts	X	X	X	X	X	X
Tolerability Evaluation[5]		X	X	X	X	X
Instruct on Study Drug Application and Provide Subject Instructions		X				
Dispense Dosing Diary		X		X	X	
Collect Completed Dosing Diary				X	X	X
Study Drug Dispensed		X		X	X	
Study Drug Collected				X	X	X
Subject Compliance			X	X	X	X
Concomitant Medications		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 7 calendar days of the Screening visit, Physical Examination, Chemistry, Hematology, PT/PTT, and UPT do not need to be repeated.

[4] Collected via pulse co-oximetry at site.

[5] Tolerability Assessments are defined in Section 4.3

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 NVN1000 Gel with the subject and obtain written informed consent.
2. Obtain demographic information and smoking history.
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 using Masimo hand held pulse co-oximeter device and instructions provided by the sponsor.
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 wart counts.
10. Collect chemistry, hematology, and PT/PTT.
11. Confirm subjects meet eligibility criteria.
12. Review prohibited medications, treatments, and supplements that should not be used prior to Baseline and during the trial.
13. Collect AEs related to study procedures performed since signing of informed consent.
14. 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 using Masimo hand held co-oximeter device and instructions provided by the sponsor.

5. Collect blood pressure and pulse rate.

6. Collect chemistry, hematology, and PT/PTT.

7. Perform wart counts and mark all wart locations on source documents. The EGW and PAW will be counted and recorded separately.

8. Confirm eligibility and randomize subject.

9. Perform tolerability assessment.

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

11. 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.).

12. Confirm the study schedule with the subject.

NOTE: If the Baseline Visit is within 7 calendar days of the Screening visit, Physical Examination, Chemistry, Hematology, PT/PTT, and UPT do not need to be repeated.

4.1.3 WEEK 2 (DAY 14 ± 3)

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 using Masimo hand held pulse co-oximeter device and instructions provided by the sponsor.
4. Collect blood pressure and pulse rate.
5. Perform tolerability evaluation.
6. Perform wart counts and mark location of all warts on source documents. The EGW and PAW will be counted and recorded separately for baseline and total wart counts.
7. Review study drug compliance, subject diary for completion; identify reasons for missed applications.
8. Review study drug application instructions with subject, ensuring drug supply is sufficient and confirm areas to be treated.
9. Review and confirm the study schedule with the subject.

4.1.4 WEEK 4 (DAY 28 ± 5)

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 tolerability evaluation.
6. Perform wart counts and mark location of all warts on source documents. The EGW and PAW will be counted and recorded separately for baseline and total wart counts.
7. Collect returned study drug and diary, perform accountability, review study drug compliance and study drug application instructions with subject and confirm areas to be treated.
8. Review subject diary for completion; identify reasons for missed applications.
9. Dispense new study drug and diary.
10. Review and confirm the study schedule with the subject.

4.1.5 WEEK 8 (DAY 56 ± 5)

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 tolerability evaluation.
6. Perform wart counts and mark location of all warts on source documents. The EGW and PAW will be counted and recorded separatelyfor baseline and total wart counts.
7. Collect returned study drug and diary, perform accountability, review study drug compliance and study drug application instructions with subject and confirm areas to be treated.
8. Review subject diary for completion; identify reasons for missed applications.
9. Dispense new supply of study drug and diary.
10. Review and confirm the study schedule with the subject.

4.1.6 WEEK 12/ET (DAY 84 ± 5)

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 using Masimo hand held pulse co-oximeter device and instructions provided by the sponsor.
6. Collect blood pressure and pulse rate.
7. Collect chemistry, hematology, and PT/PTT.
8. Perform tolerability evaluation.
9. Perform wart counts and mark location of all warts on source documents. The EGW and PAW will be counted and recorded separately for baseline and total wart counts.
10. Collect returned study drug and diary, perform accountability, and review study drug compliance with subject.
11. Review subject diary for completion; identify reasons for missed applications.

4.1.7 DISCONTINUATION/WITHDRAWAL PROCEDURES

A subject may voluntarily withdraw from study participation at any time, for any reason. 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 adhered to (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 PPD, 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 (one call, two separate days) 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 PPD 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 PPD and the Investigator will ensure that proper study discontinuation procedures are completed.

4.2 EFFICACY ASSESSMENTS

The same blinded evaluator should perform EGW/PAW 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/ET evaluations.

The evaluator will count all EGW/PAW and identify baseline warts. The location of all warts will be marked on source documents. EGW/PAW will be counted and recorded separately for baseline and all warts. At each study visit, the evaluator will note location of all warts, including new warts that have arisen since the last subject visit.

4.2.1 WART COUNTS

EGW/PAW counts will be captured separately and the location of the warts marked on source documents. The baseline warts and the total wart counts will be counted at Baseline and all post-treatment visits. EGW/PAW that arise during the study will be identified, marked on source documents and reported separately for post-baseline visits.

If an EGW/PAW clears during treatment, as determined by the Investigator, the subject will discontinue study drug application for that specific EGW/PAW, but other EGW/PAW will continue to be treated. For baseline warts that clear during treatment, the Investigtor will assess recurrence of treated and cleared EGW/PAW on subsequent study visits.

If all warts (those present at baseline and new warts that develop during the study) clear, as determined by the Investigator, the subject will not continue to apply study drug and will remain in the study for all scheduled post-baseline assessments to assess for wart recurrence.

4.3 TOLERABILITY ASSESSMENTS

The Investigator will evaluate the subject's genital/perianal area prior to the first application of investigational product in addition to evaluating at each study visit. The tolerability assessment for visits other than Baseline should be performed at least 30 minutes after study drug application and prior to wart counts. Tolerability evaluations will include erythema, edema, erosions/ulceration and burning/stinging. Burning/stinging will be based on the subject's report

of local symptoms for the previous 24 hours. The highest severity of each parameter will be recorded. Tolerability endpoints will not be reported as an AE unless they reach severe and/or result in subject's discontinuation from the study. 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

Edema

Score	Description
0-None	No edema
1-Mild	Mild edema; barely perceptible
2-Moderate	Moderate swelling localized to the wart and immediately adjacent skin
3-Severe	Extensive edema that involves non-treatment sites adjacent to treatment area

Erosions/Ulceration

Score	Description
0-None	No erosions
1-Mild	Slight erosions on some treated areas
2-Moderate	Erosions over half of the treated areas
3-Severe	Extensive full-thickness erosions over most treatment areas; or at least one area of ulceration

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. Clinically significant changes in lab results post screening will be recorded as adverse events. Subjects with hemoglobin < 10 g/dL at Screening 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 confirmed methemoglobin values of > 3.0% at Screening or Baseline will not be eligible to participate in the study. Subjects with confirmed values >5.0% during the study will be discontinued. A confirmed methemoglobin is defined as at least two readings within 0.5% of each other taken within a 30 minutes period.

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 5.

Table 5: 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.

Pregnancy tests will also be performed at Weeks 4, 8, and 12/ET. If a subject is determined to be pregnant prior to or during Week 12/ET visit, the subject will be discontinued from the study but followed until term. The outcome of the pregnancy, including status of the neonate, will be submitted.

4.5 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 be allowed to rescreen once within the 35-day screening period.

4.6 PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact PPD and the IRB, if applicable, at

the earliest possible time. All deviations as well as actions taken as the result of the significant must be documented.

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 Baseline Visit until the final evaluation (Week 12/ET).

Subjects must not have used anti-wart treatments including topical treatments or procedures as described in Section 3.7.3 for at least 28 days prior to Baseline. These medications/treatments are also prohibited during the trial.

Subjects may not be concurrently on nitroglycerin, drugs associated with methemoglobinemia, drugs to treat EGW/PAW, 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 interventional research study during the study period. Any subject who has participated in a previous study with SB204 Gel/NVN1000 Gel is ineligible for enrollment.

Any medication/therapy used by the subject following first application of study product will be considered a concomitant medication/therapy (e.g., aspirin, acetaminophen, birth control pills, vitamins, etc.). Every attempt should be made to keep concomitant medication/therapy dosing constant during the study. Any change to concomitant medications/therapies should be noted on the subject's study record and in the study database. When applicable, an AE should be completed for any subject starting a concomitant medication/therapy after randomization 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 PPD 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 as described in Section 6.5.

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 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, PPD 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) and pregnancy are considered immediately reportable events. Any SAE, whether deemed drug-related or not, must be reported to PPD by telephone or FAX within 24 hours after the Investigator or coordinator has become aware of its occurrence. Within 24 hours of notification of the event, the Investigator/coordinator must complete a Serious Adverse Event (SAE) Form in the subject's eCRF. When appropriate, Novan will notify the appropriate regulatory body of drug related Serious Adverse Events.

Serious Adverse Event (SAE) and Safety Contact Information:

PPD PVG SAE Hotline: 1-888-483-7729
PPD PVG SAE Fax: 1-888-529-3580

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

1. Report the SAE or pregnancy by telephone or fax (within 24 hours) to PPD PVG after the Investigator becomes aware of the event.
2. Complete an SAE within the eCRF or fax Pregnancy Report Form to PPD PVG 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 PPD 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 oral contraceptives, IUD, implant, NuvaRing®, injection, transdermal patch or abstinence with a documented second acceptable method of birth control should the subject become sexually active.

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

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

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

- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

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

During the study, WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle). Subjects found to be pregnant prior to Week 12 will be discontinued from the study. PPD PVG 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 or ongoing.

6.5.2 FOLLOW-UP OF POST STUDY SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) that are identified on the last scheduled contact (Week 12/ET) must be recorded in the study database and reported to PPD 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's health has returned to baseline status, until all parameters have returned to normal, remaining health issues have otherwise been explained, or the subject is lost to follow-up. The Investigator should continue to report any significant follow-up information to PPD 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 PPD 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, edema, erosions/ulcers, burning/stinging) shall be discontinued from the study.

Subjects with a confirmed methemoglobin > 5.0% at any post-baseline visit will be discontinued from the study. A confirmed methemoglobin is defined as at least 2 readings within 0.5% of each other taken within a 30 minutes period.

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 9.2 or higher 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 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.

An interim analysis may be conducted upon completion of Cohorts 1 and 2. A detailed description of the statistical methodology and data reporting for the interim and complete analysis 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 Per-Protocol (PP) population will include subjects who complete the Week 12 evaluation without noteworthy study protocol violations (e.g., 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:

- Have taken any interfering concomitant medications
- Have missed more than one interim study visit that they would have been eligible to attend as their EGW/PAW had not completely resolved
- Have not been compliant with the dosing regimen (e.g., subjects must apply 80-120% of the expected applications of study medication during participation in the study)

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, smoking history) 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.

7.5 EFFICACY ANALYSIS

Efficacy will be assessd based on wart counts at baseline and each evaluation through Week 12. Summaries based on baseline wart counts and counts for total warts will be presented.

7.5.1 PRIMARY EFFICACY ANALYSIS

The number and proportion of subjects with complete clearance of baseline warts will be summarized by treatment group and each active dose group will be compared to vehicle using pairwise Pearson's chi-square tests. The odds ratios and corresponding 95% CI will be presented. The pairwise comparisons of each active treatment group to the Vehicle Gel treatment group will be computed without concern for controlling for multiplicity.

Percentages will be calculated out of the number of subjects in the analysis population. Subjects who have a clearance of baseline warts at or before the Week 12 visit will be counted as cleared for the analysis. Subjects who do not have a documented clearance by the end of study, including subjects with missing data at the Week 12 or other assessments, will be considered not cleared for the analysis.

7.5.2 SECONDARY EFFICACY ANALYSES

The number and proportion of subjects with complete clearance of total warts, and the number and proportion of subjects with complete or partial clearance of baseline warts at or by Week 12 will be assessed in a similar manner to the primary efficacy endpoint. The response over time will be similarly assessed for the proportion of subjects and total number of warts with complete clearance of baseline and total EGW/PAW. The time to complete clearance of baseline warts will be summarized. Each active dose group will be compared to vehicle using pairwise Pearson's chi-square tests and the odds ratios and corresponding 95% CIs will be presented.

For those subjects in whom complete clearance of baseline warts is achieved prior to Week 12, recurrence of baseline warts will be assessed.

Descriptive summaries will be provided for percent change in baseline wart counts and total wart counts. Each active dose group will be compared to vehicle using pairwise t-tests and the corresponding 95% CIs for the differences in treatment means will be presented. Subgroup analysis for gender and wart location (EGW/PAW) will also be performed.

The secondary endpoints will include:

- Proportion of subjects with complete clearance of total EGW/PAW at or before Week 12;
- Proportion of subjects with a complete or partial clearance of baseline EGW/PAW at or before Week 12. A partial clearance is defined as a reduction in the number of baseline warts;
- Proportion of subjects with complete clearance of baseline EGW/PAW at Weeks 2, 4, 8 and 12;

- Proportion of subjects with complete clearance of total EGW/PAW at Weeks 2, 4, 8 and 12;
- Proportion of subjects with a complete or partial clearance of baseline EGW/PAW at Weeks 2, 4, 8 and 12;
- Percent reduction in baseline EGW/PAW wart counts at Weeks 2, 4, 8 and 12;
- Count of baseline warts and count of total warts at Weeks 2, 4, 8 and 12;
- Time to complete clearance of baseline warts;
- Recurrence of baseline warts cleared prior to Week 12.

7.6 TOLERABILITY ANALYSIS

Tolerability assessments (erythema, edema, erosions/ulcerations, burning/stinging) will be summarized using frequency distributions at Baseline, Weeks 2, 4, 8, and 12/ET, as well as the worst post-baseline assessment. The number and proportion of subjects with a severe assessment or a two step severity increase from baseline will be summarized by treatment group at Weeks 2, 4, 8 and 12/ET for each assessment and for any assessment. In addition, shift tables will be presented.

7.7 SAFETY ANALYSIS

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 Investigator 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

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

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

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

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

This study is not powered to detect a statistical difference in efficacy between treatment groups. Approximately 120 subjects will be randomized into the study in a 3:1 ratio at approximately 10 sites in the US. The number of subjects enrolled in any dosing cohort is dependent on the recommendations of the DSMB and enrollment rates. The main objective of this study is to evaluate the tolerability, safety and efficacy of topical NVN1000.

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 kits 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. Study drug will be kept refrigerated up until the time it is dispensed to subjects. After it is dispensed, it can be kept at room temperature.

If a study staff member becomes aware that the study supplies have not been properly handled (i.e., supply arrives and was not placed in refrigerator upon receipt, the subject left study drug in hot vehicle over the weekend), 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 PPD personnel. Other supplies will be stored at room temperature.

8.3 TREATMENT ASSIGNMENT AND BLINDING

Subjects will be randomized within each cohort to NVN1000 Gel or Vehicle Gel in a 3:1 ratio through utilization of the IVRS/IWRS. The evaluator, Investigator, and subject will be blinded to the subject's treatment. NVN1000 Gel and Vehicle Gel are similar in appearance and can not be differentiated.

8.4 UNBLINDING OF TREATMENT ASSIGNMENT

In the event that a subject should experience an adverse event for which it is medically required to break the blind in order to determine appropriate treatment, unblinding can be achieved by using the IVRS or IWRS. 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. Although not required, the Investigator should contact PPD Medical Monitor prior to breaking the blind.

8.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

- Dates and initials of person designated as responsible for the inventory of the investigational product
- Amount received including date
- Amount currently in refrigerator, 2-8 °C storage
- Kits 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,etc.)
- Amount returned to Novan or designee, 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, PPD, or their designees or by regulatory agencies at any time.

8.6 CLINICAL SUPPLIES RETURN AND DESTRUCTION

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

9. RECORDS MANAGEMENT

9.1 DATA COLLECTION

The full details of procedures for data handling will be documented in the Data Management Plan.

Source study records will be collected for each study subject and a study database will be maintained for all randomized study subjects.

Novan and PPD 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, PPD 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 PPD, 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, PPD 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 PPD 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 PPD and Novan at any time for review and audit to ensure the integrity of the data. The Investigator must notify PPD 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 PPD 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 PPD 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 PPD 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 PPD 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, PPD 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 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 PPD 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 PPD 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.

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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-wart medications including but not limited to imiquimod, condylox, sinecatechins
- Benzocaine & Cetacaine sprays
- Corticosteroids (oral)
- Dapsone
- EMLA Creams
- Chloroquine
- Flutamide
- L-arginine
- L-citrulline
- Lidocaine
- Nitric oxide supplements
- Nitrates
- Nitric oxide
- Nitroglycerin
- Nitroprusside
- Nitrous oxide