Novan Therapeutics

NI-WA201

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

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Statistical Analysis Plan

Version *2.2*

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan version 2.2, dated 30 JAN 2017. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
CI	confidence interval
DSMB	data safety monitoring board
eCRF	electronic case record form
ET	early termination
EGW	external genital warts
FDA	Food and Drug Administration
HPV	human papilloma virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ITT	intent-to-treat
IVRS/IWRS	interactive voice response system/interactive web response system
LOCF	last observation carry forward
MedDRA	Medical Dictionary for Regulatory Activities
NOVAN	Novan, Inc.
PAW	perianal warts
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAS	statistical analysis software
SOC	system organ class
TEAE	treatment-emergent adverse events
TIW	three times a week
UPT	urine pregnancy test
WHODD	World Health Organization Drug Dictionary
WOCBP	women of child-bearing potential

1. Introduction

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 NVN1000 Gel, and 200 subjects have been treated with the Vehicle Gel. In the completed studies for acne vulgaris, NVN1000 Gel 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.

2. 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. Investigational Plan

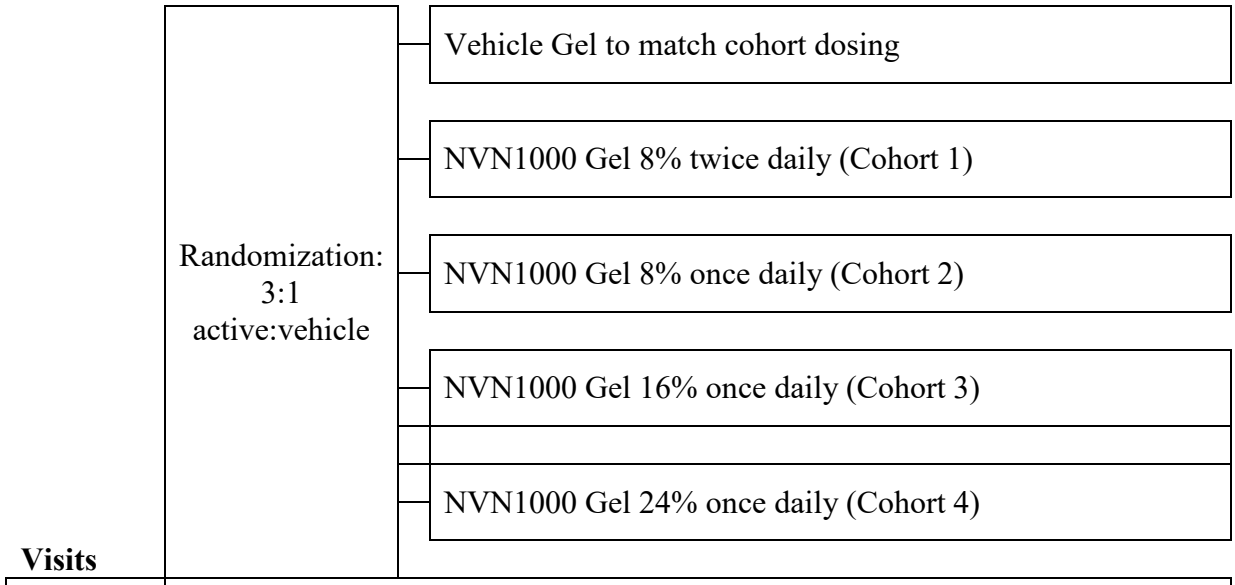
3.1. Overall Study Design and Plan

Subjects will dose for up to 12 weeks (84 days) with NVN1000 Gel or Vehicle Gel co-administered with an equal volume of a carboxymethyl cellulose hydrogel. Subjects will be randomized 3:1 to active:vehicle in 4 dose cohorts initiated at NVN1000 8% Gel. The safety/tolerability of each cohort will be assessed by an independent data safety monitoring board (DSMB) after the first 12 subjects of each cohort complete 2 weeks of dosing.

Figure 3–1 depicts the overall study design for 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.

Subjects who are found to be cleared of all warts at a visit will discontinue treatment at that time. If warts recur at a subsequent visit prior to end of treatment, subjects will be dispensed a new kit of the same treatment they previously received.

Figure 3–1: Study Diagram



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

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

- Proportion of subjects with complete clearance of baseline EGW/PAW at or before Week 12

3.2.2. Secondary Efficacy Endpoints

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
- Count of baseline warts and count of total warts at Weeks 2, 4, 8, and 12
- Percent and raw reduction in baseline EGW/PAW wart counts at Weeks 2, 4, 8, and 12
- Time to complete clearance of baseline warts
- Recurrence of baseline warts cleared prior to Week 12

3.2.3. 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.

3.2.4. Safety Endpoints

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

4. General Statistical 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. All p-values will be reported without concern for controlling for multiplicity. 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 as defined in section 4.3.2

Continuous data will be summarized with sample size (N), mean, median, standard

deviation, minimum and maximum. Categorical data will be summarized with number of subjects N, frequency counts, and percentages.

For analysis, baseline warts are defined as warts that are present at the baseline visit. Total warts include all warts present, even if they were not present at the baseline visit. Complete clearance is defined as zero warts present. Partial clearance is defined as a reduction in number of warts from baseline.

The last evaluation for each endpoint prior to the first dose of study drug will be used as baseline for all analyses.

For safety analyses including tolerability, summaries will be performed by treatment arm as well as "Pooled Active", which is a total of all NVN1000 treatment arms.

For disposition, demographics, efficacy, compliance and tolerability analyses, Vehicle Gel subjects will be summarized separately by dosing frequency (QD and BID). For other safety analyses, vehicle subjects will be combined. Subjects will be listed by actual treatment, with vehicle subjects listed separately by dosing frequency.

For subjects who are taken off treatment due to complete clearance of warts and then later restart treatment due to recurrent warts, the date of last dose for analysis purposes will be the date of last dose for the second treatment interval.

4.1. Sample Size

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 (active:vehicle) at approximately 15 sites in North America. 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 Gel.

4.2. Randomization, Stratification, and Blinding

Subjects will be randomized to variable doses of NVN1000 or Vehicle Gel in a 3:1 ratio (active:vehicle) through utilization of the interactive voice response system/interactive web response system (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 cannot be differentiated.

In the event that a subject should experience an AE for which it is medically required to break the blind in order to determine appropriate treatment, unblinding can be achieved by using the IVRS/IWRS administrator. A study subject for whom the blind is broken

will discontinue study product and will be scheduled for a follow- up safety visit and be encouraged to stay in the study until the AE is resolved or stabilized. Although not required, the Investigator should contact PPD medical monitor prior to breaking the blind.

Randomization treatment assignment and actual treatment received will be presented in a by subject listing.

4.3. Analysis Populations

4.3.1. Intent-to-Treat Population

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

4.3.2. 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. The statement that a subject had no AEs constitutes a safety assessment.

4.3.3. Per-Protocol Population

The PP population will include subjects with no noteworthy study protocol deviations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy) prior to initial clearance of baseline warts, or Week 12/early termination if the subject does not achieve complete clearance at any time during the study. The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated inclusion/exclusion criteria which have a potential impact on efficacy
- Have taken any concomitant medications likely to impact efficacy
- 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 (i.e., subjects must apply 80-120% of the expected applications of study medication during participation in the study)

All significant protocol deviations will be documented in the Significant Protocol Deviations Rules document. Each significant deviation will be assigned a rule number and indication (yes/no) if the deviation will result in subject exclusion from the PP population. 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 deviations. A by subject listing will be presented including the reason subjects are not included in any analysis population.

4.4. Assessment Windows

4.4.1. Study Day

When study day is used for display or in comparisons the following algorithm will be used:

- study day = date of assessment - date of first dose of study medication +1, if date of assessment ≥ first dose date.
- study day = date of assessment - date of first dose of study medication, if date of assessment < first dose date.

Note that this definition differs from the protocol in that the date of first dose of study medication is Day 1. The day before the date of first dose of study medication is Day -1. Study day for analysis is defined as per SDTM definition which does not include a study day Day 0.

4.4.2. Visit Windows

By-visit analyses will be performed using the reported CRF visit. The one exception is the Week 12/ET visit. For safety endpoints that are not measured at every visit (e.g. lab values and vital signs), the Week 12/ET will be mapped to Week 12 but presented in tables/listings as Week 12/ET. For all other endpoints, for subjects who complete the study, the Week 12/ET visit will be mapped to "Week 12" and used in by visit analyses. For subjects who are early terminations, the Week 12/ET visit will be mapped to "ET" (early term and will not be included in the by visit analyses. The ET visit may be used for LOCF of missing data. The ET visit will be carried forward only to visits for which the ET visit occurred prior to on the last study day of the analysis visit window using the following windows:

Table 1: Analysis Visit Windows

Analysis Visit	Visit Window (Based on Study Day)
Week 2	Day 2 to Day 22
Week 4	Day 23 to Day 45
Week 8	Day 46 to Day 71
Week 12	Day 72 +

5. Subject Disposition

5.1. Study Population

The number of subjects who were randomized and the number and percentage of subjects within each analysis population (ITT, safety, and PP) will be summarized for each treatment group for all randomized subjects. Vehicle Gel subjects will be separated into QD and BID groups. All percentages will be calculated based on the number of randomized subjects. A by subject list indicating subject's inclusion in each analysis population and reason(s) that subject is excluded from an analysis population will be presented.

5.2. Disposition

The counts and percentages of subjects who completed or discontinued from the study will be presented based on the number of subjects in each treatment group and overall for all randomized subjects. Vehicle Gel subjects will be separated into QD and BID groups. The reasons for study discontinuation will also be summarized. All percentages will be based on the number of subjects randomized. Subject disposition data will be listed as well.

5.3. Protocol Deviations

Protocol deviations will be tracked by the clinical team on an on-going basis. Specific criteria for what constitutes a significant protocol deviation will be documented in the Significant Protocol Deviations Rules document as noted above in section 4.3.3. Subjects with significant protocol deviations and protocol deviations which result in exclusion from the PP population will be tabulated for each treatment group and listed by subject for all randomized subjects. Vehicle Gel subjects will be separated into QD and BID groups. All percentages will be based on the number of subjects randomized.

6. Demographics and Baseline Characteristics

6.1. Demographics

Subject demographic and baseline characteristics will be summarized by treatment group and listed by subject for the ITT population. For continuous variables (e.g., age), mean, median, standard deviation, minimum and maximum will be presented. Categorical variables (e.g., ethnicity, race, smoking history, wart location at baseline [EGW only, PAW only, EGW and PAW]) will be summarized with frequency count and percentage by treatment group. Vehicle Gel subjects will be separated into QD and BID groups.

6.2. Medical History

Medical history will be collected in the Electronic Case Report Form (eCRF) at the screening and baseline visits and verbatim terms will be coded classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology, which will be updated whenever possible throughout the life of the study. Medical history will be summarized by the number and percentage of subjects with any medical history reported by coded system organ class, preferred term, and treatment group for the ITT population. Vehicle Gel subjects will be separated into QD and BID groups. A subject listing will also be included with start date and end date or ongoing status.

6.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations noted in the eCRF will be presented for the set of randomized subjects in a data listing.

7. Treatments and Medications

7.1. Concomitant Medications

Any medicinal product, prescribed or over-the-counter (OTC), including herbal products, vitamins, and minerals is considered a concomitant medication. Any medications used during the study will be coded with the World Health Organization Drug Dictionary (WHODD), which will be updated whenever available throughout the life of the study.

Concomitant medication use will be recorded in the eCRF beginning on baseline after the first dose of study medication until the final visit (Week 12/ET visit). Any changes in concomitant medications will also be recorded in the subject's eCRF.

Summary of concomitant medications by treatment group and preferred term will be provided. All concomitant medications will be presented in data listings. Concomitant medications will be summarized for the safety population.

7.2. Study Treatments

Approximately 250 mg of NVN1000 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 days. The test product and the hydrogel will be dispensed from separate 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.

7.2.1. Exposure and Compliance

Duration of exposure will be calculated in days as date of last dose of study medication– date of first dose of study medication+ 1. Percent compliance will be calculated as the number of total doses received divided by the number of planned doses times 100. The number of planned doses will be calculated as follows:

2 times the duration (days) of exposure - 1 for cohorts dosing twice daily,

and

1 time the duration (days) of exposure for cohorts dosing once daily,

The number of doses received will be calculated as the number of planned doses minus the total number of missed doses as indicated in the subject diaries. Descriptive statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum for duration of study exposure and percent compliance will be provided by treatment group using the safety population. Vehicle Gel subjects will be separated into QD and BID groups for both exposure and compliance summaries. Compliance and treatment duration will also be listed by subject.

In addition, number of missed doses for each subject based on subject diaries will be summarized in a frequency table and listed by subject. Doses missed specifically for tolerability reasons will likewise be summarized in a frequency table and listed by subject.

For subjects who experience complete clearance, the number of missed doses and compliance will only be calculated up to and including the date of the first visit where the subject had a total wart count of 0. Any subsequent dosing due to recurrent warts will not be considered for analysis of missed doses or compliance.

8. Efficacy Analysis

Efficacy data is collected at each study visit. Wart count data including derived primary and secondary endpoint data such as complete clearance, time to complete clearance, time to recurrence, etc. will be presented in listings by subject. Subjects may receive more than one course of treatment if they experience complete clearing and subsequent recurrence of warts. Assessment of time to clearing, time to recurrence, and clearing at or before Week 12 will be assessed based on the initial treatment course (i.e., first instance of clearing/recurrence only.) For efficacy assessments by visit (i.e., at Weeks 2, 4, 8 and 12), data will be summarized without regard to treatment course. (e.g., assessments at Week 8 may include data for subjects still on their initial treatment course as they have not yet achieved clearance, subjects off treatment as they have previously cleared but not yet

experienced a recurrence, and subjects on a second course of treatment after prior clearance and recurrence.)

Wart count data including derived primary and secondary endpoint data such as complete clearance, time to complete clearance, time to recurrence, etc. will be presented in data listings by subject.

8.1. Primary Efficacy Endpoint

8.1.1. Proportion of Subjects with Complete Clearance of Baseline EGW/PAW at or Before Week 12

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

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 Mantel-Haenszel odds ratios and corresponding 95% confidence interval (CI) will be presented. The Vehicle Gel arm will be separated into once-daily (QD) and twice-daily (BID) groups and compared pairwise to the corresponding active treatments. The three once-daily active treatment groups (8%, 16%, and 24%) will be compared to the Vehicle Gel QD group and the NVN1000 8% BID group will be compared to the Vehicle Gel BID group. The pairwise comparisons will be computed without concern for controlling for multiplicity. The primary analysis will be performed for the ITT population.

Percentages will be calculated based on the number of subjects in the ITT analysis population. Subjects who have 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.

The primary analysis will be repeated for the PP population. Subgroup analysis for gender and wart location (EGW/PAW) will also be performed for the ITT population. The subgroup summaries will be descriptive only with no statistical hypothesis testing performed.

8.2. Secondary Efficacy Endpoints

The secondary efficacy analysis will be performed for both ITT and PP.

8.2.1. Proportion of Subjects with Complete Clearance of Total EGW/PAW at or Before Week 12.

The number and proportion of subjects with complete clearance of total EGW/PAW will be summarized by treatment group and each active dose group will be compared to its corresponding vehicle group using pairwise Pearson's chi-square tests. The Mantel-Haenszel odds ratios and corresponding 95% CI will be presented.

Subjects who have 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.

Subgroup analysis for gender and wart location (EGW/PAW) will also be performed for the ITT populations. The subgroup summaries will be descriptive only with no statistical hypothesis testing performed.

8.2.2. Proportion of Subjects with Complete or Partial Clearance of Baseline EGW/PAW at or Before Week 12

The number and proportion of subjects with complete or partial clearance, defined as a reduction in the number of baseline EGW/PAW, will be summarized by treatment group and each active dose group will be compared to its corresponding vehicle group using pairwise Pearson's chi-square tests. The Mantel-Haenszel odds ratios and corresponding 95% CI will be presented.

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

8.2.3. Proportion of Subjects with Complete Clearance of baseline EGW/PAW at Weeks 2, 4, 8, and 12

The number and proportion of subjects with complete clearance of baseline EGW/PAW at each post-baseline visit will be summarized by treatment group and each active dose group will be compared to its corresponding vehicle group using pairwise Pearson's chi-square tests. The Mantel-Haenszel odds ratios and corresponding 95% CI will be presented.

Imputation of missing data will be performed using a last-observation carried forward (LOCF) method where a missing assessment is replaced by the previous visit's assessment.

8.2.4. Proportion of Subjects with Complete Clearance of Total EGW/PAW at Weeks 2, 4, 8, and 12.

The number and proportion of subjects with complete clearance of total EGW/PAW at each visit will be summarized by treatment group and each active dose group will be compared to its corresponding vehicle group using pairwise Pearson's chi-square tests. The Mantel-Haenszel odds ratios and corresponding 95% CI will be presented.

Imputation of missing data will be performed using a last-observation carried forward (LOCF) method where a missing assessment is replaced by the previous visit's assessment.

8.2.5. Proportion of Subjects with Complete or Partial Clearance of Baseline EGW/PAW at Weeks 2, 4, 8, and 12.

The number and proportion of subjects with complete or partial clearance, defined as a reduction in the number of warts, of baseline EGW/PAW at each post-baseline visit will be summarized by treatment group and each active dose group will be compared to its corresponding vehicle group using pairwise Pearson's chi-square tests. The Mantel-Haenszel odds ratios and corresponding 95% CI will be presented.

Imputation of missing data will be performed using a last-observation carried forward (LOCF) method where a missing assessment is replaced by the previous visit's assessment.

8.2.6. Percent and Raw Reduction in Baseline EGW/PAW Counts at Weeks 2, 4, 8, and 12.

Descriptive summaries will be provided for percent and raw change in baseline wart counts at each visit. Raw change will be calculated as (post-baseline count – baseline count). Percent change will be calculated as (post baseline count – baseline count) divided by baseline count times 100. Each active dose group will be compared to its corresponding vehicle group using pairwise t-tests and the corresponding 95% CIs for the differences in treatment means will also be presented.

Imputation of missing data will be performed using a last-observation carried forward (LOCF) method where a missing assessment is replaced by the previous visit's assessment.

8.2.7. Count of Baseline Warts and Count of Total Warts at Baseline and Weeks 2, 4, 8, and 12

Descriptive summaries will be provided for count of baseline warts and count of total warts at each visit. Each active dose group will be compared to its corresponding vehicle group using pairwise t-tests and the corresponding 95% CIs for the differences in treatment

means will also be presented. The mean total number of baseline warts and total number of total warts by visit will also be graphically displayed.

Imputation of missing data will be performed using a last-observation carried forward (LOCF) method where a missing assessment is replaced by the previous visit's assessment.

8.2.8. Time to Complete Clearance of Baseline Warts

The time to complete clearance of baseline warts is calculated as the number of days between the date of first dose of study medication and the date that the baseline wart count is 0. Subjects who do not have clearing of baseline warts will be censored at the date of their last study assessment.

Kaplan-Meier (KM) estimates of clearance rates at Week 2, Week 4, Week 8 and Week 12 and their 95% CIs will be presented by treatment group. Vehicle Gel subjects will be separated into QD and BID groups. For estimates by week, week will be defined by the maximum day allowable by the visit windows (e.g., the summary for Week 2 will count all subjects with clearance on or before Day 18.) Because clearance is a positive outcome, clearance rates for each week will be calculated as (1 – the KM survival probability estimate). The median time to clearing and 95% CI for each treatment group will also be summarized. Inverse KM curves based on (1 – the KM survival probability estimates) will be plotted to describe the estimated proportion of subjects with clearance over time for each treatment group.

8.2.9. Recurrence of Baseline Warts Cleared Prior to Week 12

The time to recurrence of baseline warts which have previously cleared is calculated as the number of days between the first date that baseline wart count is 0 and the first date after that for which baseline wart count is > 0. Subjects who do not have recurrence of baseline warts after clearing will be censored at the date of their last study assessment.

Kaplan-Meier estimates and plots will be presented for the time to recurrence in a similar manner to that described above for time to clearing; however as recurrence is negative outcome, the KM curves will be based on the KM survival probability estimates. Also, as clearing can occur at any visit, the KM estimates of recurrence will be based on 14 day intervals from the date of clearing: 2 Weeks (14 days), 4 Weeks (28 days), 6 Weeks (42 days), 8 Weeks (56 days), and 10 Weeks (70 days) post clearing. KM curves will be presented for each treatment arm, with Vehicle Gel subjects separated into QD and BID groups.

8.3. Tolerability Endpoints

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

Tolerability assessments (erythema, edema, erosions/ulcerations, burning/stinging) will be summarized using frequency distributions at baseline, Weeks 2, 4, 8, and 12/ early termination (ET), as well as the worst post-baseline assessment. The worst post-baseline assessment will be determined individually for each tolerability parameter. (e.g., the worst assessment for erythema may occur at a different visit than the worst assessment for edema.) 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. Vehicle Gel subjects will be separated into QD and BID groups. Additionally, the number and percentage of subjects

who have 2 or more severe assessments at the same visit for any visit will be presented. A shift table will also be presented by tolerability parameter and treatment group, and all tolerability scores will be listed.

9. Safety Analysis

9.1. 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, and occur within 30 days of the last study drug dose. Adverse events noted prior to the first study drug administration that worsen after baseline will also be reported as TEAEs and included in the summaries.

All information pertaining to an AE noted during the study will be listed by subject, detailing verbatim term given by the principal 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 to study drug initiation (in number of days). Listings will be provided for all TEAEs, adverse events prior to date of first treatment, and adverse events starting more than 30 days after last study drug use.

9.1.1. Incidence of Adverse Events

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug. Adverse events will be deemed treatment emergent if the onset date is on or after the date of first treatment, Day 1. Events with onset date during the screening period are not treatment emergent and will be listed separately.

The total number of TEAEs and the number and percentage of subjects with at least one TEAE in each SOC and having each individual TEAE based on the PT will be presented.

9.1.2. Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship to study drug will be presented in a table by total number of TEAE and incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug as Unrelated, Unlikely, Possible, Probable, and Definite. The latter three categories would constitute "Related." If a subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented in the incidence count. Treatment-emergent AEs that are missing a relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of subjects in the safety population.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table by total number of TEAE and incidence of occurrence. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are "Mild," "Moderate," and "Severe." In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented in the incidence count. Treatment-emergent AEs that are missing severity will be presented in tables as "Severe" but will be presented in the data listing with a missing severity. Percentages will be calculated based on the number of subjects in the safety population.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

9.1.4. Serious Adverse Events

Serious TEAEs will be presented in a table. At each level of subject summarization, a subject is counted once for the incidence if the subject reported one or more events. Percentages will be calculated based on the number of subjects in the safety population.

The treatment-emergent SAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.5. Serious TEAEs, Deaths and Adverse Events Leading to Treatment or Study Discontinuation

A listing of all Serious TEAEs (including deaths) and/or AEs leading to treatment or study discontinuation will be presented. Additionally, a separate listing of any deaths will be presented. Deaths and discontinuations will be assessed based on data recorded in the AE eCRF page. Subject deaths will be identified as AEs where the outcome is "Fatal". Adverse events leading to treatment discontinuation will be identified as AEs where the action taken with study drug is "Drug Withdrawn". Adverse events leading to study discontinuation will be identified as AEs where the caused study discontinuation field is marked as "Yes".

9.2. Clinical Laboratory Evaluations

The majority of laboratory assessments will be performed by a central laboratory. All summaries will be based on the units provided by the central laboratory and no conversion will be performed. Lab test names listed in the statistical analysis plan are the same as indicated in the protocol; however the tables and listings will report results using the test names based on CDISC controlled terminologies.

Blood chemistry, hematology, and PT/PTT values will be reported individually at screening, baseline, and Week 12/ET. Laboratory test results will be summarized descriptively at baseline and Week 12/ET. Changes from baseline to Week 12/ET in laboratory test results based on normal ranges will be summarized with descriptive statistics. Any clinically significant changes from baseline will be documented as an AE. Blood chemistry, hematology, and PT/PTT data will also be presented in data listings by subject.

Methemoglobin will be reported as a percentage of hemoglobin. Methemoglobin will be summarized descriptively by treatment group at baseline and Weeks 2 and 12/ET. Additionally, the change from baseline in methemoglobin will be summarized by treatment group at Weeks 2 and 12/ET. Methemoglobin data will also be presented in data listings by subject.

For the above laboratory tests, ET visits will be summarized as Week 12/ET regardless of when the visit occurs as the tests are not performed at every visit.

Urine pregnancy test results, performed at Screening, Baseline, and Weeks 4, 8, and 12, for women of child-bearing potential (WOCBP) will be presented in data listings by subject.

9.3. Vital Sign Measurements

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 Weeks 2, 4, 8, and 12. Any clinically significant changes from baseline will be documented as an AE. All visit sign measurement data will be listed.

9.4. Physical Examination

Any clinically significant changes from baseline will be documented as an AE. All physical examination data will be listed.

10. Interim Analysis

There will be 4 Data Safety Monitoring Board (DSMB) meetings during the conduct of this study to evaluate safety and tolerability prior to dose modification. A subset of the final safety and tolerability tables and listings, will be provided to the DSMB for review. Outputs to be provided to the DSMB are documented in the DSMB charter. No inferential statistics or hypothesis testing is planned for the DSMB analyses. DSMB analyses will be unblinded to actual treatment. The analyses for the DSMB will be performed by a separate, independent statistics team.

In addition, an Interim Analysis including efficacy summaries will be conducted upon completion of Cohorts 1 and 2 to assist in the planning of future trials. No stopping rules for futility or early efficacy assessment will be applied as part of the interim analysis. The analysis will only be conducted on the subjects in cohorts 1 and 2, and a subset of tables from the primary analysis will be presented. Pairwise comparisons will be done between each active treatment in the cohorts and Vehicle Gel and nominal p-values will be presented without adjustment. Additionally, no adjustments will be made to p-values in the final analysis as a result of the interim analysis.

The analysis set for the interim analysis will be subjects randomized into one of the first two cohorts. All subjects randomized on or prior to the last randomization date entered into IVRS for Cohort 2 will be included.

Table 2: Interim Analysis Outputs

Table	Population
Table 14.1-1 Subject Disposition	All Randomized Subjects

Table 14.1-2 Demographics and Baseline Characteristics	Intent-to-Treat Population
Table 14.2-1.1 Complete Clearance of Baseline EGW/PAW at or Before Week 12	Intent-to-Treat Population
Table 14.2-1.3 Complete Clearance of Baseline EGW/PAW at or Before Week 12 by Gender	Intent-to-Treat Population
Table 14.2-7.1 Percent Change in Baseline EGW/PAW at Weeks 2, 4, 8, and 12	Intent-to-Treat Population
Table 14.2-9.1 Count of Total Warts at Weeks 2, 4, 8, and 12	Intent-to-Treat Population
Table 14.3-1 Study Drug Exposure (Days) and Missed Doses	Safety Population
Table 14.3-3.1 Summary of Tolerability Evaluations	Safety Population
Table 14.3.1-2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population

11. Appendices

11.1. Schedule of Study Procedures

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 of the protocol