NCT03487549

Statistical Analysis Plan

Protocol Title	A Phase 2, Open Label Study to Evaluate the Efficacy, Safety and Tolerability of VP-102 in Subjects with Common Warts (Verruca Vulgaris)
Protocol Number:	VP-102-105 (Cohort 2)
Protocol Version:	V3- 01 November 2018
SAP Version:	V1
Date:	July 25th, 2019
Sponsor:	Verrica Pharmaceuticals, Inc. 10 North High Street, Suite 200 West Chester, PA 19380
Author:	Instat Services

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

SAP Document History

Version Number	Author	Date	Change
V1		25JUL2019	

Signatures / Approvals

Biostatistician, Instat Services	Name (Print or Type)	Date

Verrica Pharmaceuticals	Name (Print or Type)	Date

Table of Contents

List of Abbreviations

AE	Adverse Event
ATC Class	Anatomical/Therapeutic/Chemical Class
BMI	Body Mass Index
CSR	Clinical Study Report
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
ERT	Evaluation of Response to Treatment
IRB	Institutional Review Board
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
LSR	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
PERIT	Patient Evaluation of Response to Investigational Treatment
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SERT	Safety Evaluation of Response Treatment
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, Listings
WHO	World Health Organization

1. Introduction

Verrica Pharmaceuticals, Inc. is conducting a study under the protocol name "A Phase 2, Open-Label Study to Evaluate the Efficacy, Safety and Tolerability of VP-102 in Subjects with Common Warts (Verruca Vulgaris)". The study background, design and subject assessments for the study are described in the study specific protocol.

The statistical methods to be implemented during the analyses of data collected within the scope of this study (VP-102-105) will be outlined in this document. The purpose of this plan is to provide specific guidelines from which the statistical analysis will proceed. Any deviations from this plan will be documented in the clinical study report.

This Statistical Analysis Plan (SAP) specifies the planned analyses and reporting of data from Cohort 2 of this study only, as described in Version 3 dated 01 November 2018 of the study protocol. Analyses of Cohort 1 or any future cohorts or study parts will be addressed in an updated or separate SAP.

2. Study Rationale and Objectives

2.1. Study Rationale

The protocol states: "For many dermatologists, 0.7% w/v cantharidin has been the treatment of choice for warts for decades. However, cantharidin remains an unapproved drug, and there is no reliable or controlled source on the market. This study will evaluate VP-102, a controlled, highly-pure, standardized form of topical cantharidin manufactured under good manufacturing practices to address the problems associated with currently available compounded cantharidin products and the needs of subjects and medical professionals."

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objectives for Cohort 2 are (1) to evaluate the efficacy of dermal application of VP-102 when applied once every 21 days for up to 4 applications to common warts on subjects 12 years and older by assessing the proportion of subjects achieving complete clearance of all treatable warts at the EOT Visit (Day 84) and (2) to assess the safety and tolerability of VP-102 applied to common warts by assessing adverse events including expected local skin reactions, physical examinations, and concomitant medications.

2.2.2. Secondary Objectives

The secondary objectives of this study are:

- to evaluate the efficacy of VP-102 by assessing the change from baseline in the

number of treatable warts (baseline and new) at the EOT visit (Day 84).

- to evaluate the efficacy of VP-102 by assessing the change from baseline in the percent of clearance of treatable warts (baseline and new) at the EOT visit (Day 84).
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4.

2.2.3. Exploratory Objectives

Exploratory objective is:

- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at follow-up visits on Days 105, 126 and 147.
- to assess endpoints other than clearance that may be indicative of treatment efficacy.

3. Study Design

This is a Phase 2, open label, multi-center study [Study number VP-102-105; referred to as COVE-1 (Cantharidin and Occlusion in Verruca Epithelium)] that will be conducted in the United States to determine the safety, efficacy and tolerability of VP-102 treatment in subjects with common warts.

This study has two Cohorts. The second Cohort (Cohort 2) utilizes a treatment interval of 21 days between treatments. Paring of lesions is allowed in Cohort 2 only. Approximately 35 subjects (12 years and older) will be enrolled in Cohort 2. Up to 4 sites will participate in the study.

All subjects will receive the Study drug VP-102 (0.7% w/v cantharidin topical film-forming solution). Duration of warts prior to Treatment Visit 1 must be at least 4 weeks.

Study drug (VP-102) will be supplied in single-use applicators, with one applicator having sufficient volume to treat 1-6 common warts. No more than 1 applicator will be permitted per subject per treatment. VP-102 will be applied and left on the warts, under occlusive tape, for 24 hours before the subject/guardian removes the occlusive tape and washes the warts with soap and warm water. Occlusive tape and Study drug may be removed prior to the 24-hour time point in the event significant blistering, significant pain or treatment-emergent adverse events (TEAEs) are experienced.

Treatment will be applied up to four times during a 75-day treatment period for Cohort 2. The treatment interval in Cohort 2 is 21 days.

It can sometimes be challenging to determine if a wart is completely clear after treatment due to ongoing local skin reactions. At any visit where the investigator is unable to evaluate or treat some warts due to ongoing local skin reactions, an "Unscheduled" Visit should be documented. The timing of the next visit will be determined by the resolution of the local skin reaction. A Treatment Visit should be documented at every visit where Study drug is applied. Treatment should only take place at a visit when all warts are evaluable (i.e., not obscured by an ongoing LSR) and all warts that are not completely clear, should undergo treatment with Study drug. No partial treatment of warts is permitted.

For Cohort 2, study drug is to be applied to the wart site on any Treatment Visit where a new clinical assessment of complete clearance is made for that wart (e.g., if a patient returns for Treatment Visit 2 and is clinically assessed to have no visible evidence of a remaining wart, then Study drug is still to be applied to this wart site at Treatment Visit 2. However, if the patient remains completely clear at that wart site when returning for a subsequent visit such as Treatment Visit 3, then no Study drug would be applied at Treatment Visit 3.) Should it become clear that the subject will be unable to complete the EOT visit within the allowed window of Day 84 (+/- 8) days, the subject should be brought in for their EOT visit as soon as they are able. This will be documented as a protocol deviation.

In instances where the clinician can adequately assess the treatment sites but is uncertain if a residual wart is remaining, treatment should be applied, and the subject should return for evaluation per protocol. Treatment visits and assessments are to take place in order (e.g., Treatment 1, Treatment 2, Treatment 3 and Treatment 4). Subjects that receive fewer than 4 treatments within the 75-day (Cohort 2) treatment period, due to the duration of post-treatment local skin reactions, will not be considered a protocol deviation. No treatment should be administered after the 75-day treatment period in Cohort 2 without Sponsor's approval.

Subjects in Cohort 2 will undergo wart paring with a sharp surgical instrument (e.g., scalpel or flexible medical blade) to remove any adherent thick scale from a wart prior to application of Study drug. Wart paring is to be performed at any Treatment Visit when adherent thick scale is present, and the investigator considers that it can be safely performed. Paring should be conducted by a trained practitioner and in compliance with any local regulations and should be discontinued when it results in punctate bleeding or significant pain. Not all warts may require paring and, if adherent scale is not present, then Study drug can be applied without paring. Subjects should be re-treated only after 17 days (i.e., 21 +/- 4 days) have elapsed in Cohort 2, but only after any LSR has resolved

sufficiently to allow evaluation of the treatment site. Treatment should be administered within 4 days of becoming eligible due to resolution of LSRs.

For Cohort 2, subjects are to attend all visits regardless of whether they have achieved complete clearance prior to and at the Day 84, (+/- 8 days) EOT assessment.

Subjects in Cohort 2 will participate in an in-person EOT evaluation at Day 84 (+/- 8). A provider EOT Questionnaire will be completed at the EOT Visit. Cohort 2 subjects will continue in the study for 3 additional follow-up assessments at Day 105, Day 126 and Day 147. The follow- up visit window is +/- 4 days.

To assist the research team in the ERT phone calls, education materials in the form of a local skin reaction guide with specific photos identifying the various skin reactions and examples of intensity will be reviewed at the clinic with the subject/guardian by the research team. Should a subject report experiencing excessive blistering, ulceration, edema, pain or another adverse event needing physician assessment during the ERT call, they will be scheduled for an "Unscheduled" study visit and safety evaluation as soon as possible.

Subjects 18 and older must provide consent as required by the IRB before any study procedures are conducted. Parents or guardians must provide informed consent, and pediatric subjects older than 10 years must provide assent as required by the IRB before any study procedures are conducted. Subjects must meet all study eligibility criteria through a complete review of pertinent medical history, a dermatologic exam/wart count and physical examination.

4. Determination of Sample Size

The study will enroll subjects with common warts for the main efficacy purpose of obtaining information on clearance rates of the warts in response to VP-102 therapy. Subjects will continue to be enrolled into Cohort 2 of the study until approximately 35 subjects are enrolled. Due to the exploratory nature of the study, no formal sample size estimates will be carried out for powering purposes.

5. Statistical Methods

The statistical analyses described in this document are specific to Cohort 2 of this study and will be reported using summary tables, figures and listings (TFLs). Numbering for TFLs will be based on the recommended numbering convention provided by the International Conference on Harmonization. Continuous variables will be summarized with means, standard deviations, medians, minimums and maximums. Categorical

variables will be summarized by counts and percent of subjects in corresponding categories. Where appropriate, 95% confidence intervals may be included. Missing values are not considered for percent calculations, unless stated otherwise. In those cases, footnotes will specify the percent basis.

Individual subject data obtained via the electronic data capture (EDC) system and from external vendors will be presented in listings.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock. Any analysis added after the database lock will be considered *post hoc* and exploratory. *Post hoc* analyses will be labeled as such on the output and identified in the CSR. All analyses and tabulations will be performed using SAS® version 9.3 or higher. Tables and listings will be presented in .rtf or .pdf format. Upon completion, all SAS programs will be validated by an independent programmer. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables and consistency between tables and corresponding data listings.

6. Analysis Populations

Intent to Treat (ITT) Population:

The Intent-to-Treat population (ITT) will include all subjects enrolled in the study.

Per Protocol Population:

Subjects who receive all 4 planned treatments of VP-102 (e.g., up to four treatments within the 75-day treatment window or cleared of all treatable warts prior to Day 75), are assessed for clearance at the EOT visit, and have no major protocol violations, will be included in the Per Protocol population. Major protocol deviations will be evaluated prior to excluding subjects from the per Protocol population. Major deviations will be determined via a clinical review of all deviations; criteria for major deviations include the following:

- Failure to obtain informed consent;
- Informed consent was incorrect or incomplete;
- Non-compliance with inclusion/exclusion criteria;

- IP administration/dosing errors;
- Non-compliance with study protocol procedures;
- Unreported serious adverse events.

In addition, the following pre-determined reasons will exclude subjects from being included in the Per Protocol population:

- Subjects who do not come in for required treatment visits
- Subjects who do not return for the EOT study visit
- Subjects who refuse to have all of their treatable warts treated or investigators who refuse to treat all treatable warts
- Early removal of the study drug not associated with pain, blistering or other medically appropriate reason for early removal. Early removal will be determined by the defined study window of 24 hrs +/- 8 hrs.
- Subjects who begin alternative treatments for their warts after starting the study
- Subjects enrolled who did not meet the inclusion/exclusion criteria

Safety Population:

The Safety population will include subjects who receive at least one treatment of VP-102.

7. Study Population

7.1. Subject Disposition

Information regarding subject disposition will be summarized for all subjects. Summaries will include: number of subjects in each analysis population, number of subjects who completed the treatment phase of the study, number of subjects assessed for clearance at the End of Treatment Visit (EOT), number of subjects completing the study, and number of subjects who discontinue the study early. Subjects will be considered to have completed the treatment phase of the study if they had a Day 84 (EOT) visit. In order for a subject to be considered to have completed the study, they must have completed their Day 147 visit. For those who discontinue early, the primary reason for early termination will be summarized.

7.2. Protocol Deviations

Protocol deviations will be collected throughout the duration of the study. Protocol deviations will be assigned a sponsor-defined category type. Each deviation will be defined as major or minor. A tabular summary of all major deviations will be generated.

In addition, a by-subject listing of all protocol deviations (major and minor) will be produced.

7.3. Demographic and Baseline Characteristics

Demographics variables will include: age, sex, ethnicity and race. For summary purposes, age will be derived by comparing date of birth to date of informed consent.

Baseline characteristics will include: relevant medical history, wart history (including prior treatment), Fitzpatrick Skin Type, height, weight and body mass index (BMI). BMI will be calculated by weight (kg) / height (m^2). Wart history variables that will be summarized include time since clinical diagnosis (as compared to informed consent), age at clinical diagnosis and any previous treatments for warts. Time since clinical diagnosis will be derived by comparing the date of informed consent to date of clinical diagnosis. Time since clinical diagnosis will be expressed in months using the following conversion: (12 * days) / 365.25. In the event the date of clinical diagnosis is not complete ("partial date"), the date will be imputed with the earliest date possible. As an example, if only the month and year are known for date of clinical diagnosis, the first day of the month will be used for imputation purposes.

Age at clinical diagnosis will be derived by comparing date of clinical diagnosis to date of birth. Incidence of the following prior wart treatment categories will be tabulated: Cantharidin, Anti-Virals, Retinoids, Salicylic Acid, Curettage, Freezing, Other. Relevant medical history will not be summarized in a table but will be displayed in a listing.

Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using counts and percentages. Demographics, baseline characteristics, wart history and prior wart treatment will be summarized for all 3 analysis populations (ITT, Safety, Per Protocol).

8. Efficacy Analysis

The ITT and Per Protocol population will be used for efficacy analysis. Analyses based on the ITT population will be considered the primary analyses. Results will be summarized using descriptive statistics and counts/percentages. For select endpoints, 95% confidence intervals may be generated as well.

On the Wart Location and Measurement case report form (CRF), wart information is collected for each individual wart. For the purpose of efficacy analysis, clearance of each wart needs to be determined using results collected on this page. A wart will be considered to have cleared for a particular visit when a wart is reported to have a diameter of 0 mm at that visit. Should a wart return after initial clearance, a diameter > 0 mm will be recorded, and the wart will not be considered cleared at that visit. Otherwise,

if the wart does not return, the check box "Wart has cleared" will be marked for subsequent visits. For the purpose of analysis, the wart will be counted as cleared at all visits where "Wart has cleared" has been marked.

Some efficacy endpoints will be summarized by treatment visit. Treatments are planned to occur every 21 days as long as warts are present for up to 4 treatments within the 75 day treatment period. Treatment may be delayed for various reasons including, but not limited to, ongoing local skin reactions (e.g. scabbing). As a result, the timing of when subjects receive treatment may vary. For the purpose of naming treatment visits, only visits when treatment was given or the check box "Wart has cleared" for all warts will be considered. Using this method, Treatment Visit 1 will be the 1st visit treatment was applied; Treatment Visit 2 will be the 2nd visit treatment was applied, etc. Visits when treatment was planned to be given but treatment was not applied or clearance was not achieved will be recorded as "Unscheduled".

For results to be considered for any by visit analyses, visits must be within visit windows as described in this section of the analysis plan. Results that are collected between Day 11 and Day 157 will be assigned to visits according to the visit windows described below, regardless of the name of the visit. Should two or more results be collected within a specific visit window, the visit closest to the planned day with a non-missing value will be used for analysis. Results from visits that occur outside the visit windows will not be considered for analysis, but will be included in study listings. The visit windows to be considered are as follows:

- Day 21- visit falls +/- 10 days from planned visit study day (i.e., between Day 11 and Day 31)
- Day 42- visit falls +/- 10 days from planned visit study day (i.e., between Day 32 and Day 52)
- Day 63- visit falls +/- 10 days from planned visit study day (i.e., between Day 53 and Day 73)
- End of Treatment (EOT) Visit- visit falls +/- 10 days from planned visit study day (i.e., between Day 74 and Day 94)
- Day 105- visit falls +/- 10 days from planned visit study day (i.e., between Day 95 and Day 115)
- Day 126- visit falls +/- 10 days from planned visit study day (i.e., between Day 116 and Day 136)
- Day 147- visit falls +/- 10 days from planned visit study day (i.e., between Day 137 and Day 157)

8.1. Efficacy Variables

Primary endpoint:

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at the End of Treatment (EOT) Visit (Day 84).

Secondary endpoints:

- Change from baseline in the number of treatable warts (baseline and new) at the EOT visit (Day 84).
- Change from baseline in the percent of treatable warts (baseline and new) at the EOT visit (Day 84).
- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4.

Exploratory endpoints:

- Percent reduction of all treatable warts (baseline and new) from baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4.
- Change from baseline in the number of treatable warts (baseline and new) at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4.
- Proportion of subjects exhibiting ≥ 50% clearance of all treatable warts (baseline and new) at the EOT visit as compared to baseline.
- Proportion of subjects who respond to treatment defined by a ≥ 50% reduction in total wart area at EOT visit compared to baseline.
- Proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4 and at the EOT Visit.
- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at follow-up visits on Day 105, Day 126 and Day 147.
- Percent reduction of all treatable warts (baseline and new) from baseline at follow-up visits on Day 105, Day 126 and Day 147.
- Change from baseline in the number of all treatable warts (baseline and new) from baseline at follow-up visits on Day 105, Day 126 and Day 147.

8.2. Baseline Values

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first application of study drug. When applicable, unscheduled visits will be used in the determination of baseline values.

8.3. Adjustments for Covariates

No statistical analysis is planned for this study; as a result, no adjustment for covariates will be made.

8.4. Handling of Dropouts or Missing Data

All subjects who receive treatment will be evaluated in the ITT population. In the event a subject requests to be removed from the study due to study related adverse events or additional spreading of disease, data will be collected and analyzed as a treatment failure and not replaced.

Unless described otherwise in subsequent sections, analyses will be carried out with the data available using no imputation for missing data. A description of how missing data as well as warts that combine will be handled for select endpoints is included below.

8.4.1. Handling of Missing Data for Complete Clearance Endpoint

The efficacy endpoint, proportion of subjects exhibiting complete clearance of all treatable warts, is to be assessed during the study. Assessments are to be done at Treatment Visit 2, Treatment Visit 3, Treatment Visit 4, the EOT visit and follow-up visits at Day 105, Day 126 and Day 147.

Subjects who do not have an assessment of complete clearance of all treatable warts in a particular visit window for any of the scheduled assessments will be considered to have missing data for this endpoint at that visit. The primary method to handle missing data will be to assign all subjects with missing clearance data as not having achieved complete clearance. For additional considerations related to assessments of clearance, see Section 8 (Efficacy Analysis).

8.4.2. Handling of Missing Data for Treatable Wart Count Endpoints

Assessment of number of treatable warts is planned for the baseline visit, each visit where treatment is applied, the EOT visit and three follow-up visits. Endpoints that are based on these assessments include percent reduction from baseline in the number of treatable warts, change from baseline in the number of treatable warts, proportion of subjects exhibiting 50% or greater reduction in the number of treatable warts from baseline and proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline. If the number of treatable warts is not available, the number of treatable warts will be imputed from earlier assessments of wart count using last observation carried forward (LOCF). The LOCF method uses information from the last available assessment of the measurement to include subjects with missing data in analysis.

When applicable, LOCF will be used to impute other post baseline treatment visits when the assessment of number of treatable warts is not available. An exception includes the following:

- If Treatment Visit 2 is missing, LOCF will not be used to impute a result for Treatment Visit 2. No result collected prior to first dose will be carried forward.

Imputation for missing wart area will be carried out using the same methods described above when imputing for missing number of treatable warts.

8.4.3. Handling of Individual Warts that Combine Over the Course of the Study

For the endpoints associated with wart count, warts that combine could be problematic for analysis purposes. Should two warts combine into a single wart at a post baseline visit, the wart count would be reduced by 1 and the percent change reduction would be 50%. However, such calculations may not be representative of actual wart changes.

In the event two or more warts combine into a single wart, all information regarding the combined wart will be recorded on the wart with the first wart number sequentially. Warts other than the first wart that merged to create the combined wart will be marked as "Other, specify" on the Wart Location and Measurement CRF. The Other text field will begin with "WART COMBINED" to flag the wart as one that combined with other warts.

For endpoints that involve or are related to wart count, warts that combine at post baseline visits will be considered a single wart. In addition, for the complete clearance and change/percent change in number of warts endpoints, sensitivity analysis will be carried out where the number of warts that merged to create the combined wart will be imputed for all subsequent visits- as long as the combined wart does not clear.

8.5. Interim Analysis and Data Monitoring

No formal interim analysis or data monitoring is planned for this study.

8.6. Multiple Comparison/Multiplicity

No formal statistical comparisons are planned; thus, no adjustment for multiple comparisons is needed.

8.7. Examination of Subgroups

Analyses based on subgroups of interest may be carried out for exploratory purposes. Possible analyses include the following:

- Gender: Female, Male.
- Age: 12-17 years old, 18-45 years old, >45 years old
- Number of warts at baseline: 1-2 warts, >2 warts
- Fitzpatrick Skin Type: I or II, III or IV, V or VI
- Duration of warts: <1 year, 1-2 years, 3 to 5 years, >5 years. Duration of warts will be defined by comparing the date of informed consent to the date the warts were first self/parent identified. Partial dates will be imputed using the same procedure as used to calculate Time since Clinical Diagnosis. For details, see Section 7.3.

9. Methods of Efficacy Analysis

9.1. Complete Clearance of Treatable Warts

Counts and percent of subjects who have complete clearance of all treatable warts (baseline and new) will be displayed by visit. Complete clearance will be defined as no warts (treatable wart count=0) reported for a subject per the Wart Location and Measurement form. Number of common warts (treatable and untreatable) at unscheduled visits will be displayed in listings.

9.2. Change and Percent Change in Number of Warts

Number of warts present will be determined by the number of wart forms filled out with a wart diameter >0mm at each treatment visit as well as the EOT visit and 3 follow-up visits. For each post baseline treatment visit, the change in number of warts from baseline will be calculated. Summary statistics of number of warts will be displayed for each post baseline visit. Summary statistics of change in number of warts from baseline will also be displayed.

Percent change of warts will be calculated for each post baseline visit. Percent change will be calculated using the following formula (in formula below, warts refers to treatable warts):

$$\text{Percent (\%) Change} = \left(\frac{Warts\ at\ Post\ Baseline\ Visit - Warts\ at\ Baseline\ Visit}{Warts\ at\ Baseline\ Visit}\right) * 100$$

Analysis of percent change in number of warts will be carried out in the same manner as change in number of warts.

As described in Section 8.4.3, should any combined warts be reported, sensitivity analysis will be carried for change and percent change endpoints in which the number of warts which merge to create a combined wart will be imputed for all subsequent visits until the combined wart has cleared.

Section 8.4.2 specifies that the LOCF method will be used to impute result for visits with missing wart counts. This includes imputation of all treatment and follow up visits as well as the EOT visit. To investigate the potential impact the LOCF method could have on table summaries for change/percent change wart counts, an additional set of sensitivity analysis will be carried which only considers wart counts reported with no imputation. The analysis will be identical to the analysis described above, with the only difference being whether imputation is carried out or not.

9.3. Wart Percent (%) Reduction

At each treatment visit, the EOT visit and each follow-up visit, the number of warts will be reported. The percent change in number of warts will be calculated as described in

Section 9.2. Based on the percent reduction of warts, subjects will be assessed and assigned to one of 2 categories: ≥ 50% reduction of warts, <50% reduction in warts. Subject counts and percentage of subjects for each of these categories will be displayed by treatment group and visit.

In addition, subjects will be assessed and assigned to one of 2 categories for each post baseline visit: Reduction of at least 1 treatment wart from Baseline, No Reduction of Warts from Baseline. Counts and percentages of each category will be presented by visit.

9.4. Reduction of Wart Area

At each treatment visit, the EOT visit and each follow-up visit, the maximum diameter of each wart will be measured. The area of each wart will be estimated assuming the shape of the wart is a circle. Thus,the area of each individual wart will be calculated using the formula:

$$Area\ of\ Individual\ Wart = \Pi * (\frac{Diameter\ of\ Individual\ Wart}{2})^2$$

Where $\Pi =$ the constant 3.14. At each treatment visit and the EOT visit, the total wart area will be determined for the subject by summing the areas of the individual warts estimated at that visit. The change and percent change in wart area will be calculated for each treatment visit and the EOT visit and will be summarized using summary statistics. The percent change will be calculated using the same formula described in Section 9.2 (using wart area rather than number of warts).

An additional set of analyses will include reporting the number and percent of subjects with a ≥ 50% reduction in total wart area from baseline to the EOT visit. Subjects with a ≥ 50% reduction from baseline in total wart area will be considered to have responded to treatment.

10. Safety Analysis

All safety analyses will be based on the Safety Population. For any by visit analyses to be carried out, visit windows discussed in Section 8 will be applied to safety data.

10.1. Extent of Exposure

The total number of warts treated will be collected by visit over the duration of the study. For each visit, the number of warts treated will be determined by taking the sum of warts reported on the Wart Assessment and New Wart Assessment forms, where the question "Was wart treated at this visit?" was marked Yes. Summary statistics of the number of warts treated over the duration of the study will be provided. Counts and percentages of number of treatment visits over the duration of the study will be generated. In addition, the total number of treatment visits and total number of warts treated across all subjects

will be displayed. A treatment visit will be defined as a visit in which at least one wart was reported to have been treated and/or treatment was administered.

10.2. Adverse Events

Adverse events summaries will only consider TEAEs. TEAEs are defined as those adverse events that occurred after dosing and those existing adverse events that worsened during the study. If it cannot be determined whether the adverse event is treatment emergent due to an incomplete (partial) onset date, the adverse event will be considered to be treatment emergent. Adverse events with an onset day after the EOS visit will be included in listings but not considered TEAEs; therefore, such adverse events will not be considered for table summaries. Verbatim terms entered into the clinical database via the EDC system will be mapped to preferred terms and system organ classes using version 20.0 of Medical Dictionary for Regulatory Activities (MedDRA).

Each adverse event summary will be displayed by treatment group. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of the TEAEs which contain an overview of each item below.
- Subject count and incidence rate of TEAEs by MedDRA system organ class and preferred term.
- Subject count and incidence rate of TEAEs by MedDRA preferred term and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events.
- Subject count and incidence rate of TEAEs by MedDRA preferred term and closest relationship to study drug (Related/Not Related). Related AEs are those reported as “Definitely”, “Probable” or “Possibly”. At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events. Adverse events with missing relationship will be considered related for this summary.
- Subject count and incidence rate of Serious TEAEs by MedDRA system organ class and preferred term.
- Subject count and incidence rate of TEAEs leading to withdrawal of study medication by MedDRA system organ class and preferred term.

10.3. Targeted Adverse Events- Local Skin Reactions

Local skin reactions (LSRs) to treatment reported by investigators and subjects will be recorded as adverse events. Two questions on the adverse event form are “Is this Adverse Event at a location where study drug was administered?” and “Did event occur during the paring procedure?” If the answer is Yes to the location question and No to the

paring procedure question, the adverse event will be considered a Local Skin Reaction. LSRs will be coded and summarized using similar methods as described in Section 10.2 for adverse events.

Summaries of LSRs will include the following:

- Subject count and incidence rate of LSRs by MedDRA system organ class and preferred term.
- Subject count and incidence rate of LSRs by MedDRA preferred term and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events.
- Subject count and incidence rate of LSRs by MedDRA preferred term and closest relationship to study drug (Related/Not Related). Related LSRs are those reported as "Definitely", "Probably" or "Possibly". At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events. LSRs with missing relationship will be considered related for this summary.
- Subject count and incidence rate of serious LSRs by MedDRA system organ class and preferred term.
- Subject count and incidence rate of LSRs by study specific LSR categories. Mapping of LSRs will be done via a medical review. Possible categories of LSRs will include the following: Blistering, Pain, Pruritus, Erythema, Edema, Erosion/Ulceration, Flaking/Scaling/Dryness, Scabbing/Crusting, Pigmentation Changes.

Adverse events that appear at a location where drug was administered and occur during the paring procedure will not be considered LSRs. A separate summary table will be generated to summarize those adverse events that meet these conditions (i.e., the answer is Yes to the location question and Yes to the paring procedure question, therefore the adverse event will be considered as related to the paring procedure and not an LSR).

10.4. Evaluation of Response to Treatment (ERT)

For each treatment visit, an Evaluation of Response to Treatment (ERT) will be performed (in clinic) and 24 hours and 7 days post treatment (by phone). The ERT contains questions about experiences related to treatment, such as blistering and pain. Should any symptoms be reported as part of the ERT, those symptoms will be recorded on the adverse event form. Therefore, no ERT specific table summary will be generated. Any additional information collected on the ERT will be presented in listings.

10.5. Provider Questionnaire

At the EOT visit for Cohort 2, a 9-question Provider Questionnaire will be completed. Questions will include ease of use of the applicator and general experiences. Responses to the questions will be displayed in subject listings. No summary tables of the questionnaire are planned.

10.6. Vital Signs

Heart rate and temperature will be collected at each visit. Change from baseline will be calculated for each post baseline visit temperature and pulse rate. Weight and height will be collected at baseline and at the EOS visit.

Summary statistics for each vital sign and change from baseline result will be displayed by treatment group and visit for temperature and pulse rate. Baseline height and weight will be summarized as part of the baseline summary. Any other collection of height and weight will be included in by subject listings.

10.7. Physical Examination

Physical examinations results will be displayed in by subject listings. No summary tables of physical examination are planned.

10.8. Prior and Concomitant Medications

Prior and concomitant medication verbatim terms captured via the EDC system will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using the most current versions of the World Health Organization (WHO) Drug Dictionary Enhanced available.

Prior and concomitant medications will be summarized separately by WHO ATC class and preferred name. Medications with a start date prior to first dose will be considered prior medications. Medications with a start date on or after first dose date will be considered concomitant medications. Medications with a start date prior to first dose date and an end date on or after first dose or that are ongoing will be considered as prior medications. These summaries will present the number and percent of subjects using each medication. Subjects may have more than one medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if one or more medications at that level is reported for the subject. Each summary will be ordered by descending order of incidence of ATC class and preferred term.