Statistical Analysis Plan

Protocol Title	CARE-1: A Phase 2, Double-Blind, Placebo-Controlled Study to Determine the Cantharidin Dose Regimen, Efficacy, Safety, and Tolerability of VP-102 in Subjects with External Genital Warts
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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.

Signatures / Approvals

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Principal Biostatistician Instat Clinical Research	Name (Print or Type)	Date

		8/14/2020
Chief Medical Officer Verrica Pharmaceuticals, Inc.	Name (Print or Type)	Date

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List of Abbreviations

AE	Adverse Event
ATC Class	Anatomical/Therapeutic/Chemical Class
BMI	Body Mass Index
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus 19
CRF	Case Report Form
CSR	Clinical Study Report
EDC	Electronic Data Capture
EGW	External Genital Wart
EOS	End of Study
EOT	End of Treatment
ERT	Evaluation of Response to Treatment
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
LSR	Local Skin Reactions
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measure
PP	Per Protocol
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, Listings
WHO	World Health Organization

1. Introduction

The purpose of this document is to ensure the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives. The study background, design and subject assessments for the study are described in the study specific protocol. Results obtained from the analyses outlined in this document will be the basis of the final clinical study report (CSR) for this protocol. Any deviations from this statistical analysis plan (SAP) will be documented in the final CSR.

2. Study Rationale and Objectives

2.1. Study Rationale

There have been no studies with VP-102 conducted in subjects with genital warts. This is a new indication for VP-102. It is anticipated that subjects in this study who are randomized to VP-102 will experience similar therapeutic benefits as those subjects previously treated with VP-102 or 0.7% w/v cantharidin.

2.2. Study Objectives

2.2.1. Primary Objectives

Part A (Dose Regimen Finding)

The primary objectives for Part A are:

- to evaluate the three regimens of application of VP-102 (2-hour, 6-hour, 24-hour duration of skin exposure) in subjects with external genital warts (EGW) and identify the two best regimens by assessing safety and tolerability of VP-102 when administered topically after all subjects have completed a 48-hour assessment
- to evaluate the efficacy of VP-102 when administered topically to EGW once every 21 days for up to 4 applications by assessing the proportion of subjects achieving complete clearance of all treatable warts (baseline and new) at the Study Day 84 End-of-Treatment (EOT) Visit.

Part B (Safety and Efficacy)

The primary objective for Part B is to evaluate two regimens of application of VP-102 in subjects with EGW and identify the regimen with the best risk:benefit profile when administered topically once every 21 days for up to 4 applications.

2.2.2. Secondary Objectives

The secondary objectives of this study for Part A and B are:

- to assess the safety and tolerability of VP-102 in subjects with EGW by evaluating adverse events (AE) including expected local skin reactions (LSR), vital signs, and concomitant medications.
- to evaluate the efficacy of VP-102 when administered topically to EGW once every 21 days for up to 4 applications by assessing the proportion of subjects achieving complete clearance of all treatable warts (baseline and new) at Treatment Visit 2, 3, 4, and Follow-up Visits on Study Day 112 and 147 End of Study (EOS).
- to evaluate the efficacy of VP-102 by assessing the change from baseline in the number of treatable warts (baseline and new) at each scheduled post baseline visit.
- to evaluate the efficacy of VP-102 by assessing the percent change from baseline in the number of treatable warts (baseline and new) at each scheduled post baseline visit.
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting 75% and 90% clearance of all treatable warts (baseline and new) at each scheduled post baseline visit.

2.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- to evaluate the efficacy of VP-102 by assessing the proportion of subjects exhibiting reduction of ≥ 1 treatable wart from baseline at each scheduled post baseline visit.
- to evaluate the efficacy of VP-102 by assessing the proportion of subjects who are clear at the Study Day 84 EOT Visit and remain clear at the Follow-up Visits on Study Days 112 and 147 EOS.
- to evaluate the efficacy of VP-102 by assessing the change from baseline in total wart area (sum of individual warts) at the scheduled post baseline visits Day 84, 112, and 147.
- to evaluate the efficacy of VP-102 by assessing the percent change from baseline in total wart area (sum of individual warts) at the scheduled post baseline visits Day 84, 112, and 147.

3. Study Design

This is a phase 2, double-blind, placebo-controlled study to determine the dose regimen, safety, tolerability, and efficacy of VP-102 in subjects with EGW. The study population will consist of adult subjects (18 years of age or older) with a wart count of 2-30 and a duration greater than or equal to 4 weeks at baseline. The study is divided into two parts: Part A (dose regimen finding) and Part B (safety and efficacy). The study will consist of

a screening period (up to 14 days prior to first treatment), treatment period (4 visits), and a follow-up period.

In Part A, approximately six subjects will be enrolled into one of three groups for treatment skin exposure (for a total of 18 subjects): Group 1: 2-hour, Group 2: 6-hour, or Group 3: 24-hour. Each group will include a minimum of two subjects from each gender and will be randomized to VP-102 or placebo in a 5:1 ratio within each group. Study drug will be administered once every 21 days (+/- 4 days) for up to four applications. Enrollment will begin in Group 1 and then proceed to Group 2 and finally 3 after completion of a blinded review of the safety and tolerability data by a Safety Review Panel performed 48 hours post treatment during Treatment Period 1. After Group 3 subjects have completed, an additional blinded review will be conducted to determine the dose selections for Part B.

In Part B, approximately 90 subjects will be enrolled and randomized to one of four treatment arms: VP-102 Regimen 1, Placebo Regimen 1, VP-102 Regimen 2, or Placebo Regimen 2, in a 3:2:3:2 ratio, respectively and stratified by gender. Regimen 1 and 2 refer to one of the skin exposure times (2-hour, 6-hour, or 24-hour) selected from Part A. Procedures for Part B will follow those in Part A with the exception of the Safety Review Panel.

4. Determination of Sample Size

No formal power calculations were performed for this study. The study will enroll approximately 18 subjects in Part A to determine the dose selection and approximately 90 subjects in Part B to evaluate wart clearance rates and support future trials.

5. Statistical Methods

The statistical analyses 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 will 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 and sorted by subject number and visit/visit date if appropriate. Data will be summarized in tables and/or figures by treatment group.

Treatments in Part A will be pooled with Part B where applicable. For example, if VP-102 24-hour exposure is one of the treatments selected for Part B, then the data from Group 3 (24-hour exposure) in Part A will be pooled with the 24-hour exposure data in Part B. The data from Part A will be summarized separately in a descriptive manner. Treatment comparisons will be made separately for each regimen, i.e., VP-102 Regimen 1 vs Placebo Regimen 1 and VP-102 Regimen 2 vs Placebo Regimen 2.

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 for tables 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 with tables and consistency between tables and corresponding data listings.

6. Analysis Populations

The Intent-to-Treat population (ITT) will include all randomized subjects.

The Per-Protocol (PP) population will include subjects who receive all planned treatments of study drug (i.e., complete up to four treatments within the Day 75 treatment window or achieved complete clearance prior to Day 75), had no major protocol violations, and were assessed for clearance at Study Day 84 (up to 92 days) EOT Visit.

The Safety population will include all randomized subjects who receive at least one application of study drug.

7. Study Population

7.1. Subject Disposition

The number of subjects randomized and number of subjects in each population will be summarized by treatment group. Also included will be the number of subjects who completed through Day 84, number of subjects assessed for clearance at Day 84 based on analysis windows, number of subjects with major protocol violations, number of subjects who received all planned treatments of study drug by Day 75 or achieved complete clearance prior to Day 75, number of subjects completing and discontinuing the study, along with the primary reason for discontinuation. The completion/discontinuation status refers to the subject's participation in the study; therefore, the data is collected at the last

scheduled visit, Study Day 147 EOS. If a subject discontinues the study prematurely, then the case report form is completed at the time of discontinuation.

7.2. Protocol Deviations

Protocol deviations will be collected throughout the study. Deviation type, as reported in the EDC, will be summarized by treatment group for those deviations classified as major.

7.3. Demographic and Baseline Characteristics

Demographic variables will include age, sex, ethnicity and race. Age will be calculated using the date of informed consent.

Baseline characteristics will include wart history, Fitzpatrick Skin Type, height, weight and body mass index (BMI). BMI will be calculated as weight (kg) / height (m^2). Wart history variables that will be summarized include time since clinical diagnosis in years (as compared to informed consent), age at diagnosis in years (derived using birth date year), number of months warts have been present (derived using informed consent date and clinical diagnosis date) and any previous treatments for warts. If the clinical diagnosis date is not complete, the date will be imputed as follows: (a) if the day is missing then it will be set to the first day of the month; (b) if the month is missing then it will be set to January; (c) if the year is missing then the date will be set to missing and will therefore not be included in the summary of time since clinical diagnosis.

The baseline efficacy data will be summarized by treatment group also. Specifically, the number of warts, anatomical location by gender, and wart area diameter will be presented.

Demographics and baseline characteristics will be summarized by treatment group for all 3 analysis populations (ITT, PP, Safety).

8. Efficacy Analysis

The primary analysis population will be the ITT population. However, the PP population will also be used for efficacy analysis. Results will be summarized by the treatment group to which each subject was randomized. Where appropriate, 95% confidence intervals and p-values may be generated as well. Efficacy parameters will be summarized for both Part B pooled with Part A for the applicable treatments and separately for the treatment not selected from Part A. Treatment comparisons will be made separately for each regimen, i.e., VP-102 Regimen 1 vs Placebo Regimen 1 and VP-102 Regimen 2 vs Placebo Regimen 2. A sensitivity analysis in which each of the VP-102 Regimens will be compared individually to the pooled Placebo Regimens on the primary endpoint will be conducted on the ITT population. Additionally, the VP-102 Regimens will be pooled

and compared to the pooled Placebo Regimens for the primary endpoint on the ITT population.

On the Wart Count case report form (CRF), the total number of overall EGW warts is collected. Genital warts that develop in areas that are unable to be treated or other types of warts will not be evaluated, documented, or considered in the analysis.

Some efficacy endpoints will be summarized by treatment visit. Treatments are planned to occur every 21 (+/- 4) 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 LSRs. As a result, the timing of when subjects receive treatment may vary. For the purpose of summarizing treatment visits, only visits when treatment was given will be considered. Moreover, a window will be applied to each visit to ensure that subjects are compared at the same treatment durations. A window of +/- 10 days from the targeted treatment schedule will be used. The table below summarizes the windows. These windows will be used on all by-visit summaries.

Visit	**Target Day**	**Window**
1	1	N/A
2	21	11 – 31
3	42	32 – 52
4	63	53 – 73
Day 84 EOT	84	74 – 94
Follow-up Day 112	112	95 – 129
Follow-up Day 147	147	130 – 157

If more than one visit falls within a window, then the visit closest to the target day will be used in the analysis. Visits when treatment was planned but treatment was not applied will be recorded as “Unscheduled”. Unscheduled visit information will not be considered for by-treatment visit summary tables. However, all efficacy data will be presented in data listings.

8.1. Efficacy Variables

Primary endpoint:

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

Secondary endpoints:

- Proportion of subjects exhibiting complete clearance of all treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4, Follow-up Day 112, and Follow-up Day 147 EOS.

- Proportion of subjects exhibiting 90% and 75% clearance of all treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4, Study Day 84 EOT, Follow-up Day 112, and Follow-up Day 147 EOS.
- Change from baseline in the number of treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4, Study Day 84 EOT, Follow-up Day 112, and Follow-up Day 147 EOS.
- Change from baseline in the percent of treatable warts (baseline and new) at Visit 2, Visit 3, Visit 4, Study Day 84 EOT, Follow-up Day 112, and Follow-up Day 147 EOS.

Exploratory endpoints:

- Proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline at Visit 2, Visit 3, Visit 4, Study Day 84 EOT, Follow-up Day 112, and Follow-up Day 147 EOS.
- Proportion of subjects who are clear at the Study Day 84 EOT Visit and remain clear at the Follow-up Day 112 and 147 EOS Visits.
- Change from baseline in total wart area (sum of individual warts) at Study Day 84 EOT, Follow-up Day 112 and Follow-up Day 147 EOS.
- Change from baseline in the percent of total wart area (sum of individual warts) at Study Day 84 EOT, Follow-up Day 112, and Follow-up Day 147 EOS.

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

Adjustments for gender and baseline values will be made for statistical analyses.

8.4. Handling of Dropouts or Missing Data

All subjects who were randomized will be evaluated in the ITT population. If 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. If a subject discontinues use of study drug but remains in the study, the subject will be analyzed as a non-responder as well. Per the study protocol, subjects who achieve complete clearance of all lesions prior to Day 84 are required to attend all Treatment Visits but will not receive treatment at those visits where all lesions are clear. These subjects will not be considered as having prematurely discontinued use of the study drug.

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 will be handled for select endpoints is included below.

8.4.1. Coronavirus 19

Due to the coronavirus 19 (COVID-19) outbreak during the course of the study, there may be several subjects who will have missing assessments which could affect the primary analysis. Subjects who are unable to attend a study visit due to COVID-19 will be documented in the protocol deviation log. The protocol deviation date will be used as the COVID-19 affected date (or visit). If a subject reports an adverse event of COVID-19, then the event start date will be used as the affected date. In the event that a subject has an affected COVID-19 date from both sources, the earlier of the dates will be used.

Subjects who were affected by COVID-19 will be summarized in a data listing. The listing will contain the following information: subject number, treatment, gender, age, first date affected by COVID-19, duration in study prior to the affected COVID-19 date, total study duration, exposure to study drug, any COVID-19 related adverse events, completion/discontinuation of the study, and reasons for discontinuation. All data listings will include a flag to denote whether the subject and/or visit was affected by COVID-19.

8.4.2. 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 (blinded assessment only) at Treatment Visits 2, 3, 4, Study Day 84 EOT visit, and Follow-up visits Day 112 and 147.

For the primary efficacy analysis, subjects who do not have an assessment of complete clearance of all treatable warts at any of the scheduled assessments (with applicable visit windows applied) will be considered to have not achieved complete clearance of all treatable warts at that visit.

Due to COVID-19, sensitivity analyses will be performed to assess the robustness of the primary analysis. The purpose of these analyses is to assess any potential bias due to subject assessments or missing data due to COVID-19. There will be two sensitivity analyses on the primary efficacy endpoint, complete clearance at Day 84.

- Exclude COVID-19 affected data: The first analysis will be to conduct the planned analysis only on the subjects who were not affected by COVID-19 at or before Day 84 (with visit window), i.e., if a subject was affected by COVID-19, then the subject will be removed from the analysis.
- Multiple imputation of missing data: The second analysis will be to use the multiple imputation regression method. For monotone missing data patterns, data in each treatment group will be imputed using the regression method on the basis of the predicted future pattern for the same treatment group. One hundred imputed

datasets will be generated. Each imputed dataset is analyzed separately using the method for the efficacy endpoint described in 9.1. The final estimate of treatment difference will be the average of the estimates based on the 100 individual imputed datasets. The pooling of the individual estimates and inferences based on the combined estimate will be handled by the SAS procedure MIANALYZE.

8.4.3. Handling of Missing Data for Treatable Wart Count Endpoints

Assessment of number of treatable warts is planned for the baseline visit, the EOT visit, follow-up visits (including EOS), and each treatment visit. Endpoints that are based on these assessments include percent reduction from baseline of treatable warts, change from baseline in treatable warts, percent reduction from baseline in total wart area, change from baseline in total wart area, and proportion of subjects exhibiting reduction of at least 1 treatable wart from baseline. No imputation will be done on missing data for these endpoints.

8.5. Interim Analysis and Data Monitoring

No formal interim analysis or data monitoring is planned for this study. However, a safety review panel will conduct blinded reviews during Part A and select the doses to be used in Part B.

8.6. Multiple Comparison/Multiplicity

This is a dose-finding study with no formal sample size calculation; thus, no adjustment for multiple comparisons is performed. All statistical comparisons planned for this study are exploratory.

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.
- Wart Location: Medial Thigh, Supra-Pubic, Perineal, Perianal Area, Glans Penis, Penis Shaft, Scrotum, Foreskin, Vulva
- Wart Location by Gender
- Number of warts at baseline: 2-10, 11-20, 21-30
- Fitzpatrick Skin Type: I or II, III or IV, V or VI
- Duration of warts: <1 yr., 1-2 yrs., >2 to 5years, >5 years.

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 will be displayed by visit; however, the primary analysis is complete clearance at Study Day 84 EOT. The row mean scores statistic from the Cochran-Mantel-Haenszel (CMH) test will be used to analyze differences in each treatment regimen (VP-102 Regimen 1 vs Placebo Regimen 1 and VP-102 Regimen 2 vs Placebo Regimen 2) by gender. Complete clearance will be defined as no warts (treatable wart count=0) reported for a subject per the blinded EGW Wart Count form. This analysis will be done on the primary endpoint, Study Day 84, as well as each of the other visits.

Also analyzed will be the proportion of subjects who have complete clearance at Day 84 and remained clear through the end of the study, follow-up visit Day 147. The CMH test will be used to test for treatment differences.

9.2. Change and Percent Change in Number of Warts

Number of warts present will be recorded at each treatment visit as well as 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 treatment visit. Summary statistics of change in number of warts from baseline will also be displayed. Statistical analyses on each treatment regimen will be performed. A restricted maximum likelihood–based repeated-measures approach, using a Mixed effect Model Repeat Measurement (MMRM) will be used. The MMRM model will include the fixed, categorical effects of treatment, gender, visit, and treatment-by-visit interaction as well as the continuous, fixed covariate of baseline wart count. An unstructured (co)variance structure shared across treatment groups will used to model the within-subject errors. If convergence is not met, then the Akaike's Information Criteria will be used to select the best covariance structure to model the data. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

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

$$\text{Percent (\%) Change} = \left(\frac{\text{Number of warts at post baseline visit} - \text{Number of warts at baseline}}{\text{Number of warts at baseline}} \right) * 100$$

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

An additional analysis will be carried out by visit to report the number and percent of subjects who had a reduction of one or more treatable warts from baseline. The proportion of subjects with 90% and 75% clearance of warts will also be analyzed using a CMH test.

9.3. Reduction of Wart Area

At Visit 1, Study Day 84 EOT, 112, and 147, the total wart area will be measured and reported on the CRF. The change and percent change in wart area will be calculated for each post baseline 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).

10. Safety Analysis

All safety analysis will be based on the Safety Population. Analyses using the Safety population will be based on the treatment received.

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 number of warts reported on the EGW Wart Count at Visit 1 and from the Blinded Assessment of Warts form at subsequent visits. The total number of treatment visits and total number of warts treated will be displayed.

10.2. Adverse Events

Adverse events summaries will only consider Treatment Emergent Adverse Events (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 treatment emergent. Verbatim terms entered into the clinical database via the EDC system will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

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 system organ class, 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 system organ class, 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 to study drug 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 study discontinuation by MedDRA system organ class and preferred term.
- Subject count and incidence rate of TEAEs by MedDRA system organ class and preferred term by gender

In addition to the above, TEAEs by system organ class and preferred term will be summarized on events that occurred prior to a subject's COVID-19 affected date and also for events that occurred after a subject's COVID-19 affected date.

10.3. Local Skin Reactions

Local skin reactions (LSRs) to treatment reported by investigators and subjects will be recorded as adverse events. LSRs will include adverse events taking place at the site of study drug administration such as, blistering, pain, pruritus, burning, erythema, edema/swelling, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting, scarring, ring wart, and pigmentation changes. These events of interest are denoted on the CRF by the investigator as events occurring at a location where drug was administered. These will be mapped to the appropriate MedDRA classification 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 system organ class, 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 system organ class, preferred term and closest relationship to study drug (Related/Not Related). Related LSRs 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. 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 MedDRA system organ class and preferred term by gender

10.4. Evaluation of Response to Treatment (ERT)

For each treatment visit, an Evaluation of Response to Treatment (ERT) will be performed (in clinic) at each visit, including 48 hours after first dose in Part A only and 24-hour, 7 Day, and 14 Day post treatment (by phone). ERT data will be presented in listings.

10.5. Provider Questionnaire

At the EOT visit, 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 in clinic visit. Change from baseline will be calculated for each post baseline visit temperature and pulse rate. Height and weight will be recorded at screening and follow-up visits (including EOT).

Summary statistics for each vital sign and change from baseline result will be displayed by treatment group and visit for temperature and pulse rate. By-visit summaries will utilize visit windows as discussed in Section 8. Baseline height and weight will be summarized as part of the baseline summary. Any other collection of height and weight will be included in the data listing.

10.7. Physical Examination

Physical examinations results will be displayed in a data listing. 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 World Health Organization (WHO) Drug Dictionary Version September 2017.

Prior medications will be defined as those medications starting and ending before the first dose of study drug, or if the start date is missing and the end date is present and is prior to the first dose of study drug. Concomitant medications are any medications that are being taken on or after the first date of study medication. Prior and concomitant medications will be summarized for each treatment group by WHO ATC class and preferred name. 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.