Statistical Analysis Plan

Protocol Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Pivotal Study to Evaluate the Safety and Efficacy of VP-102 Topical Film-Forming Solution [0.7% (w/v) Cantharidin] in Subjects (2 years and older) with Molluscum Contagiosum
Protocol Number (version):	VP-102-102 (V5- 01FEB2018)
SAP Version:	V1
Date:	October 17th, 2018
Sponsor:	Verrica Pharmaceuticals, Inc. 10 N. High Street, Suite 200 West Chester, PA 19380
Authors	Pieter d'Arnaud 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.

Document History

Version Number	Author	SAP Date	Change
V1	Pieter d'Arnaud	17 October 2018	

Signatures / Approvals

DocuSigned by:
Pieter d"Arnaud
F08DCAABDA1D04E5...

Lead Biostatistician, Instat Services	Pieter d"Arnaud	11/3/2018 3:54:38 PM ED
	Name (Print or Type)	Date

DocuSigned by:
Patrick Burnett
AA03115011BA4B1...

Verrica Pharmaceuticals	Patrick Burnett	11/6/2018 3:42:25 PM ES
	Name (Print or Type)	Date

Table of Contents

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC Class	Anatomical/Therapeutic/Chemical Class
CDLQI	Children's Dermatology Life Quality Index
ConMeds	Concomitant Medications
CSR	Clinical Study Report
EDC	Electronic Data Capture
EOS	End of Study
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
MMRM model	Mixed Model, Repeat Measures model
PERIT	Patient Evaluation of Response to Investigational Treatment
RTF	Rich Text Format
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 two identical Phase 3, Randomized Double-Blind, Placebo-Controlled Pivotal studies to evaluate the safety and efficacy of VP-102 Topical Film-Forming Solution [0.7% (w/v) Cantharidin] for the treatment of molluscum contagiosum (Protocols VP-102-101 and VP-102-102). The study background, design and subject assessments for each study are described in the respective study specific protocols.

The statistical methods to be implemented during the analyses of data collected within the scope of this study (VP-102-102) 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.

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 molluscum 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 in order 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 objective of this study is to evaluate the efficacy of dermal application of VP-102 relative to placebo, when applied once every 21 days for up to 4 applications, to treatable molluscum contagiosum (molluscum) lesions on subjects 2 years and older by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit.

2.2.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the safety of VP-102, when applied once every 21 days for up to 4 applications, to treatable molluscum lesions on subjects 2 years old and older by assessing adverse events including expected local skin reactions, physical examinations and concomitant medications at End of Study compared to baseline.
- To evaluate the efficacy of VP-102 relative to placebo by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions at

Visit 2. Separate assessments for clearance will be repeated for both Visit 3 and Visit 4.

3. Study Design

This is a Phase 3, multi-center, randomized, double-blind, placebo (vehicle)-controlled, pivotal study that will be conducted in the United States to determine the efficacy and safety of VP-102 following treatment of molluscum lesions for up to 4 treatments, 3 weeks apart, with VP-102/placebo in approximately 250 pediatric subjects (2 years or older). Subjects will receive active VP-102 (0.7% w/v cantharidin) or placebo in a 3:2 ratio, respectively. Duration of molluscum lesions prior to Treatment Visit 1 will be recorded but will not be an inclusion/exclusion requirement.

Study drug (VP-102 or placebo) will be supplied in single-use applicators, with one applicator sufficient to treat up to approximately 50 molluscum lesions. If required due to the number and size of lesions, a second single-use applicator may be used. No more than 2 applicators will be permitted per subject per treatment. The film-forming Study drug solution will be applied and left on the lesions for 24 hours before the subject and/or parents/guardian washes the lesions with soap and warm water. Study drug may be removed prior to the 24-hour timepoint in the event significant blistering, uncontrollable pain or treatment emergent AEs are experienced.

Molluscum lesions will be treated without occlusion in all anatomic areas including the face, trunk, back, arms, legs, hands, feet, anogenital region and buttocks. For study enrollment, the physician must be willing to treat all lesions initially present. Lesions that develop during the course of the study within 10mm of the eyelid margins or the margin of any mucosal surface should be evaluated carefully to ensure that they can be safely treated. Non-mucosal genital area lesions and inflamed lesions are considered treatable.

The study duration from Treatment Visit 1 through the Day 84 (EOS) visit is approximately 84 days (12 weeks). Pre-study screening for eligibility (informed consent, and assent (if assent is applicable), demographics, physical exam, prior and concomitant medications and molluscum and medical history) will occur up to 14 days before, or on Treatment Visit 1. Subjects who do not meet the inclusion criteria at Treatment Visit 1 will be discontinued and treated per standard of care. Those subjects that continue to meet criteria will be randomized per IWRS and treated with application of VP-102 or placebo solution to all molluscum lesions every 21 days (± 4 days) for a maximum of 4 treatment sessions. Subjects who completely clear all treatable lesions prior to Day 84 will complete the remainder of the Treatment Visits in order to monitor safety. If new lesions appear on a previously cleared subject, they should be treated. In the event of scheduling conflicts in subsequent visits after the first treatment, subjects may be

scheduled 21 ± 4 days following their previous treatment. The next study visit should then be scheduled 21 days after the previous treatment. In the event a subject misses a treatment visit and is outside the 4-day study window, they may return and be treated at the next available opportunity with the subsequent treatment visit scheduled 21 days later to facilitate up to 4 treatments within 84 days.

The final study visit assessment must be completed on or before Day 100. Should it become clear that the subject would be unable to complete the EOS on or before Day 100, the subject should be brought in for their EOS visit on or before Day 100, regardless of the number of days since their last Treatment Visit (e.g., a missed treatment may cause the subject to fall outside this window of 16 days).

Subjects who are unable to attend the in-office EOS visit may have the option of an EOS home visit by a qualified member of the research team if this is within the site's standard of practice. Consent for Home Visit will be included in the initial consent process. Subjects who continue to require treatment outside the specified study windows must be treated allowing for EOS to occur before or on Day 100. Subjects who are not assessed as 100% cleared of all treatable lesions at the EOS visit will have completed the study and will be further treated per standard of care at their physician's discretion but may not be re-enrolled in this study.

Evaluation of Response to Treatment (ERT) will be performed by the investigator or trained member of the research team, who is not a blinded assessor for that subject, at each treatment visit. An additional 24-hour in-office assessment will be conducted within 48 hours (+1 day) after the first treatment and at the EOS visit. Qualified study personnel who are not blinded assessors for the subject, will conduct ERT phone calls at 7 and 14 days after Treatment Visits 1. In addition, ERT phone calls at 24-hours as well as 7 and 14 days after Treatment Visits 2, 3 and 4 will be performed to assess treatment response, document any local skin reactions and any medical interventions taken if treatment was administered. The following clinical responses will be recorded as part of the Evaluation of Response to Treatment (ERT) with type and intensity recorded on the AE log: blistering, pain, pruritus, erythema, edema, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting, and pigmentation changes (hyperpigmentation or hypopigmentation). Scarring will be assessed at each treatment visit and the EOS visit by a qualified medical professional. Scarring information will not be collected as part of the phone assessment. Additional information related to AEs and ConMeds will also be collected during each assessment.

Subject quality of life and measure of impact of skin disease will be collected using the Children's Dermatology Life Quality Index Questionnaire. The CDLQI questionnaire is designed for use in children and will be administered to all study subjects regardless of

age. It should be handed to the subject who is asked to fill it in with the help of a parent/guardian as needed. The subject or guardian will be given completion instructions to evaluate their skin condition as it specifically relates to molluscum contagiosum. They will be guided to disregard the impact of any other concomitant skin conditions like atopic dermatitis during completion. The CDLQI should be scored by the site using the guidelines in Appendix 1 of the protocol.

Subjects will be given take-home instructions describing the potential local skin reactions and what they might expect throughout the course of the study. The instructions include recommendations for wound care, when it is important to call their doctor, who to contact in the event of emergency and a 24-hour emergency number. The additional scheduled visits and calls up through the next treatment visit, or EOS, will also be indicated on this form. Take-home instructions will be reviewed and provided at each treatment visit.

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 or another adverse event needing physician assessment during the ERT call, they will be scheduled for an unplanned study visit and safety evaluation at the next available opportunity.

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/lesion count and limited physical examination.

4. Determination of Sample Size

The sample size for the study is calculated based on the hypotheses of the primary endpoint (see Section 9.1 for primary endpoint hypotheses). The primary endpoint for this study is the proportion of subjects with complete clearance of all treatable lesions (baseline and new) at the EOS visit. A Pearson Chi-Square test will be used to test for treatment differences in the proportion of subjects who achieve complete clearance.

Subjects will be randomized and treated in a double-blind manner with either VP-102 or placebo in a 3:2 ratio. Study assumptions include (see protocol for justification of assumed clearance rates):

- a 10% drop out rate;

- a 20% clearance rate for subjects treated for placebo;

- a 44% clearance rate for subjects treated with VP-102.

Using these assumptions, a sample size of 250 subjects (150 subjects treated with VP-102, 100 Placebo) based on a two-sided Pearson-Chi Square test with a significance level of 0.05 will give >=95% power to detect treatment differences in clearance rates. The Pearson-Chi Square test is the test that will be used when analyzing the primary endpoint.

Included in this sample size calculation is the assignment of dropouts as non-responders. Subjects with missing data for the primary endpoint (complete clearance at the Day 84 visit) will be considered non-responders; see Section 8.4.1 for details. Assuming a 10% dropout rate and 250 subjects in the study, 25 dropout subjects (~15 subjects treated with VP-102 and ~10 subjects treated with Placebo) are expected. These subjects were assigned as non-responders when carrying out sample size calculations. The assumed clearance rates mentioned above were then applied to the remaining 225 subjects (135 subjects treated with VP-102 and 90 subjects treated with Placebo) to complete the power calculation.

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. Unless noted otherwise, all statistical tests will be two-sided with a significance level of $\alpha = 0.05$. Tests will be declared significantly significant if the calculated p-value is ≤ 0.05. 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. Missing values are not considered for percent calculations, unless stated otherwise. In those cases, footnotes will specify the percent basis. All summary tables will be presented by treatment arm. Select baseline tables may also include a total summary.

Randomization through an interactive web response system (IWRS) will be used to assign treatment in a 3:2 ratio (expected 150 subjects treated with VP-102 to 100 subjects treated with placebo). Trial sites will have access to an internet-based randomization system. Randomization will be conducted in a centralized manner.

Subjects with molluscum lesions presenting from the same household may be enrolled in the study. For ethical and practical considerations, subjects in the same household will be

assigned to the same treatment group. After a subject is randomized to a treatment, any other subject enrolled in the study from that household will be assigned the same randomization number and be given the same treatment. As a result, the unit of randomization is the household- not the subject. Randomizing by household at the site level could lead to strong differences from the desired treatment ratio at individual sites. Therefore, randomization by household will be carried out at the study level. Since randomization is not done by site, analyses will not be stratified by site.

Though the analysis will not be stratified by site, an assessment of the results across sites will be performed. A Breslow-Day test will be performed to consider any potential site-to-site variability of study results. A site with a strong deviation in treatment effect from other sites will be further investigated to try to gain a better understanding of why differences at the site may exist.

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

The analyses described in this plan are considered *a priori*, in that they have been defined prior to the blind being broken and the database locked. Any analysis performed after breaking the blind 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 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 with tables and consistency between tables and corresponding data listings

6. Analysis Populations

The Intent to Treat population (ITT) will include all subjects randomized to either placebo or VP-102.

Subjects who receive all 4 planned treatments of VP-102/Placebo and have no major protocol violations will be included in the Per Protocol population. The following pre-determined reasons will exclude subjects from being included in the Per Protocol population:

- Subjects treated with the incorrect study drug.
- Subjects that do not come in for scheduled study visits.
- Subjects who refuse to have all of their treatable lesions treated or Investigators who refuse to treat all treatable lesions.

- Early removal of the study drug not associated with pain, blistering or other medically appropriate reasons for early removal.
- Subjects with missing lesion counts or clearance assessments
- Subjects who begin alternative treatments for their molluscum after starting the study.
- Subjects enrolled who did not meet the inclusion/exclusion criteria.
- Subjects whom have their blind broken as to their treatment group without following study procedures.

The Safety population will include randomized subjects who meet the screening eligibility criteria for the study and receive at least one application of VP-102 or placebo.

7. Study Population

7.1. Subject Disposition

Information regarding subject disposition will be summarized for all subjects by treatment group. Summaries will include: number of subjects enrolled, number of subjects in each analysis population, number of subjects completing the study, number of subjects who discontinue the study early. For those who discontinue early, the primary reason for discontinuation 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. In addition, each deviation will be defined as major and 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. Age will be calculated by comparing date of birth to date of informed consent.

Baseline characteristics will include: medical history, disease specific medical history, height and weight. Included in the disease specific medical history will be the variables of baseline lesion count and presence or absence of active atopic dermatitis.

Continuous variables will be summarized using descriptive statistics. For select continuous variables, differences between the treatment groups at baseline will be tested using a two-sample t-test. Categorical variables will be summarized using counts and percentages. For select categorical variables, differences between the treatment groups

will be tested using a chi-square test. Demographics and baseline characteristics will be summarized for all 3 analysis populations (ITT, Per Protocol, Safety).

8. Efficacy Analysis

The ITT population will be used for the primary analysis. Analysis carried out on the Per Protocol population will be considered secondary in nature. Analysis carried out on the ITT and Per Protocol populations will be based on the treatment group subjects were randomized to.

Many of the variables used for efficacy analysis are based on assessing treatable lesions. Lesions that are untreatable are not included in the analysis. A lesion is considered to be untreatable if the lesion is within 10mm of the eyelid margin or the margin of any mucosal surface. All other lesions will be considered treatable, including non-mucosal genital area lesions.

8.1. Efficacy Variables

The primary efficacy variable is the proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit (EOS).

Secondary variables for efficacy to be considered include:

- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 63 visit.
- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 42 visit.
- Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 21 visit.

Exploratory endpoint includes:

- Change from baseline of the composite score from the Children's Dermatology Life Quality Index (CDLQI) assessment at the EOS visit to measure the quality of life and impact of skin disease in the subset of subjects 4-16 years of age
- Percent reduction of all treatable molluscum lesions (baseline and new) from baseline at the EOS visit.
- Change from baseline in the number of treatable molluscum lesions (baseline and new) at the EOS visit.
- Proportion of subjects exhibiting a 75% or greater reduction of all treatable molluscum lesions (baseline and new) at the EOS visit.

- Proportion of subjects exhibiting a 90% or greater reduction of all treatable molluscum lesions (baseline and new) at the EOS visit.

- Subject reported spread to household members as measured by any new occurrence of molluscum in household members of subject.

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

Baseline lesion count will be used as a covariate when analyses using an ANCOVA model are utilized. No other covariate adjustments are planned.

8.4. Handling of Dropouts or Missing Data

Subjects who do not complete the EOS assessment will be considered dropouts. Subjects who are randomized in the study but never receive study drug will also be considered dropouts. Dropouts will not be replaced.

All subjects who receive treatment will be evaluated in the ITT population. Those subjects that do not complete the full treatment due to protocol adherence or request to be discontinued from the study will be not be replaced. 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 will be handled for the primary endpoint and select endpoints is included below.

8.4.1. Handling of Missing Data for Primary Endpoint

The primary efficacy endpoint (proportion of subjects exhibiting complete clearance of all treatable lesions) is to be assessed a maximum of four times during the study. Assessments are to be done at Day 21, Day 42, Day 63 and Day 84 (EOS).

Subjects who do not have an assessment of complete clearance of all treatable lesions at Day 84 will be considered to have missing data for the primary endpoint. The primary method to handle missing data will be to assign all subjects with missing complete clearance data as not having achieved complete clearance. It is assumed that the proportion of subjects with missing data will be greater for subjects treated with VP-102 than subjects treated with placebo. Under this condition, one would expect there to be less chance to detect treatment differences (conservative approach). Rates of subjects

with missing data of the primary endpoint will be compared by treatment group. Significant deviations in rates of subjects with missing data that may affect study conclusions will be included in the study report.

8.4.2. Handling of Missing Data for Other Select Endpoints

Missing data for the secondary endpoints of clearance of all treatable lesions at Day 63, Day 42 and Day 21 will be handled using the same methods as described in Section 8.4.1 for the primary endpoint.

Assessment of number of treatable lesions is planned for the baseline visit, the EOS visit and each visit where treatment is applied. Other endpoints that are based on these assessments include percent reduction from baseline of treatable lesions, change from baseline in treatable lesions and proportion of subjects exhibiting 75%/90% or greater reduction of treatable lesions from baseline. If the EOS assessment of number of treatable lesions is not available, the number of treatable lesions will be imputed from earlier assessments of lesions 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. Similarly, LOCF will be used to impute other post baseline visit where lesion count is not available. One exception is if only the baseline lesion count is available for a subject. In that instance, the baseline value will not be carried forward and the number of treatable lesions will be left as missing.

Missing composite CDLQI scores at the EOS visit will be handled using the same method of LOCF as described above for imputing missing lesion counts. For handling individual questions with missing responses, see Section 9.2.1 for more details.

8.5. Interim Analysis and Data Monitoring

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

8.6. Multiple Comparison/Multiplicity

Sequential testing will be used to control the overall study-wise alpha. If the primary endpoint is significant at the $\alpha = 0.05$ level, then testing of the secondary endpoints for confirmatory purposes may occur. Secondary endpoints will be tested in the following order to assess significance:

1. Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 63 visit.

2. Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 42 visit.

3. Proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 21 visit.

Testing of any primary or secondary endpoint listed below an endpoint that does not meet significance at the $\alpha = 0.05$ level will not be carried out for confirmatory purposes. For such endpoints, any significant differences detected will be considered only exploratory.

The following exploratory endpoints will be tested only for supportive purposes.

- Change from baseline of the composite score from the Children's Dermatology Life Quality Index (CDLQI) assessment at the EOS visit to measure the quality of life and impact of skin disease in the subset of subjects 4-16 years of age.
- Percent reduction of treatable lesions from baseline at the EOS visit
- Change from baseline in the number of treatable lesions at the EOS visit.
- Proportion of subjects exhibiting 75% or greater reduction of all treatable lesions at the EOS visit
- Proportion of subjects exhibiting a 90% or greater reduction of all treatable lesions at the EOS visit
- Subject/guardian reported spread of lesions to household members of subject.

8.7. Examination of Subgroups

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

- Active Dermatitis at Baseline: With active dermatitis, without active dermatitis.
- Baseline Lesion Count: 1-20 lesions, 21-40 lesions, 41 or more lesions. Note: lesion count categories may be adjusted based on distribution of baseline lesion counts.
- Age: 2-5 years old, 6-11 years old, 12 years or older
- Subject 12 or older with genital lesions being 50% or greater percent of lesions at baseline. A separate analysis will be run for those subjects who do not qualify for this subgroup.

9. Methods of Efficacy Analysis

9.1. Primary Efficacy Analysis

Counts and percent of subjects who have complete clearance of all treatable molluscum lesions at Day 84 (EOS) will be displayed by treatment group.

The primary efficacy comparisons will use the ITT population and test the following hypotheses:

H_0: The proportion of subject exhibiting complete clearance of all treatable molluscum lesions at the EOS visit is equal when comparing the subjects treated with VP-102 versus the subjects treated with placebo.

H_1: The proportion of subject exhibiting complete clearance of all treatable molluscum lesions at the EOS visit is different when comparing the subjects treated with VP-102 versus the subjects treated with placebo.

Treatment groups will be compared using a Pearson Chi-Square test.

The EOS visit is scheduled to occur on Day 84 and 21 days (+/- 4 days) after their last treatment visit. For the analyses of the primary endpoint, only EOS visits that occur on Day 68 to Day 100 (+/- 16 days from planned visit study day) and at least 17 days after their last treatment visit will be considered for determining complete clearance. Subjects without an assessment of lesion count within this EOS visit window will be counted as not cleared.

9.1.1. Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses of the primary endpoint using the ITT population will include the following:

- Analysis using only non-imputed data (complete case analysis);
- Analysis in which all subjects with missing data are assigned as having achieved complete clearance;
- Analysis in which subjects with missing data and treated with placebo are considered to have complete clearance; subjects with missing data and treated with VP-102 are considered to not have complete clearance (worst case analysis).
- Analysis using the Per Protocol population.

9.2. Secondary Efficacy Analysis

9.2.1. Clearance of all Treatable Lesions as Day 63, Day 42 and Day 21

Assessment of lesion counts for the purpose of determining clearance will be carried out at Day 21, Day 42 and Day 63 - in addition to Day 84. Analyses of the rate of clearance will be carried out for Day 21, Day 42 and Day 63 using similar methods as those described in Section 9.1.

Section 9.1 describes a visit window that the Day 84 (EOS) visit must fall within in order for a report of clearance to be considered. Valid visit windows for Day 21, Day 42 and Day 63 are described below:

- Day 21- visit must fall between Day 17 to Day 25 (+/- 4 days from planned visit study day).
- Day 42- visit must fall between Day 34 and Day 50 (+/- 8 days from planned visit study day).
- Day 63- visit must fall between Day 51 to Day 75 (+/- 12 days from planned visit study day)

9.3. Analysis of Exploratory Endpoints

9.3.1. Children's Dermatology Life Quality Index (CDLQI)

At each study visit, the CDLQI will be administered with specific instruction to focus on the impact of molluscum and not any other possible concomitant skin ailments. The CDLQI is a 10-item questionnaire completed by subject/parent to assess skin condition over the past week. From responses to that questionnaire, a composite score is calculated. The calculated composite score is the sum of the individual 10 items of the CDLQI and can range from 0-30. For each item on the CDLQI, a score of 0-3 is assigned using the following scores per response:

- Not at all= 0
- Only a little= 1
- Quite a lot= 2
- Very much (or Prevented School, Question 7 only) = 3

Larger composite CDLQI scores indicate skin condition is having more effect on subjects' lives. If only 1 item from the questionnaire is missing, then that item is assigned a value of 0 for the purpose of calculating a composite CDLQI score. If more than 1 item is missing, a composite CDLQI score will not be calculated and left as missing. Question 7 has 2 parts: one applicable if the subject is in school; the other if the subject is on vacation (holiday). Subjects are supposed to only respond to 1 of these questions. Should the subject respond to both questions, the response that results in the higher value will be used.

The composite score from the CDLQI will be treated as a continuous variable. Descriptive statistics of the composite score will be displayed by visit and EOS for each treatment group considering all subjects. The CDLQI has only been validated for subjects between 4-16 years old age. As a result, analyses to test for treatment differences will only consider 4-16 year old subjects. The analyses to be carried out will be similar to the analyses described in Section 9.2.1 for the EOS summary. The difference will be that the independent variable for the model will be the composite score from the CDLQI.

Descriptive statistics for each of the individual items (questions) in the CDLQI will be generated by visit. The CDLQI has a series of domains, each with its own score. The domain scores are calculated based on responses to specific question(s) within the CDLQI. Descriptive statistics of each domain score will be provided by visit. Those domains along with the questions used to derive and the maximum score for each domain are include in Table 1 below:

Table 1

Domain	CDLQI Question(s)	Maximum Domain Score
Symptoms and Feelings	1,2	6
Leisure	4,5,6	9
School or Holidays	7	3
Personal Relationship	3,8	6
Sleep	9	3
Treatment	10	3

In addition, a sensitivity analysis of the composite CDLQI score will be performed to support the findings of the analyses described above. For the sensitivity analysis, the same methods described above with the only exception that all subjects enrolled in the study will be included in the analysis. That means subjects below 4 years of age as well as subject greater than 16 years of age will be considered. This analysis will be included so that summaries will be available that include all subjects enrolled in the study.

9.3.2. Change in Number of Treatable Lesions

Number of treatable lesions present will be recorded at each treatment visit as well as EOS. For each post baseline treatment visit, the change in number of treatable lesions from baseline will be calculated. Summary statistics of number of treatable lesions will be displayed for each treatment visit by treatment group. Summary statistics of change in number of treatable lesions from baseline will also be displayed. Summary statistics will also be generated for the EOS visit by treatment. Specific to the EOS summary, an ANCOVA model will be used to test for treatment differences in the change of treatable lesions from baseline. For the ANCOVA model, the independent variables will include treatment with a covariate for baseline lesion count.

9.3.3. Percent Change in Number of Treatable Lesions

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

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

Analysis of percent change in number of treatable lesions will be carried in the same manner as change in number of treatable lesions. For more details, see Section 9.3.2.

9.3.4. Treatable Lesion Percent (%) Reduction at EOS

At the EOS visit, the number of treatable lesions will be reported. The percent change in number of treatable lesions will be calculated as described in Section 9.3.2. Based on the percent reduction of treatable lesions at EOS, subjects will be assessed and assigned to one of 2 categories: ≥ 75% reduction of treatable lesions, <75% reduction in treatable lesions. Subject counts and percentage of subject for each of these categories will be displayed by treatment group.

The proportion of subjects treated with VP-102 will compared to the proportion of subjects treated with placebo to test for treatment differences. Analysis will be carried out using a Pearson Chi Square test; the methods used will be the same as those described in Section 9.1.

This analysis will be repeated, with the only difference being the percent (%) reduction being used for consideration. In this second analysis, the percent reduction used for consideration will be 90%. This means that subjects will be assigned to either a ≥ 90% reduction of treatable lesions category or a <90% reduction of treatable lesions category.

9.3.5. Subject Reported Spread of Molluscum Lesion to Household Members

Household member information will be collected for subjects enrolled in the study. Subjects who have at least one household member who does not exhibit molluscum lesions at baseline will be considered for this analysis. For those subjects, the count and percent of subjects who had a household member who was clear at baseline but showed lesions post baseline will be summarized by treatment group. A chi-square test will be performed to test for treatment differences in the rate of subjects who have a household member who contracts post baseline lesions. Note: subjects who do not have a household member free of molluscum lesions at baseline will not be considered for this analysis.

10. Pharmacokinetic Analysis

No pharmacokinetic analysis is planned for this study.

11. Safety Analysis

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

11.1. Extent of Exposure

The total number of lesions treated will be collected by visit over the duration of the study. For the purpose of calculation, every lesion reported to be treatable at visit Day 1,

Day 21, Day 42 and Day 63 will be considered to be treated. Summary statistics of number of lesions treated will be generated by treatment group.

For each visit, subjects will be identified as to whether they had to have at least one treatment removed prior to the planned 24-hour duration. Counts and percentages of subjects who had at least one treatment removed prematurely will be displayed by treatment group for each visit and for any time during the study.

11.2. 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. Pre-treatment adverse events and adverse events reported 30 days after the EOS visit will be listed but not included in TEAE summaries. Local skin reactions will be considered targeted AEs and will be included in adverse events summaries. 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. Verbatim terms entered into the clinical database via the EDC system will be mapped to preferred terms and system organ classes using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) available.

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 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.

11.3. Targeted Adverse Events - Local Skin Reaction

Local skin reactions (LSRs) to treatment reported by investigators and subjects will be recorded as adverse events. LSRs will include the following adverse events: blistering, pain, pruritus, erythema, edema, erosion/ulcerations, flaking/scaling/dryness, scabbing/crusting and pigmentation changes. LSRs will be coded and summarized using similar methods as described in Section 11.2 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 LSRs by MedDRA system organ class, preferred term and treatment visit. LSRs will be assigned to visits based on the onset date of the reported LSR. The following visit windows will be subject specific and used to assign LSRs to visits:
    - Visit 1 (Day 1): LSR onset day on Day 1
    - Visit 2 (Day 21): LSR onset day from Day 2 to date of Visit 2
    - Visit 3 (Day 42): LSR onset day from the day after Visit 2 to date of Visit 3.
    - Visit 4 (Day 63): LSR onset day from the day after Visit 3 to the date of Visit 4.
    - EOS (Day 84): LSR onset day from the day after Visit 4 to the date of the EOS visit.
    - Post EOS: LSR onset day from one to 30 days after the EOS visit.
- Subject count and incidence rate of LSRs by MedDRA system organ class, preferred term and body region.

11.4. Vital Signs

Heart rate and temperature will be collected at each visit. Change from baseline will be calculated for each post baseline visit for each vital sign. Height will be recorded only at baseline. Weight 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. 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.

11.5. Physical Examination

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

11.6. 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 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.