

# Topical Remedy, LLC

## **PROTOCOL TR-H-212**

A Multicenter, Placebo-Controlled, Randomized, Double-Blind Study of the Safety and Efficacy of Merlin (ethanol and glycolic acid mixture) for the Episodic Treatment of Recurrent Herpes Labialis

### **STATISTICAL ANALYSIS PLAN**

Version 1.0

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**CONFIDENTIAL**

**SIGNATURE PAGE**

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1.0	Aug 23, 2017	Initial Draft

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event
EE	efficacy evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
NASID	non-steroidal anti-inflammatory drug
PT	preferred term
SOC	system organ class
TEAE	treatment emergent adverse event

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## 1 Introduction

Topical Remedy, LLC is developing Merlin, a novel topical formulation that can be used to treat viral infections of the skin. It is composed of two commonly used compounds, glycolic acid (0.6%) and ethanol (10%), each with known safety and side effect profiles. This product, intended for over-the-counter distribution, will consist of single treatment foam applicators pre-filled with the Merlin solution.

## 2 Trial Design

### 2.1 Study Objectives

The primary objective of this study is to assess the efficacy of Merlin solution on the clinician assessed duration of the classical herpetic lesion as compared to placebo treatment. Duration is based on staging of the lesion. Staging is graded as follows: 0=prodromal, 1=erythema, 2=papula/edema, 3=vesicle/pustule, 4=ulcer/soft crust, 5=hard crust, 6=residual swelling/dry flaking, 7=normal skin. The duration of a classical lesion is defined as the time, in hours, from the beginning of treatment to the onset of Stage 6, or, if Stage 6 is never observed, Stage 7. A classical lesion is defined as one that progresses through any of stages 3, 4 or 5.

The secondary objectives of this study are to compare the active and placebo treatment groups with regard to:

- clinician assessed
  - duration of the herpetic episode (classical and non-classical)
  - duration until complete healing of the herpetic episode (classical and non-classical)
  - prevention of progression to a classical lesion
  - maximum lesion area of the classical lesions
  - cumulative lesion area of the classical lesions
  - cumulative lesion area of all lesions
  - duration of classical herpetic lesion hard scab
- safety

Based on patient diary entries, other objectives of this study are to compare the active and placebo treatment groups with regard to:

- subject assessed:
  - duration of the classical herpetic lesion
  - duration of the herpetic episode (classical and non-classical)
  - duration of complete healing of the herpetic episode (classical and non-classical)
  - prevention of progression to a classical lesion
  - duration of classical herpetic lesion hard scab
  - severity of lesion pain
  - duration of lesion pain

## 2.2 Study Design

This current clinical study is a Phase 2 trial using the same Merlin formulation as was used in the Phase 1 TR-H-111 and Phase 2 TR-H-211 trials. This trial will have two treatment groups comparing the safety and efficacy of Merlin solution to that of a placebo (10% ethanol) with treatment at first visible signs of a herpetic episode.

The present trial is designed to examine the efficacy and safety of treatment with Merlin as compared to treatment with placebo (10% ethanol) in subjects treating at first visible signs of a herpes labialis lesion (i.e. erythema [Stage 1] or papule/edema [Stage 2]).

Approximately four hundred and fifty (450) subjects will be enrolled into the study, with a goal of approximately one hundred and fifty (150) of these subjects who will actually enter the Treatment Phase of the study. Eligible subjects will be randomized in a 1:1 ratio to one of two treatment groups:

- 1) treatment of three (3) applications of Merlin solution or
- 2) treatment of three (3) applications of 10% ethanol, as a placebo,

performed within a time period of 40 minutes or less, while allowing time for the solution to dry on the lesion between applications.

A total of twelve (12) Merlin or placebo treatments, i.e. thirty-six (36) applications, will be administered over the ensuing ninety-six (96) hours (four (4) days) after the first treatment. On each day, treatments will be administered six (6) hours apart, with a maximum of three treatments each day. The first treatment will be administered on Treatment Day (Day 0), and then repeated at 6 and 12 hours after the first treatment, time permitting.

After being enrolled and randomized into the study, subjects will be sent home with a sealed kit for either Merlin (active) or 10% ethanol (placebo). At first signs and/or symptoms of a recurrent herpetic episode (Stage 0, prodrome Stage 1, erythema, or Stage 2, papule/edema), subjects will call the clinic to confirm by telephone interview, the presence of a lesion and the lesion stage. Subjects reporting either a Stage 1 or Stage 2 lesion will be interviewed to review the eligibility criteria. If they meet all the eligibility criteria they will then be instructed to begin treatment immediately, thereby initiating the Treatment Phase of the study. Subjects will then be instructed to return to the clinic as soon as possible within 24 hours of starting treatment. Subjects reporting only Stage 0 symptoms, i.e. no visible signs of a cold sore lesion, will be instructed to monitor their lesion and to call the clinic immediately upon observing any early visible sign of a cold sore, i.e. a Stage 1 or Stage 2 lesion.

Subjects will report daily for a minimum of 3 consecutive days, with the last clinic visit at the time of complete healing (Stage 7 - normal skin) or at 14 days, whichever is earlier. Subjects will be contacted by phone, for a safety assessment, 2 weeks after they complete the Treatment Phase of the study. Subjects will also be provided a diary that he or she will be instructed to fill out daily from the first day of treatment until their final clinic visit.

Both treatment groups will continue to accept subjects into the Treatment Phase of the study until there are at least seventy five (75) subjects in each group.

### 3 Sample Size

The sample size for this study was based upon the results of the previous Phase 2 study, TR-H-211. In that study, Merlin demonstrated a statistically significant ( $p=0.0276$ ) effect on the duration of classical lesion endpoint for subjects beginning treatment at Stage 1 (erythema) with only 32 subjects treated with Merlin and 22 placebo subjects. Clinical investigations with Famvir and other independent studies, that initiate treatment within hours of the onset of prodromal symptoms (Stage 0) have demonstrated that 1/3 of all subjects enrolled in herpes labialis studies will have spontaneously aborted lesion. Any calculation of clinical trial size, therefore, must consider that factor. When, however, treatment is initiated at the erythema stage (Stage 1), as in the Merlin Phase 2a (TR-H-211) study, the incidence of spontaneously aborted lesions declines to 25%. As a result, a larger percentage of subjects will demonstrate classical lesions in Merlin studies than was seen in the Famvir, or similar previous studies. This was factored in when performing power calculations for this Phase 2b clinical study. Those calculations determined that 144 subjects would provide a 95% likelihood of statistical significance for the herpetic episode endpoint. Merlin decreased the duration of herpetic episode in subjects that began treatment at stage 1 by 41 hours, with a p-value of 0.055 in the Phase 2a study. The herpetic episode endpoint includes the subjects with aborted lesions.

As a result, a 150 subject clinical trial will have approximately 60 subjects progress to classical lesions in each treatment group and we can be very confident of having the power to demonstrate a highly significant difference for the duration of classical lesion endpoint, as shown in the Phase 2a results. In addition, a 150 subject clinical trial should have greater than 95% likelihood of demonstrating a statistically significant Merlin effect on herpetic episode as a secondary endpoint.

### 4 Inclusion/Exclusion Criteria

#### 4.1 Inclusion Criteria

1. Subject has a visible herpes simplex labialis lesion, in an area around the mouth, assessed by the subject, and confirmed by telephone contact, to be at the erythema stage (Stage 1) or Papule/Edema stage (Stage 2) as defined below:  
**Stage 1:** **Erythema stage** is defined as any redness with no skin swelling or other signs of advanced stages.  
**Stage 2:** **Papule/Edema stage** is defined as any skin swelling or solid raised area above the normal surface without evidence of more advanced stages such as fluid filled blisters.
2. Female subjects must be using a medically acceptable form of birth control during the study. Acceptable birth control measures include but are not limited to: abstinence, oral contraceptive pills or patch, injectable contraception, barrier contraceptives (condom, diaphragm with spermicide), intrauterine device, vaginal

contraceptive ring, surgical (hysterectomy, tubal ligation), vasectomized partner, and natural post-menopausal inability to conceive. Menopause is defined for this protocol as starting one year after the time of the last menstrual period.

3. Subject has immediate access to the kit containing the clinical trial material. (The subject will demonstrate access to the clinical trial material kit by reading the Randomization Number printed on the label on the kit.)
4. Subject is able to appear for a clinic visit within 24 hours from the time of enrollment into the Treatment Phase of the study (from the time the subject called to establish entry into the Treatment Phase of the study) and is able to return to the clinic for the full 14 day duration of the study if necessary.

#### **4.2 Exclusion Criteria**

1. Subjects with any evidence of active malignancy or immunodeficiency disease within the last 30 days. Subjects who have completed therapy and are considered unlikely to relapse or who have had surgery and do not have any evidence of disease, are eligible for the study.
2. Subject using topical steroids on or near the face or immunomodifying drugs, e.g. systemic (oral, intravenous) steroids within the last 30 days; use of inhaled steroids does not exclude a subject from the study.
3. Subject using a nonsteroidal anti-inflammatory drug (NSAID), except for low doses of aspirin ( $\leq 325$  mg/day) used for cardiovascular purposes, or any other analgesic, within 12 hours of calling clinic to report visible signs of a herpetic lesion.
4. Subject has used an investigational drug and/or device within the last 30 days.
5. Subjects who have used any anti-viral drug, or any other systemic or topical medications, including home remedies, intended to treat cold sores (e.g. lysine, topical tea tree oil, topical honey) within the last 30 days.
6. Subject has had a vaccine for herpes simplex virus type 1 (typically oral herpes) or 2 (typically genital herpes).
7. Subject is more than 75 years of age.
8. Subject is pregnant, as checked by subject questioning prior to dosing.
9. Subject has abnormal skin conditions (e.g. acne, eczema, psoriasis, albinism, or chronic vesiculobullous disorders) that occur in the area of the cold sore lesion, or has significant facial hair in the area of the cold sore, that might affect the normal course of the cold sore or might impair accurate evaluation of the cold sore lesion.
10. Subject is currently enrolled in another clinical trial involving a drug and/or device.
11. Subject requires chronic use of analgesics or NSAIDs, except for low doses of aspirin ( $\leq 325$  mg/day) used for cardiovascular purposes. If a subject is unlikely to get through the treatment phase of the protocol without requiring the use of analgesia for a chronic condition, e.g. back pain, recurrent daily headaches, the subject should be excluded.
12. Subject has a recent history of renal dysfunction or serious hepatic disease. Renal dysfunction encompasses both acute and chronic renal failure, the former resulting from the sudden loss of the ability of the kidneys to excrete wastes,

concentrate urine, and conserve electrolytes and the latter resulting from the gradual and progressive loss of these capabilities.

Examples of serious hepatic disease would include alcoholic liver disease, chronic hepatitis, autoimmune hepatitis and a variety of inherited diseases. The underlying cause of a documented recent mild increase in liver enzymes should be considered when deciding whether or not to exclude such a subject.

13. Subject has a history of alcoholism or drug abuse within the preceding 12 months. A subject with a history of a pathological pattern of alcohol use that causes a serious impairment of social or occupational functioning should be excluded. Such subjects may exhibit symptoms of tolerance and withdrawal along with other behavioral symptoms.
14. Subject is institutionalized.
15. Any history which, in the Investigator's judgment, makes the subject ineligible or places the subject at undue risk.
16. Subject is unwilling to comply with the restrictions outlined in Section 5.4 below.

#### **4.3 Restrictions During the Treatment Phase**

1. The subject is not to use any oral or topical prescription or over-the-counter medications to treat the current herpes labialis lesion, or apply any cosmetics, lip balms, ointments, moisturizers or home remedies to the affected area.
2. The subject is not to use any pain medication or NSAID agent, except low doses of aspirin ( $\leq 325$  mg/day) used for cardiovascular purposes, during the Treatment Phase of the study.
3. The subject is not to mechanically disrupt the lesion (i.e. scrubbing, lancing, shaving the area, rubbing with alcohol, etc.).
4. Merlin contains an alpha hydroxyl acid that may increase the skin's sensitivity to the sun and particularly the possibility of sunburn. Subjects should therefore limit sun exposure while using Merlin, and for one week afterwards.

A subject who does not meet one or more of the Inclusion Criteria or certain Exclusion Criteria may still be eligible for continuing in the study. Those subjects would be instructed that they cannot be entered into the Treatment Phase of the study at that time, but must wait until their next outbreak at which time they can call in again to see if they qualify to begin the study treatment.

## 5 Summary of Events

EVENT	Screening <sup>1</sup>	(Day 0) Treatment Day <sup>7</sup>	Visit Day 1	Visit Day 2	Visit Day 3 <sup>8</sup>	Visit Day 4	Visit Day 5	Visit Day 6	Visit Day 7	Visit Day 8	Visit Day 9	Visit Day 10	Visit Day 11	Visit Day 12	Visit Day 13	Visit Day 14	F/U <sup>11</sup>
Clinic visit <sup>2</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X																
Enrollment	X																
eligibility criteria																	
Treatment Phase		X <sup>3</sup>															
eligibility criteria																	
Medical history;	X																
Physical Exam and																	
Vitals																	
Pregnancy test	X	(see footnote 6)															
Treatment		X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	(X) <sup>4</sup>	(X) <sup>4</sup>	(X) <sup>4</sup>									
Subject Diary <sup>2</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diary Review <sup>2</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinician lesion		X <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
assessment <sup>2</sup>																	
Adverse events <sup>2,10</sup>		X <sup>9</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con meds <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

<sup>1</sup> To be conducted prior to dosing. At this time, subject is instructed on how to apply Merlin and given study materials to take home. If the subject comes into the clinic for screening with an already existing lesion that meets the study criteria, then the subject could begin treatment immediately. In that instance the Screening and Treatment Day would coincide with the Visit Day 1 clinic visit.

<sup>2</sup> All subjects will be followed daily until Stage 7, reporting daily for a minimum of 3 consecutive days, with the last clinic visit at the time of complete healing or at 14 days, whichever is earlier.

<sup>3</sup> Treatment Phase eligibility criteria are checked via telephone prior to dosing.

<sup>4</sup> To be performed by subject. Merlin administrations will begin on Treatment Day. Most typically, it is expected that subjects will treat outside of the clinic on Treatment Day, and come in within 24 hours, (on Visit Day 1), for their first lesion evaluation. If, however, a subject can come in to the clinic for a lesion evaluation the same day as their treatment starts, then Treatment Day and Visit Day 1 will coincide. Treatments will continue through at least Visit Days 1, 2, and 3. If Treatment Day and Visit Day 1 are separate days, then treatment on Visit Day 4 will be administered only if the subject was unable to complete all three (3) sets of treatments on Treatment Day. If Treatment Day and Visit Day 1 coincide, then treatment on Visit Day 5 will be administered only if the subject was unable to complete all three (3) sets of treatments on Treatment Day (Visit Day 1). In either instance a total of twelve (12) treatments (36 applications) over 96 hours from the time of the first treatment is the maximum duration of treatments.

<sup>5</sup> The first lesion scores, up until first visible signs of a herpetic lesion, are determined by the subject prior to the first treatment. All other lesion scores are determined in the clinic by the Investigator or the Investigator's trained designee.

<sup>6</sup> For women with child-bearing potential. On Treatment Day "Pregnancy Status" will be determined by asking the subject if she is pregnant or if she has changed her contraceptive practice such that there might be a significantly increased likelihood that she could have become pregnant.

<sup>7</sup> Treatment Day is the first day a subject reports visible signs of a herpetic lesion, as confirmed by telephone, and is instructed to begin treatment. If the subject can visit the clinic that same day, Treatment Day will coincide with Visit Day 1.

<sup>8</sup> Minimum duration of study for all subjects, i.e., three (3) consecutive days of clinic visits for lesion, adverse event and concomitant medication assessment.

<sup>9</sup> Treatment Day Adverse Events will be reported to clinic at the first clinic visit on Visit Day 1.

<sup>10</sup> Subjects who discontinue prior to Visit Day 3 but have administered any treatment should be followed for safety until at least Visit Day 3.

<sup>11</sup> The follow-up (F/U) study visit for safety is to be conducted by telephone 2 weeks, or up to 3 weeks, if there are scheduling issues, after the subject completes the Treatment Phase of the study

## 6 Study Endpoints

### 6.1 Efficacy Endpoints

#### 6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the clinician assessed duration of the classical herpetic lesions.

#### 6.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- clinician assessed
  - duration of the herpetic episode (classical and non-classical)
  - duration until complete healing of the herpetic episode (classical and non-classical)
  - prevention of progression to a classical lesion
  - maximum lesion area of the classical lesions
  - cumulative lesion area of the classical lesions
  - cumulative lesion area of all lesions
  - duration of classical herpetic lesion hard scab

#### 6.1.3 Other Efficacy Endpoints

Based on patient diary entries, the other efficacy endpoints include:

- subject assessed:
  - duration of the classical herpetic lesion
  - duration of the herpetic episode (classical and non-classical)
  - duration of complete healing of the herpetic episode (classical and non-classical)
  - prevention of progression to a classical lesion
  - duration of classical herpetic lesion hard scab
  - severity of lesion pain
  - duration of lesion pain

#### 6.1.4 Efficacy Endpoint Definitions

Definitions of the efficacy endpoints are detailed below.

**Duration of the classical herpetic lesion:** Duration is based on staging of the lesion.

Staging is graded as follows: 0=prodromal, 1=erythema, 2=papula/edema, 3=vesicle/pustule, 4=ulcer/soft crust, 5=hard crust, 6=residual swelling/dry flaking, 7=normal skin. The duration of a classical lesion is defined as the time, in hours, from the beginning of treatment to the onset of Stage 6, or, if Stage 6 is never observed, Stage 7. A classical lesion is defined as one that progresses through any of stages 3, 4 or 5.

**Duration of the herpetic episode (classical and non-classical):** For a classical lesion, the duration of the herpetic episode is defined as the time, in hours, from the beginning of treatment until the loss of hard crust (stage 6; residual erythema can be present after loss of

hard crust). For non-classical (aborted) lesions, duration is defined as the time, in hours, from the beginning of treatment until complete resolution of all local signs and symptoms (stage 7).

**Duration until complete healing of the herpetic episode (classical and non-classical):** Duration until complete healing of the herpetic episode is defined as the time, in hours, from the beginning of treatment to the onset of Stage 7, for both classical and non-classical lesions. All subjects will visit the clinic daily, for a minimum of 3 days and a maximum of 14 days, until the lesion reaches Stage 7 with no signs or symptoms of a herpetic lesion.

**Prevention of progression to a classical lesion:** Prevention of progression to classical lesions will be defined as yes for subjects who experience a classical herpetic lesion (i.e., one that passes through any of Stages 3, 4 or 5 (vesicle/pustule, ulcer/soft crust, or hard crust)) and as no for subjects with only aborted, non-classical lesions.

**Maximum lesion area of the classical lesions:** Maximum lesion area of the classical lesions is defined as the maximum lesion area (length x width) for classical lesions during the vesicular, ulcerative, and hard crust stages.

**Cumulative lesion area of the classical lesions:** Cumulative lesion area of the classical lesions is defined as the cumulative lesion area, for which classical lesion areas, day by day, will be added.

**Cumulative lesion area of all lesions:** Cumulative lesion area of all lesions is defined as the cumulative lesion area of both classical and non-classical recurrences.

**Duration of classical herpetic lesion hard scab:** Duration of classical herpetic lesion hard scab will be defined as the assessed duration of the hard crust, stage 5, for the classical lesions. This duration will represent the onset of stage 5 until the time of classical lesion healing at stage 6 or 7, whichever occurs earlier. For lesions that bypass stage 5, duration of hard scab phase will be calculated as time between the two adjacent assessments either side of stage 5.

**Severity of lesion pain:** Pain will be evaluated based on the subject's diary, where the subject will record, just prior to each treatment and three times daily once treatment is complete, the level of pain caused by the defined lesion. The rating scale for pain assessment has four levels for severity: none (1), mild (2), moderate (3), and severe (4).

**Duration of lesion pain:** Duration of pain will be measured in hours from the time of the first occurrence of a pain level of mild, moderate, or severe until a consistent score of a pain level of none has been achieved over at least 2 consecutive pain assessments, or until the lesion is completely healed, whichever occurs first. Subjects who do not reach the no-pain level within 14 days will be considered censored immediately following their last pain assessment. Subjects who never reach a pain level of mild, moderate, or severe will be assigned a duration of pain value of 0 hours.

## 6.2 Safety Endpoints

Adverse events (AEs) are the only safety endpoints captured in this study.

# 7 Data Analysis and Statistical Considerations

Statistical summary tables and subject data listings will be prepared using SAS Version 9 or higher (SAS Institute, Cary, North Carolina, USA).

## 7.1 Analysis Populations

### 7.1.1 Safety Population

All subjects who have been entered into the Treatment Phase of the study and self-administered any treatment will be included in the Safety Population. A subject will be included in a treatment group for analysis based upon the treatment actually administered, rather than the group to which he or she has been assigned. For example, a subject who is randomized to receive placebo treatments but inadvertently receives active treatment will be included in the group receiving active treatment.

Should a subject gain access to their clinical trial materials and treat themselves without having called in to the clinic and been given permission to open their Treatment kit, that subject will also be included in the Safety Population if follow-up safety data are available.

The Safety Population will be used for all subject listings and for summary tables of the safety endpoints. No formal statistical analyses are planned for the safety endpoints.

### 7.1.2 Modified Intent-to-Treat (MITT) Population

All subjects who have been entered into the Treatment Phase of the study will be included in the modified intent-to-treat (MITT) Population. It is considered a “modified” intent to treat population in that it does not include all randomized subjects but includes only those randomized subjects who access their treatment, i.e., are told to open their kit. A subject will be included in a treatment group for analysis based upon the treatment to which he or she has been assigned; imputation on the primary endpoint only is planned for the MITT Population – see section 7.13. The MITT Population will be used as the primary analysis population and for all efficacy analyses.

### 7.1.3 Efficacy Evaluable (EE) Population

All subjects who have been entered into the Treatment Phase of the study were reported to have successfully completed treatment, and have been followed successfully until their lesion heals, or until 14 days, whichever is earlier, will be included in the efficacy evaluable (EE) Population. Prior to breaking the study blind, study data will be reviewed to determine which subjects need to be excluded from the EE Population. A subject will be included in a treatment group for analysis based upon the treatment actually administered, rather than the group to which he or she has been assigned. For example, a subject who is randomized to receive a placebo treatment but inadvertently receives an active treatment will be included in the group

receiving an active treatment, and vice versa. Only actual observations will be included in the analyses; no imputation for missing data will be performed. The EE Population will be used for all efficacy analyses.

## **7.2 General Analysis**

All statistical tests will be done using two-sided tests and a Type I error rate of 0.05.

Data listings will be based on all subjects in the Safety Population.

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum values. Categorical variables will be summarized by frequencies and percentages.

The primary analyses will compare the active treatment group to the placebo control group. Aside from any placebo effect, there should be no efficacy associated with the placebo solution. In addition to the overall analyses, all statistical comparisons will be performed with the subjects stratified based on whether they were treated at erythema (Stage 1) or papule/edema (Stage 2). Inference testing will be completed on efficacy data to compare the groups. Safety data will be summarized with descriptive statistics, but no inference testing will be completed to compare the groups statistically.

## **7.3 Disposition**

The number and percentage of subjects completing the study and terminating early, with the reason for termination, will be summarized for each treatment and overall for the Safety Population. The number of subjects screened, randomized and in each study population will be summarized for each treatment and overall for the Safety Population.

## **7.4 Demographics**

Demographics and baseline characteristics will be summarized with descriptive statistics by treatment and overall for all three analysis populations. For continuous variables, summary statistics (mean, median, standard deviation, minimum, and maximum) will be provided. For categorical variables, the frequency and percent in each category will be presented.

## **7.5 Medical History**

Medical history will be summarized by treatment and overall for all three analysis populations.

## **7.6 Prior and Concomitant Medication**

A listing of concomitant medications will be provided for the Safety Population.

## **7.7 Physical Examinations**

A listing of physical examination findings will be provided for the Safety Population.

## **7.8 Vital Signs**

A listing of vital signs will be provided for the Safety Population.

## 7.9 Pregnancy

A listing of vital signs will be provided for the Safety Population.

## 7.10 Compliance

Estimating compliance with diary data is subjective and often unreliable. Attempts will be made to estimate compliance and calculate confidence intervals. It will be more informative, however, to use individual data rather than summary data. Subject listings with combined data, therefore, will be provided, including: when the clinical lesion assessment reached stage 4, expected number of treatments, actual number of treatments, and time between treatments from the diaries.

## 7.11 Diaries

Diary data will be summarized by treatment group and visit for the Safety Population. Severity (1=none, 2=mild, 3=moderate, 4=severe) and stage (0=prodromal, 1=erythema, 2=papula/edema, 3=vesicle/pustule, 4=ulcer/soft crust, 5=hard crust, 6=residual swelling/dry flaking, 7=normal skin) will be summarized with counts and percentages.

## 7.12 Safety Data

The Safety Population will be used for all summaries of safety data. The safety analysis will be performed on the Safety Population. Assessment of safety and tolerability will be based on AEs. Each AE will be graded with respect to its relationship to treatment using five categories: not related, unlikely, possible, probable, and highly probable. Each AE will also be graded on a three-point severity scale: mild, moderate, and severe. AEs will be coded by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects experiencing treatment emergent adverse events (TEAE) will be tabulated for each treatment group by system organ class (SOC) and preferred term (PT). TEAEs are those occurring on or after first dose of study product. A subject having the same TEAE more than once over the course of the study will be counted only once in the incidence calculation for that TEAE. Similarly, if a subject had more than one TEAE in a SOC, the subject will be counted only once in the total number of subjects with TEAEs for that SOC. The number and percentage of subjects experiencing TEAEs will also be tabulated for those related to treatment (i.e., including possible, probable and highly probable), those that are severe, and those that are serious. If a TEAE is reported more than once for a subject, only the most related event will be counted in the summary for related TEAEs. For the summary of severe TEAEs, if a TEAE is reported more than once for a subject, only the most severe event will be counted in the summary. For the summary of serious TEAEs, if a TEAE is reported more than once for a subject, only the most serious event will be counted in the summary.

## 7.13 Efficacy Analyses

The efficacy analysis will be performed on both the MITT and the EE Populations; and stratified based on whether they were treated at erythema (Stage 1) or papule/edema (Stage 2). Groups will be compared at each visit for which the endpoint of interest is captured.

### **7.13.1 Duration**

Imputation will only be used for analyses of duration endpoints and only in the MITT Population. Duration for subjects who drop out prior to healing will be imputed with a duration of 336 hours (14 days x 24 hours) for the main analyses of duration endpoints in the MITT Population. Hodges-Lehmann technique will be used for estimation and Wilcoxon rank sum tests will be used to compare the groups on duration endpoints in the MITT Population. In addition, subjects who drop out prior to healing will be considered censored in a sensitivity analysis of duration endpoints in the MITT Population and Kaplan-Meier estimation methods will be used with log-rank tests for comparison of the groups.

For analysis of duration in the EE Population, no imputation is required since these are complete cases. Hodges-Lehmann technique will be used for estimation and Wilcoxon rank sum tests will be used to compare the groups on duration endpoints in the EE Population.

### **7.13.2 Prevention of Progression**

For all endpoints on the occurrence of prevention of progression, counts and percentages will be summarized, and chi-square tests, or Fisher's exact test will be used to compare groups, as appropriate. Fisher's exact tests will be used if any of the expected cell counts in the Rx C crosstabulations are less than 5.

### **7.13.3 Area**

For area endpoints, means, medians, standard deviations and ranges will be summarized. T-tests will be used to compare groups if the sizes are approximately normally distributed, or Wilcoxon rank sum tests will be used if the sizes are markedly non-normally distributed.

### **7.13.4 Pain Severity**

For pain severity, counts and percentages will be summarized for all levels of severity, and Cochran-Mantel-Haenszel tests will be used to compare the groups.

### 7.13.5 Analysis Matrix

For all efficacy endpoints the following matrix will be used for analyses:

Endpoint	Popu- lation	Analysis	Description	Methods
Duration	MITT	Main Analysis	Impute duration for subjects who drop out prior to healing with a duration of 336 hours (14 days x 24 hours).	Hodges-Lehmann estimation methods; Wilcoxon rank sum test to compare groups
		Sensitivity Analysis	Subjects who drop out prior to healing will be considered censored.	Kaplan-Meier estimation methods; Log-rank test to compare groups
	EE	Main Analysis	No imputation required since these are complete cases.	Hodges-Lehmann estimation methods; Wilcoxon rank sum test to compare groups
Prevention of Progression	MITT/EE	Main Analysis	No imputation	chi-square or Fisher's exact test to compare groups
Area	MITT/EE	Main Analysis	No imputation	t-test or Wilcoxon rank sum test to compare groups
Pain Severity	MITT/EE	Main Analysis	No imputation	Cochran-Mantel-Haenszel test to compare groups

\*All analyses in this matrix will be completed for all subjects in the specified Analysis Population, then the analyses will be stratified for subjects treated at Stage 1 and those treated at Stage 2.

### 7.13.6 Pooling of Centers

This is a multi-center study planned at multiple investigational sites. As all sites will be functioning under the same protocol, it is assumed that no substantial differences between sites will be evidenced in the data and the data from all centers will be pooled together for analyses. However, formal statistical assessment of these assumptions will be explored. In order to assess pooling of data from multiple centers or whether there are differences among centers in treatment effects, a Cox proportional hazards model analysis of the duration of herpetic episode will also be performed for the primary duration endpoint and for both the MITT and EE Populations. The model will include terms for treatment, center, and treatment by center interaction. A test will be performed to test for the significance of the interaction. This test will be conducted at the 0.10 level of significance. If the interaction is found to be significant, estimates of treatment effect will be provided by center, as well as overall.

## 8 Handling of Missing Data

All missing data will be queried. Missing efficacy data on duration endpoints for subjects in the MITT Population which are not retrievable through queries will be handled using imputation of 336 days. Other missing data, including missing safety data, will not be imputed.

## **9 Changes from the Protocol**

No changes in the analyses described in the original protocol or subsequent amendments are planned. If changes are made prior to unblinding, this document may be amended and such changes will be described. Changes made after unblinding will be noted in the clinical study report.

## 10 Tables

Disposition

Demographics – Safety

Demographics – MITT

Demographics – EE

Medical History – Safety

Medical History – MITT

Medical History – EE

Efficacy – Duration Endpoints – MITT

Efficacy – Duration Endpoints – EE

Efficacy – Prevention of Progression – MITT

Efficacy – Prevention of Progression – EE

Efficacy – Area Endpoints – MITT

Efficacy – Area Endpoints – EE

Efficacy – Pain Severity – MITT

Efficacy – Pain Severity – EE

Summary of Subjects with TEAEs – Safety

Occurrence of TEAEs by SOC and PT – Safety

Occurrence of TEAEs Related to Treatment by SOC and PT – Safety

Occurrence of Severe TEAEs by SOC and PT – Safety

Occurrence of Serious TEAEs by SOC and PT – Safety