

# Topical Remedy, LLC

## CLINICAL STUDY PROTOCOL

## 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**

Version 1

## **Protocol History:**

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Topical Remedy, LLC.  
c/o Benu BioPharma, Inc.  
5 Commonwealth Rd., Suite 2A  
Natick, MA USA 01760  
Telephone: (508) 651-3700

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## PROTOCOL FOR TOPICAL REMEDY, LLC

## CLINICAL STUDY

**TITLE: 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**

## Topical Remedy, LLC

IND Number: 116,789

**Sponsor's Representative:** Eric Morrel, PhD  
VP, Clinical Research  
Phone: (508) 651-3714  
Fax: (508) 651-3703  
Mobile: (508) 208-5634

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**Signature**

Date

## Medical Monitor:

Nadia Tullio, MD  
Assistant Director Medical Affairs, Accelovance Inc.  
Phone: (240) 238-4961  
e-mail: [atullio@accelovance.com](mailto:atullio@accelovance.com)

**Sponsor:**

Topical Remedy, LLC  
c/o Benu BioPharma, Inc.  
5 Commonwealth Rd.  
Suite 2A  
Natick, MA 01760  
Phone: (508) 651-3700  
Fax: (508) 651-3703

The above signed confirms herewith to have read and understood this study protocol, furthermore, to accomplish this study according to the protocol and the Good Clinical Practice guidelines, as well as local regulations, and to accept respective revisions conducted by authorized personnel of Topical Remedy, LLC and by competent authorities.

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## 1. STUDY SYNOPSIS

<b>Name of Sponsor/Company:</b> Topical Remedy, LLC	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>	<b>(For National Authority Use only)</b>
<b>Name of Finished Product:</b> Merlin		
<b>Name of Active Ingredient:</b> Ethanol and Glycolic Acid	<b>Page:</b>	
<b>Title of Study:</b> 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		
<b>Study Centers:</b> There will be approximately 5 - 10 study centers.		
<b>Publication (reference):</b> Not applicable		
<b>Study Duration:</b> Approximately 9 months		
<b>Objectives:</b> The primary efficacy endpoint of this study is the clinician assessed duration of the classical lesion.		
<b>Methodology:</b> This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Merlin (10 % ethanol and 0.6% glycolic acid) for the treatment of herpes labialis lesions. Subjects who meet the eligibility requirements at the screening/randomization visit will be randomized in a 1:1 ratio to one of two treatment groups: 1) twelve (12) treatments with Merlin solution, administered 6 hours apart (up to 3 per day) over the ensuing 96 hours (4 days) from the time of the first treatment; or 2) twelve (12) treatments with 10% ethanol, as a placebo, administered 6 hours apart (up to 3 per day) over the ensuing 96 hours (4 days) from the time of the first treatment. Each treatment of Merlin or placebo consists of applying the solution three (3) times, within a time period of 40 minutes or less, while allowing time for the solution to dry on the lesion between applications; this will result in a total of thirty six (36) applications over 96 hours (4 days). 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.		

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<b>Name of Finished Product:</b> Merlin	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Ethanol and Glycolic Acid	<b>Page:</b>	

**Methodology (cont.):**

After being enrolled and randomized into the study, subjects will be sent home with a kit containing a bottle filled with either Merlin (active) or the 10% ethanol placebo solution and a packet of foam-tipped applicators sufficient to apply three (3) study treatments (nine (9) applications). The subject will be instructed to contact the clinic by telephone at the first signs and/or symptoms of a recurrent herpetic episode (Stage 0, prodrome, Stage 1, erythema, or Stage 2, papule/edema). The lesion and lesion stage then will be confirmed by telephone interview with the subject. Subjects reporting either a Stage 1 or Stage 2 lesion will be instructed to begin treatment immediately, thereby initiating the Treatment Phase of the study. 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 signs of a cold sore, i.e. redness or swelling, representing a Stage 1 or Stage 2 lesion. Once the subject calls in and confirms by telephone interview that their lesion has reached Stage 1 or 2, they will be instructed to begin treatment immediately. The subject will be told to continue treatment for the remainder of the day with the treatment schedule outlined above, and to continue to treat with a set of three (3) applications, three (3) times each day, for a total of twelve (12) treatments resulting in thirty-six (36) applications in total. The subject also will be instructed to return to the clinic within 24 hours of the initial treatment for evaluation of the stage of the herpetic 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.

**Number of Subjects:** Approximately four hundred and fifty (450) subjects will be enrolled into the study, 225 into the active treatment group and 225 into the placebo treatment group. At least 75 subjects in the active treatment group, and 75 subjects in the placebo treatment group, will enter the Treatment Phase of the study and administer treatments.

**Diagnosis and Main Criteria for Inclusion:** All enrolled subjects must be 18 to 75 years of age. To be enrolled, he or she must also have a history of recurrent herpes labialis and report at least 3 recurrences during the preceding 12 months. To enter the Treatment Phase of the study, the subject must have a herpes labialis lesion assessed by the subject and confirmed by telephone contact to be at either Stage 1 (erythema) or Stage 2 (papule/edema), and the subject must be able to report to the clinic for an initial lesion assessment within 24 hour of detection of first signs and/or symptoms of a herpetic episode. The subject must also be able to report to the clinic for up to 14 days.

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<b>Name of Finished Product:</b> Merlin			
<b>Name of Active Ingredient:</b> Ethanol and Glycolic Acid			
<p><b>Test Product and Mode of Administration:</b> Merlin is the name given to a novel formulation intended for the treatment of topical viral infections. The formulation consists of 10% ethanol and 0.6% glycolic acid, with a pH of 2.5. A single-use, foam-tipped applicator will be used for application to the skin.</p> <p><b>Duration of Treatment:</b> Each subject, for each set of treatments, will administer three (3) applications of Merlin or placebo, depending upon how a subject has been randomized, 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 treatments, i.e. thirty-six (36) applications, will be administered over the ensuing 96 hours (four (4) days), following the time of the first treatment. On each day, treatments will be administered six (6) hours apart, with a maximum of three (3) 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.</p>			
<p><b>Reference Therapy, Dose and Mode of Administration:</b> The reference therapy will be a set of three (3) applications of 10% ethanol, applied twenty (20) minutes apart with the same dosing schedule as outlined above in "Duration of Treatment."</p> <p><b>Criteria for Evaluation:</b> The primary efficacy endpoint is the clinician assessed duration of the classical herpetic lesion.</p> <p>Secondary efficacy endpoints are as follows:</p> <ul style="list-style-type: none"> <li>• Clinician assessed duration of the herpetic episode</li> <li>• Clinician assessed duration of complete healing of the herpetic episode</li> <li>• Clinician assessed prevention of progression to a classical lesion</li> <li>• Clinician assessed lesion size (maximum lesion area; cumulative lesion area)</li> <li>• Clinician assessed duration of the herpetic lesion hard scab</li> </ul> <p>Based on patient diary entries, other efficacy endpoints will be:</p> <ul style="list-style-type: none"> <li>• Subject assessed duration and severity of lesion pain</li> <li>• Subject assessed duration of the classical herpetic lesion</li> <li>• Subject assessed duration of the herpetic episode</li> <li>• Subject assessed duration of complete healing of the herpetic episode</li> <li>• Subject assessed prevention of progression to a classical lesion</li> <li>• Subject assessed duration of the herpetic lesion hard scab</li> </ul> <p>The only safety endpoint is adverse events.</p>			

<b>Name of Sponsor/Company:</b> Topical Remedy, LLC	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use only)</b>
<b>Name of Finished Product:</b> Merlin	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Ethanol and Glycolic Acid	<b>Page:</b>	
<p><b>Statistical Methods:</b> Generally, statistical hypothesis tests will be two-tailed, and statistical significance will be declared when the p-value is less than 0.05. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages.</p> <p>All subjects who received (at least some) treatment, whether they were formally entered into the Treatment Phase of the study or applied the test material without formal authorization, will be included in the Safety Population. The safety analysis will be performed on the Safety Population.</p> <p>All subjects who have been entered into the Treatment Phase of the study will be included in the Modified Intent to Treat (MITT) population. The MITT population will be used as the primary analysis population. All subjects who have been entered into the Treatment Phase of the study and have been followed successfully until their lesion healed, or until 14 days, whichever is earlier, will be included in the Efficacy Evaluable population. The efficacy analysis will be performed on both the MITT and the Efficacy Evaluable populations.</p> <p>No imputation of missing data will be performed for the efficacy analyses for the Efficacy Evaluable population.</p> <p>The duration of the classical herpetic lesion (both clinician and patient assessed) will be analyzed using the Hodges-Lehmann method as the primary efficacy analysis method for estimating the median difference between the two arms. Duration of the herpetic episode (both clinician and patient assessed), duration of complete healing of the herpetic episode (both clinician and patient assessed), duration of the herpetic lesion (both clinician and patient assessed), duration of the herpetic lesion hard scab (both clinician and patient assessed), and duration of pain will be analyzed in the same manner as the duration of the classical lesion.</p> <p>The proportions of subjects in each treatment group who do not display classical lesions (prevention of progression to classical lesions) will be compared using Fisher's Exact Test.</p> <p>For pain, the maximum severity will be analyzed using the Cochran-Mantel-Haenszel Test to test for differences between treatment groups.</p>		

## 2. 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.

Approximately 20 to 40% of the adult population experience recurrent outbreaks of herpes labialis, or cold sores.<sup>1</sup> In almost all cases, the disease is due to reactivation of chronic, latent herpes simplex virus type 1 infection from the ganglion of the trigeminal nerve. When the latent infection is activated by any one of a variety of triggers, virions descend through the sensory nerve axons and reinfect the peripheral epithelium. The new herpes labialis lesion matures within 8 hours after onset<sup>2</sup>, leaving very little time for successful chemotherapeutic intervention.

The current standard of care for recurrent herpes labialis involves an oral or topical antiviral given episodically at the onset of each recurrence. A variety of topical over-the-counter preparations are available, but in most cases the mechanism of action is ambiguous and very few clinical trials have been performed to define their efficacy. Studies of acyclovir ointment have provided little evidence of efficacy for herpes labialis in immunocompetent subjects.<sup>3,4</sup> Acyclovir and penciclovir cream-based formulation are both approved for treatment of herpes labialis, but while both do penetrate the skin more effectively than the acyclovir ointment, both exhibit relatively limited efficacy with regard to shortening the duration of a herpetic episode.<sup>5,6</sup> Docosanol 10% cream (Abreva; GlaxoSmithKline) is the most well-studied over-the-counter product, with 2 randomized trials suggesting some efficacy of treatment. However, because an unrelated placebo was used in these studies, the true level of efficacy cannot be objectively determined.<sup>7</sup> All these approved topical treatments, as well as Valtrex and Famvir, the approved oral treatments, provide, at best, approximately a one day shortening of the duration of a herpetic episode, and none of them results in a reduction in the percent of the worst outbreaks, the so-called classical lesions. Even the most recently approved new treatment, Xerese, a combination of acyclovir and hydrocortisone, provides less than one day shortening of the herpetic episode, and an only slightly better, 1.5 day, decrease in the time until complete healing of the outbreak. Xerese does claim to significantly reduce the percent of classical lesion outbreaks, but the increase in the percent of so-called “aborted lesions” with Xerese is only modestly better than the essentially ineffective acyclovir cream (42% for Xerese versus 35% for acyclovir cream).<sup>7</sup>

A pilot clinical study (Protocol TR-H-111) was performed by the sponsor to investigate the potential skin irritancy of Merlin. The study involved the application in 40 subjects, of a total of thirty-six (36) treatments over four (4) days. More specifically, each subject administered three (3) applications of Merlin or placebo, depending on how a subject was randomized, twenty (20) minutes apart, for each set of treatments. These sets of treatments were repeated two (2) more times at six (6) and twelve (12) hour after the start of the initial treatments, for a total of nine (9) treatments of active or placebo on Day 1. The sets of treatments were then re-applied three (3) times each day for three (3)

additional days, resulting in the above noted total of four (4) days of treatment with thirty-six (36) applications of active or placebo.

On Day 1, scoring of the skin reaction was performed at the treatment site within 5 min prior to each initial application in a set of 3 applications, and within 5 minutes after the third application in the set of 3 applications. On Days 2 through 4, scoring of the treatment site was performed only for the first set of applications, when the subject was in the clinic for the first set of test article applications. Similarly to the timing for the evaluations on Day 1, scoring of the skin reaction in the treatment site was performed within 5 min prior to the initial application in the first set of 3 applications, and within 5 minutes after the third application in the first set of 3 applications. Skin reaction scoring on Day 5 was performed at 24 hours ( $\pm$  1 hour) from the time of the first treatment on Day 4. Any skin reactions noted on Day 5 were to be followed either with daily clinic visits or telephone contacts, as deemed appropriate, until the event was resolved.

The results of the skin irritation portion of the study revealed that all treatments were very well tolerated by all subjects, with no significant skin irritation and only a few, mild adverse events. Minimal erythema was the most notable reaction observed immediately after treatment in three subjects, and this resolved in all subjects within 1 hour. The only other reported adverse drug related adverse event was mild burning on treatment application in one subject; this also resolved rapidly.

Merlin, therefore, appears to be safe as the only reported adverse events were very mild skin irritation in three subjects and mild burning on application in one subject.

This was followed by Phase 2 study (TR-H-211) the primary objective of which was to assess the efficacy of Merlin as compared to a placebo treatment, on the clinician assessed duration to complete healing of the herpetic episode. Other endpoints included the clinician assessed: 1) prevention of progression to a classical lesion associated with herpes labialis; 2) duration of classical herpetic lesions; and 3) duration of the herpetic episode. The safety of Merlin was also evaluated.

A total of 469 subjects were enrolled in the study with 172 subjects actually treated. After being enrolled and randomized into the study, subjects were sent home with a kit containing a bottle filled with either Merlin (active) or the 10% ethanol placebo solution and a packet of foam-tipped applicators sufficient to apply three study treatments (nine (9) applications). The subject was instructed to contact the clinic by telephone at the first signs and/or symptoms of a recurrent herpetic episode (Stage 0 or 1, prodromal or erythema). The lesion then was confirmed by telephone interview with the subject, and upon confirmation of the lesion, the subject was instructed to begin treatment immediately, thereby initiating the Treatment Phase of the study. The subject was told to continue treatment for the remainder of the day with the treatment schedule as described above for the Phase 1 study, and to continue to treat with a set of three (3) treatments, three times each day, for a total of twelve (12) sets of treatments resulting in thirty-six (36) applications in total. The subject also was instructed to return to the clinic within 24 hours of the initial treatment for evaluation of the stage of the herpetic lesion.

Subjects reported 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.

The results of this study found that twelve (12) treatments with Merlin solution, administered 6 hours apart (up to 3 per day) over 96 hours, was generally safe and tolerable in the treatment of subjects with lesions associated with herpes simplex labialis. The majority of treatment-related AEs were classified as mild in intensity. No treatment related AEs in any cohort were classified as severe.

An a priori analysis found that those subjects, who treated with Merlin at first visible signs of a herpetic lesion, erythema, rather than immediately at first symptoms of a herpetic lesion, the prodromal stage, exhibited statistically significant efficacy as compared to placebo for the duration of the classical lesion. The same a priori analysis found trends towards significance for the endpoints of complete healing, duration of the herpetic episode, cumulative lesion size, duration of the hard scab, and the subject assessed severity of lesion pain.

This current clinical study is a follow-up Phase 2 trial using the same Merlin formulation as was used in the studies described above. This trial, as the previous Phase 2 study, will have two treatment arms 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.

### **3. 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. 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 the vesicle/pustule, ulcer, or crust stages (stages 3, 4 or 5).

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

1. The clinician assessed duration of the herpetic episode. 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).
2. The clinician assessed duration until complete healing of the herpetic episode (classical and non-classical lesions) as compared to placebo treatment. For

both classical and non-classical lesions, the duration until complete healing of the herpetic episode is defined as the time, in hours, from the time of treatment until complete resolution of all local signs and symptoms (Stage 7).

3. The clinician assessed prevention of progression to a classical lesion associated with herpes labialis.
4. The clinician assessed lesion size (maximum lesion area; cumulative lesion area).
5. The clinician assessed duration of the herpetic lesion hard scab (end of stage 5/beginning of stage 6).
6. The safety of Merlin

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

7. Subject assessed duration and severity of lesion pain
8. Subject assessed duration of the classical herpetic lesion
9. Subject assessed duration of the herpetic episode
10. Subject assessed duration of complete healing of the herpetic episode
11. Subject assessed prevention of progression to a classical lesion
12. Subject assessed duration of the herpetic lesion hard scab
13. Subject assessed duration and severity of lesion pain.

More detailed explanations of these endpoints are provided in Section 10.7.

#### **4. SUMMARY OF 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. The TR-H-111 study showed that Merlin appears to be safe to use even with repeated dosing over several days in healthy normal subjects. The Phase 2 TR-H-211 trial similarly demonstrated that Merlin was generally safe and tolerable in the treatment of subjects with lesions associated with herpes simplex labialis. TR-H-211 also revealed, in an a priori analysis, that those subjects who treated with Merlin at the first visible signs of a herpetic lesion, erythema, rather than immediately at first symptoms of a herpetic lesion, the prodromal stage, exhibited statistically significant efficacy as compared to placebo for the duration

of the classical lesion. The same a priori analysis found trends towards significance for the endpoints of complete healing, duration of the herpetic episode, cumulative lesion size, duration of the hard scab, and the subject assessed severity of lesion pain.

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, 18 to 75 years of age, who meet the eligibility criteria, including a history of at least 3 recurrences of herpes labialis in the preceding 12 months, will be enrolled into the study. Eligible subjects will be randomized in a 1:1 ratio to one of two treatment groups: 1) a treatment of three (3) applications of Merlin solution, performed within a time period of 40 minutes or less, while allowing time for the solution to dry on the lesion between applications; or 2) a 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 containing a bottle filled with either Merlin (active) or 10% ethanol (placebo) and a packet of foam-tipped applicators sufficient to apply three study treatments (nine (9) applications). 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. Though subjects reporting a Stage 2, papule/edema, lesion will be allowed to treat, subjects should be strongly encouraged to call at the first visible signs of a herpetic lesion. A subject observing a lesion at Stage 1, erythema, therefore, should call in immediately rather than assume they may wait until their lesion reaches Stage 2, papule/edema, to call in. 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. Once the subject calls in and confirms by telephone interview that their lesion has reached Stage 1 or 2, and that they still meet all eligibility criteria, they will be instructed to begin treatment immediately. Subjects will then be instructed to return to the clinic as soon as possible within 24 hours of starting treatment.

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 the lesion is healed.

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. Once the enrollment objectives for the Treatment Phase of the study have been met, the study will be closed to any further enrollment.

**Table 4-1: Treatment Groups and Sample Sizes**

Group	Treatment	Approximate Number of Randomized Subjects	Minimum Number of Subjects Entering Treatment Phase
<b>A</b>	Merlin (10% ethanol; 0.6% glycolic acid)	225	75
<b>B</b>	Placebo (10% ethanol)	225	75

Aside from any placebo effect, there should be no efficacy with the 10% ethanol solution.

## 5. SUBJECT SELECTION

### 5.1 Source of Subjects

Non-institutionalized subjects consisting of members of the community at large will be used in this study.

Approximately four hundred and fifty (450) subjects with a history of recurrent herpes labialis, who meet the eligibility requirements, will be randomly assigned to one of two treatment groups and provided with study materials. Upon noticing visible signs of a herpes labialis lesion which meet the study criteria, the subject will call their clinical study site at which time he or she will be required to answer specific questions to confirm if he or she meets the eligibility requirements. If the subject is eligible for entry into the Treatment Phase of the study, the subject will be instructed to begin treatment immediately. The study will continue until at least 75 subjects have entered the Treatment Phase in each group (Table 4-1), at which time the study will be closed to any further enrollment.

### 5.2 Study Enrollment Eligibility Criteria

The following criteria will be used for the initial Screening-Randomization visit. The Vice President of Clinical Research at Topical Remedy, their designee, or the Medical Monitor, should be consulted to confirm the eligibility of a subject if there is any question as to whether they meet all of the Inclusion or Exclusion criteria.

### **5.2.1 Inclusion Criteria**

1. Male or female subject 18-75 years of age
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), IUD, 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 must have a history of recurrent herpes labialis and report at least 3 separate recurrences (i.e. multiple herpetic lesions in one outbreak count as only one episode) during the preceding 12 months.
4. Subject must have a history of experiencing prodromal symptoms of cold sores (e.g. itching, tingling, or burning) during at least half of their previous cold sore episodes.
5. Subject must have a history of at least half of their cold sore episodes producing classical lesions (i.e., episodes that progressed through macule, papule, vesicle, crust, and healed).
6. Subject must provide voluntary written informed consent to participate in this study.

### 5.2.2 Exclusion Criteria

1. Subjects with 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 requires chronic use of immunomodifying drugs (e.g. systemic steroids) or topical steroids on or near the face; use of inhaled steroids does not exclude a subject from the study. If a subject is unlikely to get through the Treatment Phase of the protocol without requiring the use of an immunomodifying drug for a chronic condition the subject should be excluded.
3. Subject requires chronic use of anti-viral medication.
4. In females of childbearing potential, a positive urine pregnancy test at time of screening.
5. Nursing mothers.
6. Subject is considered unreliable or unable to understand or follow the protocol directions or is unable to comprehend or satisfactorily assess a herpetic lesion as determined by Investigator or designee at screening.
7. Subject has abnormal skin conditions (e.g. acne, eczema, rosacea, psoriasis, albinism, or chronic vesiculobullous disorders) that occur in the area ordinarily affected by cold sores 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.
8. Subject has had a vaccine for herpes simplex virus type 1 (typically oral herpes) or 2 (typically genital herpes).
9. Subject is currently enrolled in another clinical trial involving the use of a drug and/or a device.
10. Subject has previously participated in the current study (TR-H-212).
11. Subject requires chronic use of analgesics or non-steroidal anti-inflammatory agents (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 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 shares a household with another subject already enrolled in the study (TR-H-212). If the other household member has already completed the study, then the currently enrolling subject is not excluded.
15. Subject is institutionalized.
16. Any history which, in the Investigator's judgment, makes the subject ineligible or places the subject at undue risk.

### 5.3 Study Treatment Phase Eligibility Criteria

The following criteria will be used to enter subjects into the study Treatment Phase when a subject previously enrolled into the study calls to report first visible signs of a herpes simplex labialis lesion. Subjects who call in to report experiencing prodromal symptoms (e.g. tingling, itching) are not to be screened for eligibility until they report observing visible signs of a cold sore lesion. The Vice President of Clinical Research at Topical Remedy, their designee, or the Medical Monitor, should be consulted to confirm the eligibility of a subject if there is any question as to whether they meet all of the Inclusion or Exclusion criteria.

#### 5.3.1 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), IUD, 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.

### 5.3.2 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 an 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.

## 5.4 Restrictions During the Treatment Phase

- 5.4.1 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.
- 5.4.2 The subject is not to use any pain medication or non-steroidal anti-inflammatory agent (NSAID), except low doses of aspirin ( $\leq 325$  mg/day) used for cardiovascular purposes, during the Treatment Phase of the study.
- 5.4.3 The subject is not to mechanically disrupt the lesion (i.e. scrubbing, lancing, shaving the area, rubbing with alcohol, etc.).
- 5.4.4 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. See Section 7.2.3 for further details.

## 6 MATERIALS

### 6.1 Drug Supply

All study materials will be supplied by Topical Remedy, LLC and dispensed by the clinic pharmacy at the study site.

Test treatment:

Merlin (10% Ethanol and 0.6% glycolic acid, pH 2.5)

Placebo treatment:

10% Ethanol

Merlin, or the placebo, will be supplied in 4.0 mL HDPE bottles along with single-use foam swabs for application to the skin. The clinic pharmacy will be supplied preassembled Treatment kits, consisting of sealed, hinge top containers, each containing one bottle of Merlin or placebo solution, the bottle blinded with a label noting only the study number, along with one (1) pouch containing nine (9) single-use foam swabs, sufficient for three (3) treatments (9 applications). Based upon how a subject is randomized, Merlin or placebo group, an appropriate Treatment kit will be assigned to that subject.

For Visit Days 1, 2, and 3 study materials, the pharmacy will be supplied in bulk with pouches, each containing nine (9) foam swabs, one for each application over the next 24 hours. The study site will provide a new pouch of foam swabs to the subject each study day after the evaluation of the treatment site.

## **6.2 Drug Identification**

Bottles (4.0 mL HDPE), containing either Merlin or placebo, will be supplied. For blinding purposes, the lot number label on the bottle will be over-labeled by the Sponsor with a label noting only the Study Number along with other required regulatory information. That bottle will be placed in the Treatment kit along with a supply of foam swabs. The pouch of foam swabs will be labeled with the Study Number, a listing of the contents, and the Sponsor address. The Treatment kit will have a double tear-off label. The label adhering to the container will: 1) list the Study Number; 2) have a pre-printed Randomization Number; 3) have a space for filling in the Subject Number associated with that Randomization Number; and 4) contain other required regulatory information and the Sponsor address. The tear-off portion of the label will: 1) list the Study Number; 2) have a pre-printed Randomization Number; 3) have a space for filling in the Subject Number associated with that Randomization Number; and 4) have a pre-printed lot number which will be used for unblinding if necessary.

Randomization to a treatment group will be accomplished through a pre-determined sequence at each site. When a subject is randomized, the site will assign the next available randomization number which corresponds to an identical Randomization Number on the label on the Treatment kit. Once assigned, the pharmacist, or designee, will complete the double, tear-off label on the container by filling in the appropriate Subject Number. The tear-off portion of the label will then be removed and placed into the pharmacy study record.

As noted in Section 6.1, the site will also be supplied, in bulk, with pouches, each containing nine (9) swabs. The study site will provide a new pouch of foam swabs to the subject on Visit Days 1, 2, 3, 4 (if needed on Days 4 and 5), after the evaluation of the treatment site. As with the pouch in the Treatment kit, these pouches will be labeled with the Study Number and Sponsor address.

## **6.3 Drug Storage**

All clinical trial materials should be stored at the clinical site at controlled room temperature in a limited access area.

## **6.4 Randomization**

Approximately four hundred and fifty (450) subjects will be randomized into one of two treatment groups in a 1:1 ratio and will be assigned a sealed kit consisting of enough single use swabs for three (3) treatments (9 applications) and either: 1) Merlin (10%

ethanol and 0.6% glycolic acid, pH 2.5); or 2) placebo (10% ethanol). The randomization code will be generated by Topical Remedy, LLC, or its designee.

A total of at least one hundred and fifty (150) of these subjects, with at least seventy-five (75) subjects in each group, will be instructed to administer drug upon a qualifying lesion outbreak.

#### **6.4.1 Blinding Procedure and Code Breaks**

The study will be double-blinded for all treatment arms. Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of the subject, may the Investigator request that a subject's study treatment assignment be unblinded. Wherever possible the Investigator (or designee) must contact the Medical Monitor prior to breaking the blind. Should it be determined that the blind needs to be broken, the Medical Monitor will contact the Vice President of Research and Development at Topical Remedy who will be able to perform any required unblinding. The Investigator must document the reason for breaking the code. The randomization code will be broken in order to perform the statistical analysis only after all the data of the study have been cleaned and audited and the database locked.

#### **6.5 Drug Accountability/Retention**

Clinical Trial Material Accountability Logs must be kept current and should contain the following information:

- Identification of the subject to whom a kit was dispensed including randomization numbers and initials
- The date a kit was dispensed to a subject
- The date a kit was sent back to Topical Remedy.
- The date and quantity of any disposed kits, and the initials of the person who disposed of the kits.

The method of destruction of any used kits will be documented in a material of destruction form that will be maintained in the Regulatory Binder and with the Clinical Trial Materials Accountability Log.

The inventory will be maintained in a limited access area and must be available for inspection by the study monitor. A clinical trial material inventory and storage facility inspection will be conducted at appropriate time intervals throughout the clinical investigation, depending on enrollment and the length of the study. Clinical trial material inventory must be current and reflect all used and unused materials. Any discrepancy and/or deficiency must be accounted for by the Principal Investigator or designee.

Clinical trial materials, including unused kits, must be returned at the end of the study to Topical Remedy, LLC. Any missing supplies will be indicated on the Clinical Trial Materials Accountability Log; the original Clinical Trial Materials Accountability Log will be retained in the Trial Master File and a copy retained in the Investigator's

Regulatory Binder. Any used kits returned with the HDPE bottles of test material must be destroyed at the site and not returned to Topical Remedy.

## 7 STUDY CONDUCT

This section describes the study procedures to be followed. These procedures are summarized in Table 7.1 on the next page.

**Table 7-1: 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 eligibility criteria	X																
Treatment Phase eligibility criteria		X <sup>3</sup>															
Medical history; Physical Exam and Vitals	X																
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 assessment <sup>2</sup>		X <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X		
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

## 7.1 Screening and Enrollment Visit

### 7.1.1 Screening

The following items must be assessed and collected by the Investigator or his/her designee prior to enrolling the subject into the study.

1. Informed Consent. All prospective subjects will have the study explained by a member of the research team. The nature of the Merlin solution to be evaluated will be explained together with potential hazards involving allergies and possible adverse reactions to the test material.

Prior to enrollment into the study, acknowledgment of the receipt of this information and the subject's freely-tendered offer to participate will be obtained in writing from each subject in the study using an IRB-approved informed consent form. The subject will be given a copy of the signed informed consent form.

2. Enrollment Eligibility Criteria. The subject's potential eligibility to participate in the study will be evaluated using the inclusion and exclusion criteria listed in Section 5.2.
3. Medical History. A thorough medical history will be obtained including significant medical conditions over the previous 10 years and a subject's history of herpes labialis including the number of separate outbreaks per year (i.e. multiple lesions during one outbreak are counted as only a single outbreak).
4. Physical Exam and Vital Signs. A baseline physical examination and vital signs collection should be performed with all subjects following collection of the Medical History.
5. Pregnancy Test. All female subjects of child-bearing potential will be given a urine pregnancy test.
6. Concomitant Medications. A determination will be made of the medications currently being taken by the subject. Concomitant medications will be collected for the 30 days prior to enrollment into the study, the 30 days prior to enrollment into the Treatment Phase of the study, and throughout the Treatment Phase of the study. For any exclusionary medications that have been discontinued prior to entry into the Treatment Phase, stop dates for those medications must be obtained prior to allowing the subject into the Treatment Phase with particular attention as to whether the medications were discontinued within the appropriate timeframe.

### **7.1.2 Enrollment into Study**

The subject's potential eligibility to participate in the study will be evaluated using the inclusion and exclusion criteria listed in Section 5.2. If the subject meets all of the inclusion and none of the exclusion criteria in Section 5.2, the subject will be enrolled into the study and assigned the next available Randomization Number at the study site. The assigned Randomization Number corresponds to an identical Randomization Number on the label on the Treatment kit, as described in Section 6.1, which is to be allocated to the enrolled subject. The label on the Treatment kit will include a duplicate tear-off label that will also have a space for entry of the Subject Number, the preprinted Randomization Number, and the preprinted Lot Number. This tear-off label will be separated from the Treatment kit prior to dispensing to the subject, and that label will be placed into the pharmacy study record. The label in the pharmacy study record will provide confirmation of the Randomization Number on the Treatment kit the subject was assigned along with the lot number representing which group, active or placebo, into which the subject was randomized. Neither the pharmacy, nor anyone else at the study site, will be aware of which lot number represents the active and which represents the placebo treatment.

At the time of enrollment, the subject will be trained in application of the clinical trial material for later at-home application. Subjects will also be provided a diary in which he/she will record the lesion stage, the patient assessed severity and duration of pain of the herpes lesion, and assessment of attributes as listed in Section 3. Subjects will be instructed to call in to the clinic as soon as possible in order that they may begin treatment no more than 1 hour after detecting first signs and/or symptoms of an incipient herpes labialis lesion. The subject will be given training to enable them to assess the stage of their lesion when he or she subsequently calls in to the clinical site to report a lesion and for completion of the diary.

## **7.2 Study Treatment Phase (Treatment Day)**

### **7.2.1 Subject Eligibility Determination**

Immediately upon noticing first signs and/or symptoms of a herpes labialis lesion, the subject is to call in to the study clinic. Subjects will then be questioned to determine if they in fact are experiencing a herpetic outbreak and, if so, the stage of the lesion.

Subjects reporting a lesion at the erythema stage (Stage 1) or the papule/edema stage (Stage 2) will then be asked to answer specific questions to confirm whether they meet the inclusion/exclusion criteria described in Section 5.3 so that they may enter the Treatment Phase. Note that while subjects will be allowed to begin treatment at the papule/edema stage (Stage 2), subjects should be strongly encouraged to call in to begin treatment at the erythema stage (Stage 1), if at all possible. The clinic will also inquire about any concomitant medications taken in the last 30 days including a review of any changes in concomitant medications as reported by the subject at the time of enrollment into the study. All exclusionary concomitant medications must have a stop date noted.

Subjects calling in to report a herpetic lesion at the prodrome stage (Stage 0) should be instructed to begin frequently monitoring their lesion so as to be able to call the study clinic again at the first visible signs of the lesion, erythema or papule/edema. As mentioned above, while subjects will be allowed to treat at the papule/edema stage, they should be strongly encouraged to call in when their lesion reaches the erythema stage, if at all possible. Once subjects call in to report a visible lesion, the subjects will then be screened to confirm whether they meet the inclusion/exclusion criteria described in Section 5.3 so that they may begin the Treatment Phase. The clinic also will inquire, as described above, about any concomitant medications. All exclusionary concomitant medications must have a stop date noted.

If a subject who has first called in to report a lesion at the prodrome stage has not called back to report visible signs of the lesion, the clinic should try to contact the subject by telephone 6 -18 hours after the time of the initial phone contact. (Subjects should be contacted later the same day of their initial phone call, if possible.) If, when contacted, the subject reports visible signs of a herpetic lesion (Stage 1 or 2, but not a later stage), they should be screened, as described above, for entry into the Treatment Phase of the protocol. Otherwise, if the subject is still reporting prodromal symptoms, they should be reminded to continue to monitor their lesion for any visible signs of the lesion or until their lesion resolves without any visible signs of a cold sore. Should, after the first clinic call, the subject still not call in to report visible signs of a lesion or resolution of the episode, the clinic should continue to contact the subject by telephone every 6 -18 hours until the subject reports visible signs of a lesion or until the subject reports that the lesion has resolved without exhibiting any visible signs of a cold sore. If a subject does not report visible signs of a herpetic lesion within 96 hours of initially calling to report prodromal symptoms, the site may discontinue contacting the subject; the subject, however, should be instructed to contact the clinic if their lesion progresses to a visible stage or if they experience a new herpetic outbreak. If the subject's lesion progresses beyond stage 2 prior to, or when calling to enter the treatment phase of the study, the subject should be instructed that they no longer will be able to treat the current outbreak, but may try again, at their next lesion outbreak, to enter the treatment phase of the study.

### **7.2.2 Lesion Assessment**

Subjects will have been trained at screening to recognize whether they are at the prodromal stage (Stage 0), the erythema stage (Stage 1), the papule/edema stage (Stage 2) or a more advanced herpetic stage, with particular attention to distinguishing between Stage 2 and any later stages. Only subjects with a lesion in Stage 1 or Stage 2, the early visible signs of a herpetic outbreak, will be entered into the Treatment Phase of the study and therefore allowed to treat themselves. Subjects reporting a more advanced herpetic lesion, beyond Stage 2, will be instructed that they are still in the study but must wait until their next lesion outbreak before again calling in to attempt to enter the Treatment Phase of the study. Subjects reporting a lesion in the prodromal stage, Stage 0, will be instructed to monitor their lesion for first visible signs of a cold sore, and followed as described above. If a subject has two or more distinct lesions, the subject will treat the first lesion that appeared as long as it has not progressed beyond Stage 2. If any lesions

have progressed beyond Stage 2, as noted above, the subject will be instructed to wait until their next outbreak before calling to enter the Treatment Phase of the study.

### 7.2.3 Entry into Study Treatment Phase

If a subject has met all the inclusion and exclusion criteria described in Section 5.3, and has a herpes labialis lesion in Stage 1 or Stage 2, the subject will then be allowed into the Treatment Phase of the study and instructed to open the Treatment kit containing the study material and begin treatment. The subject will be asked to schedule their Visit Day 1 clinic visit for later that day, if possible; otherwise the visit must be scheduled as early as possible the following day anytime within 24 hours of the time at which a subject calls and is allowed to enter the Treatment Phase of the study.

A subject who does not meet one or more of the Inclusion Criteria (Section 5.3.1), or certain Exclusion Criteria (specifically Treatment Phase Exclusion Criterion #1 - #5; Section 5.3.2) may still be eligible for continuing in the study. Those subjects will 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. The list of those criteria where subjects who do not meet those criteria can still participate in the study, but must defer their entrance into the Treatment Phase until their next cold sore recurrence, is provided below:

- The subject reports a lesion stage later than Stage 2 (Treatment Phase Inclusion Criterion #1).
- A female subject is not using a medically acceptable form of birth control (Treatment Phase Inclusion Criterion #2). In this instance, the subject will be instructed to return to the clinic for another pregnancy test. Once that test is shown to be negative, the subject will be told to resume proper contraception and can then call in again at the next lesion outbreak.
- The subject does not have immediate access to the clinical trial material kit (Treatment Phase Inclusion Criterion #3). In this case they will be asked to call again when he or she has the kit at hand. At the time of their second phone call they also will be asked again about the stage of their lesion to be certain that the lesion has not progressed beyond Stage 2.
- The subject cannot appear for a clinic visit within 24 hours from the time of enrollment into the Treatment Phase of the study (the time of the subject's call to establish entry into the Treatment Phase of the study), or is unable to return to the clinic daily for the full 14 day duration of the study if necessary (Treatment Phase Inclusion Criterion #4).
- The subject has any evidence of active malignancy or immunodeficiency disease within the last 30 days (Treatment Phase Exclusion Criterion #1). As also noted in

Exclusion Criterion #1, 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 and therefore could begin the study treatment provided they meet all other inclusion and exclusion criteria.

- A subject has used topical steroids on or near the face or systemic (oral, intravenous) steroids within the last 30 days (Treatment Phase Exclusion Criterion #2). As also noted in Exclusion Criterion #2, use of inhaled steroids does not exclude a subject from the study; such subjects, providing they meet all other criteria, can be entered into the Treatment Phase of the protocol.
- A subject has used an NSAID within the last 12 hours of calling the clinic to report the lesion (Treatment Phase Exclusion Criterion #3).
- A subject has used an investigational drug and/or device within the last 30 days (Treatment Phase Exclusion Criterion #4).
- A subject has used any anti-viral drug, or any other medication, including home remedies, intended to treat cold sores (e.g. lysine, tea tree oil, honey) within the last 30 days, or used any topical medication to treat the current active herpes simplex labialis lesion (Treatment Phase Exclusion Criterion #5).

Except for those Treatment Phase Exclusion Criteria noted above, specifically #1 - #5, a subject meeting any of the other exclusion criteria will no longer be able to participate in the study and he or she will be asked to report to the clinic in order to return their sealed kit.

#### **7.2.4 Drug Administration**

Each subject, upon entering the Treatment Phase of the study, will be instructed to treat their lesion immediately using the solution and single-use applicators in the Treatment kit. The subjects, according to the randomization scheme, will begin self-administration of the applications of either Merlin or placebo solution. Treatment Day is the first day of treatment for all subjects.

At the time of the subject's call to enter the Treatment Phase of the study, the clinic should review the method and schedule of treatment applications with the subject.

For the first and all subsequent treatments, each subject will administer three (3) applications of Merlin or placebo, depending upon how a subject has been randomized, 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 96 hours (4 days) from the time of the first treatment. On each day, treatments will be administered six (6) hours apart ( $\pm$  1 hour), with a maximum of three treatments each day. The first treatment will be administered on Treatment Day (Day 0), and then repeated at 6 ( $\pm$  1 hour) and 12 hours ( $\pm$  1 hour) after the first treatment, time permitting.

Subjects who, upon self-examination outside of the clinic, or upon evaluation in the clinic, are found to have herpetic lesions that have reached the ulcer/soft crust stage (Stage 4) should be instructed to discontinue all remaining treatments. If the observation of the lesion reaching Stage 4 is made by the subject outside of the clinic, the subject should call into the clinic as soon as possible after making this observation to confirm the accuracy of their assessment and to report the event.

Subjects who are unable to begin treatment for any reason, aside from those listed in Section 7.2.3, are to be discontinued from the study; those subjects are to return to the clinic to turn in their clinical trial materials and are not to be followed for safety or efficacy. Subjects, though, who are able to complete any part their treatment, even only a single application of the solution to the face, are to continue to participate in the study as planned, including appearing for all safety and lesion assessment clinic visits.

## 7.2.5 Subject Diaries

Each subject will be instructed to record into their diaries the date and time of their first treatment, the stage of their lesion, and his or her assessments of pain as described in this section. The recording of the assessments of lesion stage and pain level are to be done three times per day, just prior to initiation of each treatment (i.e. just prior to the first application in a set of three (3) applications). After the course of treatment is completed, assessment of lesion stage and pain level will continue 3 times daily with approximately 6 hours in between each assessment until the lesion is healed. The subject will also be instructed to bring the diary to each office visit so that the Investigator or trained designee can review it.

### 7.2.5.1 Pain Assessment

At the time of the subject's call to enter the Treatment Phase of the study, the clinic will ask the subject to provide the time of the onset of any pain caused by the herpes lesion to be treated along with the severity of any lesion pain.

The severity of lesion pain will be based on the following rating scale:

1 = None	No pain
2 = Mild	Pain is present in such a way that the subject is only vaguely aware of it and it does not interfere with daily activities
3 = Moderate	The subject is aware of pain at all times, but it does not interfere with daily activities
4 = Severe	Level of discomfort of pain is such that it interferes with daily activities.

As noted in Section 7.2.5, the subject will also record in the diary, just prior to each treatment, the severity of any lesion pain. After the course of treatment is completed, assessment of pain level will continue 3 times daily with approximately 6 hours in between each assessment until the lesion is healed.

### **7.3 Follow-up Visits (Visit Days 1-14)**

Each subject entered into the Treatment Phase of the study is to come in for an office visit every day, (preferably about the same time of day each day, if possible), following treatment until the clinician or trained designee determines that the treated lesion has reached Stage 7, up until at least Visit Day 3 and at most until Visit Day 14. As subjects might call any time of the week, and the Treatment Phase of the study could last as many as 14 days, clinics must be staffed with personnel, trained in lesion assessment, 7 days a week. Every effort should be made to get the subject to come to all their study visits. If a subject misses a visit, the study clinic visits still end for them on Visit Day 3 if their lesion has reached Stage 7 by then, or on the day their lesion reaches Stage 7, or Visit Day 14, whichever comes first.

#### **7.3.1 Clinical Lesion Assessment**

When possible, clinical lesion assessment of a subject should be performed by the same evaluator on each day. If the same lesion evaluator cannot perform all the lesion assessments for a given subject, the person taking over the lesion assessment of that subject should observe the lesion with the previous assessor to ensure they are in agreement with the stage. (The name(s) of any clinical staff member(s) involved in the evaluation of a given subject's lesion stage for that day should be noted in the subject's source documents.) The Investigator, or trained designee, acting as the lesion evaluator, will mark, on the first clinic visit, the location of the treated lesion on a facial diagram included in the subject's source records and will score the lesion on each subject at each visit. A trained designee should be a member of the clinical personnel who is a dermatologist/ physician or someone with a clinical background with the ability to evaluate the stages of a herpetic lesion.

The herpes lesion treated by the subject will be considered part of the primary recurrence for evaluation. Any other herpes lesions that appear within 10 mm of that first lesion, on the same calendar day, will also be considered part of the primary lesion complex. All other lesions located at least 10 mm from the first lesion, or occurring within 10 mm of the first lesion on any other day after the day of the first lesion outbreak, will be defined as secondary lesions. Only lesions within the primary lesion complex will be scored for lesion staging for efficacy analysis. Secondary lesions will not be scored for lesion staging. If the Investigator determines that secondary lesions are typical for a given subject, then the observation of such secondary lesions in that subject need not be captured in the CRF. If, however, the Investigator concludes that secondary lesions are not usual for a given subject, then the observance of a secondary lesion in that subject may be captured and followed as an Adverse Event.

The lesion scores are defined as follows:

0. Prodrome
1. Erythema
2. Papula/edema
3. Vesicle/pustule
4. Ulcer/soft crust
5. Hard crust
6. Residual swelling/dry flaking
7. Normal skin

Classical lesions are those lesions that pass through Stages 3, 4 **or** 5 at any lesion assessment. Non-classical (aborted) lesions are lesions that never pass through Stages 3, 4, **or** 5 prior to healing at Stage 7.

A herpetic lesion typically progresses to higher level stages and therefore would not be expected to proceed from a higher number stage to a lower number stage. The exception to this would be the case where a subject has a Stage 5, hard crust, lesion in which the scab is inadvertently knocked off, e.g. while washing. In that instance, the lesion would “go backwards” from a Stage 5 lesion to a Stage 4. This expected progression of the herpetic lesion should be kept in mind as a guideline in the evaluation of the lesion stage. Any time, therefore, a lesion is observed to “go backwards,” a note should be made in the CRF as to why, if the reason can be determined, the lesion reversed its progression.

The study clinic visits end for a subject when (1) the treated lesion is no longer present (Lesion Stage 7 for both classical and non-classical lesions) and there have been clinic assessments every day up until at least Visit Day 3, or (2) at Visit Day 14, whichever occurs earlier.

### 7.3.2 Diary Review

At each clinic visit, the investigator, or trained designee, will assess the subject's cold sore lesion before reviewing entries in the diary. In reviewing the diary, the investigator, or trained designee, will review the subject assessments for consistency and completeness. Should any apparent errors or incomplete entries be found in the diary, the subject will be informed of these issues, and instructed as to how to properly complete the diary in the future; no retroactive changes, though, are to be made in the diary. Any blanks that should have been completed prior to the clinic visit should be marked by the diary reviewer, so as to prevent later completion, and initialed and dated by the reviewer.

### **7.3.3 Lesion Size Assessment**

At each clinic visit, the Investigator, or trained designee, will use a disposable ruler, supplied by the sponsor, to measure the lesion size. Two measurements will be taken: 1) the length of the longest dimension of the lesion; 2) the maximum length of the lesion dimension perpendicular to the axis of the first measurement taken.

### **7.3.4 Pain Assessment**

At each clinic visit, the Investigator, or trained designee, will review the subject entries in the diary. In reviewing the diary, the Investigator, or trained designee, will inspect the subject entries for timing of dosing and pain assessments with regard to consistency and completeness. Should any apparent errors or incomplete entries be found in the diary, the subject will be informed of these issues, and instructed as to how to properly complete the diary in the future; no retroactive changes, though, are to be made in the diary. Any blanks that should have been completed prior to the clinic visit should be marked by the diary reviewer, so as to prevent later completion, and initialed and dated by the reviewer.

### **7.3.5 Safety Assessments**

The subjects will be questioned concerning their well-being at the time of each clinic visit. Questions will be posed in a non-specific manner so as not to bias the response. The subjects will also be instructed to inform the study physician and/or nurses of any adverse events that may occur at any time during the study. On Visit Day 1 the subject should be asked about any adverse events occurring since treatment on Treatment Day, so as to capture any adverse events that took place since their treatment. Subjects who discontinue prior to Visit Day 3 but have administered any treatment must be followed for safety, by telephone or clinic visits, as deemed appropriate by the Investigator, until at least Visit Day 3.

#### **7.3.5.1 Pregnancies**

Any subject who becomes pregnant during the course of treatment will be instructed to immediately stop all treatments and will be discontinued from the study. Also, any subject who becomes pregnant in the two week period following their completion of the treatment phase of the study, or their discontinuation from the study (for reasons other than pregnancy), will be instructed to contact the clinic to report the pregnancy. All treated study subjects who report a pregnancy during the course of the trial will be followed during the course of their pregnancy by the study doctor to determine the outcome of the pregnancy.

### **7.3.6 Concomitant Medications**

The identity of all concomitant medications taken 30 days prior to enrollment into the study, 30 days prior to enrollment into the Treatment Phase of the study, and during the Treatment Phase of the study, as well as their total daily dose, duration of use, and

indication for use, will be reported on the case report form (CRF). Any possible exclusionary medication must have a stop date prior to eligibility for treatment.

### **7.3.7 Subject Return of Unused Test Material to the Clinic**

All subjects will be instructed to return their Treatment kit, with any unused test materials, to the clinical site on whichever is the first clinic visit following completion of all their treatments. The subjects should have disposed of the used swabs at home.

At the conclusion of the study, those subjects who have been enrolled, but never entered the Treatment Phase of the study, will be contacted and asked to return their unused Treatment kit. Should a subject not return their clinical trial material when requested, at least one additional phone call should be made, and, if necessary, a certified letter should be sent to request return of those materials. If these efforts are unsuccessful the subject's clinical trial materials will be considered missing. The return of both used study solution bottles and unused clinical trial materials is important with regard to drug accountability.

Study subjects who have entered the Treatment Phase of the study and administered their lesion treatment, will be offered compensation for bringing in their used clinical study solution bottle after completion of all their study treatments. This incentive is important as the immediate return of the materials to the clinic will minimize loss or misuse. Those subjects who forget to bring in their used clinical materials immediately after completion of all their study treatments will be offered a lower compensation to return the materials at a later date. Those subjects who were enrolled into the trial but did not enter the study Treatment Phase will be offered compensation for the return of all unused clinical trial materials at the termination of the study.

### **7.4 Follow-Up Telephone Assessment**

Two weeks, or up to 3 weeks, if there are scheduling issues, after the subject has completed the Treatment Phase of the study (complete healing of the herpetic episode or Visit Day 14, whichever is earlier) the clinic will contact the subject by phone for a final safety evaluation. Any new adverse events that have occurred since the subject's last clinic visit should be collected at this time.

## **8 ADVERSE EVENTS**

All adverse events occurring during the Treatment Phase of this clinical trial will be recorded on the case report form provided. Adverse events occurring before the onset of treatment will be classified as non-treatment emergent adverse events and will not be captured on the CRF. Adverse events occurring after the application of study treatment will be assigned as treatment emergent adverse events and will be recorded on the CRF. The Investigator will review each event and assess its relationship to the treatment (not related, unlikely, possible, probable and highly probable). The following definitions will be used for rating relationship to treatment:

- Not related – The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Unlikely – The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; **and** does not follow a known response pattern to the investigational product.
- Possible – The event follows a reasonable temporal sequence from the time of investigational product administration; **and/or** follows a known response pattern to the study treatment; **but** could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Probable – The event follows a reasonable temporal sequence from the time of investigational product administration; **and** follows a known response pattern to the investigational product; **and** cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Highly Probable – The event follows a reasonable temporal sequence from the time of investigational product administration; **and** follows a known response pattern to the investigational product; **and** cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; **and** either occurs immediately following investigational product administration, **or** improves on stopping the investigational product, **or** reappears on repeat exposure, **or** there is a positive reaction at the application site.

Each adverse event reported will be graded on a 3-point severity scale (mild, moderate, or severe) and the date and time of onset, time relationship to treatment, duration, and outcome of each event will be noted on the case report form.

The following definitions for rating severity will be used:

- Mild – easily tolerated, causing minimal discomfort and not interfering with normal everyday activities.
- Moderate – sufficiently discomforting to interfere with normal everyday activities.
- Severe – incapacitating and/or prevents normal everyday activities.

If any of the above adverse events are serious, as defined by the FDA Code of Federal Regulations (CFR), Title 21, special procedures will be followed. All serious adverse events will be reported within 24 hours by fax or e-mail to the Drug Safety Group at (866) 857-8839, whether or not the serious events are deemed treatment-related. The

Drug Safety Group will notify Topical Remedy's Vice President of Clinical Research of the serious adverse event. All serious event reporting will adhere to 21 CFR 312.32 for IND drugs. The central IRB and other study sites will be notified by Topical Remedy, LLC of the Alert Reports per FDA regulations. Sites using their own institutional IRB will be instructed by Topical Remedy, LLC to notify their institutional IRB of the Alert Report.

The following is the definition for serious adverse events per FDA regulations:

A Serious Adverse Event is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, in-patient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If a serious adverse event occurs to a subject on this study, the Investigator will complete the SAE form provided and fax it, along with the front cover sheet provided, to the Drug Safety Group at (866) 857-8839. The Medical Monitor will be responsible for ensuring completeness of the SAE form and for reviewing the SAE versus source documentation and the CRF.

Once the SAE form is complete, the Medical Monitor will forward it, by email, to the Vice President of Clinical Research at Topical Remedy (email: emorrel@benubio.com; fax: 508-651-3703) for review. The Vice President of Clinical Research will send any comments to Drug Safety. Drug Safety will track the SAE information and forward a desk copy of the complete SAE report to Topical Remedy, LLC.

Adverse events, whether serious or non-serious, will be followed to resolution or until the condition stabilizes, is otherwise explained, or the subject is lost to follow-up, up to a maximum of 30 days following the subject's last clinic visit. Adverse events, whether serious or non-serious, will be captured up to 2 weeks following the last clinic visit, and followed up to a maximum of 30 days following the subject's last clinic visit. Where appropriate, medical tests and examinations will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up). Following the resolution of any study associated adverse events or after the completion of the Treatment Phase of the study, there will be no further adverse event reports for that subject.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE (as appropriate). A spontaneous abortion is always considered to be a SAE.

## 9 REMOVAL OF SUBJECTS FROM STUDY

Subjects will be advised that they are free to withdraw from the study at any time without consequence. The Investigator may remove a subject if he/she feels this action is in the best interest of the subject. When a subject withdraws from the study after treatment, all of the necessary safety and tolerability assessments should be obtained if possible.

Subjects experiencing adverse events should be followed until the event has resolved or until the condition stabilizes, is otherwise explained, or the subject is lost to follow-up, up to a maximum of 30 days following the subject's last study visit. Appropriate supportive and/or definitive therapy will be administered as required. As with other subjects in this study, compensation will be offered for return of a used or unused study kit.

Subjects withdrawn from this study cannot re-enter or be used as replacements for other subjects in this study.

## 10 STATISTICAL METHODS

### 10.1 Introduction

This trial will be conducted to test the superiority of the Merlin solution to placebo solution in the treatment of recurrent herpes labialis at first visible signs and/or symptoms of a herpetic lesion. The primary efficacy endpoint for the study will be the clinician assessed duration of the classical herpetic lesion. 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 the vesicle/pustule, ulcer, or crust stages (stages 3, 4 or 5). Duration of the classical herpetic lesion will be analyzed using the Hodges-Lehmann method as the primary efficacy analysis method for estimating the median difference between the two arms. Duration of the herpetic episode, duration of complete healing of the herpetic episode, duration of the herpetic lesion, duration of the herpetic lesion hard scab, and duration of pain will be analyzed in the same manner as the duration of the classical lesion.

### 10.2 Study Endpoints

#### 10.2.1 Efficacy Endpoints

##### Primary:

- Clinician assessed duration of the classical herpetic lesions

##### Secondary:

- Clinician assessed duration until of the herpetic episode
- Clinician assessed duration of until complete healing of the herpetic episode
- Clinician assessed prevention of progression to a classical lesion

- Maximum clinician assessed lesion size
- Clinician assessed duration of the herpetic lesion hard scab
- Clinician assessed duration and severity of lesion associated pain

Other Endpoints:

- Subject assessed duration and severity of lesion pain
- Subject assessed duration of the classical herpetic lesion
- Subject assessed duration of the herpetic episode
- Subject assessed duration of complete healing of the herpetic episode
- Subject assessed prevention of progression to a classical lesion
- Subject assessed duration of the herpetic lesion hard scab

### 10.2.2 Safety Endpoints

- Adverse events (AEs)

## 10.3 Study Populations

### 10.3.1 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.

### 10.3.2 Efficacy: Modified Intent-to-Treat (MITT) Population

All subjects who have been entered into the Treatment Phase of the study will be included in the 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. The MITT population will be used as the primary analysis population. A subject will be included in a treatment group for analysis based upon the treatment to which he or she has been assigned.

### **10.3.3 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 population. Prior to breaking the study blind, study data will be reviewed to determine which subjects need to be excluded from the efficacy evaluable 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.

## **10.4 General Methodology**

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 arm to the placebo control arm. Aside from any placebo effect, there should be no efficacy associated with the placebo solution. As a secondary analysis, all statistical comparisons will be performed with the treated subjects stratified based on whether they treated at erythema (Stage 1) or papule/edema (Stage 2).

## **10.5 Baseline Demographics**

Baseline demographic information will be summarized for the safety population. 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.

## **10.6 Safety and Tolerability Analysis**

The safety analysis will be performed on the safety population. Assessment of safety and tolerability will be based on adverse events. 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. Adverse events will be coded by body system and preferred term using the MedDRA (Medical Dictionary for Regulatory Activities) dictionary.

The number and percentage of subjects experiencing adverse events will be tabulated for each treatment group by body system and preferred term. The number and percentage of subjects experiencing AEs will also be tabulated by relationship to drug treatment and by severity. If an AE is reported more than once for a subject, only the most related event will be counted in the analysis by relationship to drug treatment. For the analysis by severity, if an AE is reported more than once for a subject, only the most severe event will be counted in the analysis.

## 10.7 Efficacy Analysis

The efficacy analysis will be performed on both the MITT and the efficacy evaluable populations. For all duration endpoints the following matrix will be used for analyses:

Population	Analysis	Description	Methods
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 arms
	Sensitivity Analysis	Subjects who drop out prior to healing will be considered censored.	Kaplan-Meier estimation methods; Log-rank test to compare arms
EE	Main Analysis	No imputation required since these are complete cases.	Hodges-Lehmann estimation methods; Wilcoxon rank sum test to compare arms

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 arms, 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.

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

For the severity endpoints, counts and percentages will be summarized, and Cochran-Mantel-Haenszel tests will be used to compare the arms.

In order to assess 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.

#### **10.7.1 Duration of Classical Lesions (clinician and patient assessed)**

A classical herpetic lesion is defined as one that passes through any of Stages 3, 4 or 5 (vesicle/pustule, ulcer/soft crust, or hard crust). Therefore, all aborted lesions will be excluded from this analysis. 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.

#### **10.7.2 Duration of Herpetic Episode (clinician and patient assessed)**

Duration of herpetic episode is measured by assessment of treated lesion stage daily up until Stage 6 for classical lesions or Stage 7 for non-classical lesions for a maximum of 14 days, with a minimum of 3 consecutive days of assessment. 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). A classical lesion is defined as one that progresses through any of the vesicle/pustule, ulcer/soft crust, or hard crust stages (stages 3, 4 or 5). For non-classical lesions, duration of herpetic episode is defined as the time from the beginning of treatment until complete resolution of all local signs and symptoms (Stage 7).

#### **10.7.3 Duration until Complete Healing of the Herpetic Episode (clinician and patient assessed)**

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.

#### **10.7.4 Prevention of Progression to Classical Lesions (clinician and patient assessed)**

A classical herpetic lesion is defined as one that passes through any of Stages 3, 4 or 5 (vesicle/pustule, ulcer/soft crust, or hard crust). Prevention of progression to classical lesions will be analyzed by comparing the proportions of subjects in each treatment group who do not display classical lesions. (These are considered aborted lesions.)

#### **10.7.5 Clinician Assessed Lesion Size**

For each subject, the subject's maximum lesion area (length x width) for ulcerative lesions during the vesicular, ulcerative, and hard crust stages will be determined. In

addition, the cumulative lesion area, for which ulcerative lesion areas, day by day, will be added. Last, the cumulative lesion area “all lesions” will be determined; for this parameter, all patients will be included (i.e. both ulcerative and non-ulcerative recurrences).

#### **10.7.6 Duration of the Herpetic Lesion Hard Scab (clinician and patient assessed)**

Duration of the hard scab will be defined as the assessed duration of the hard crust, stage 5, for all subjects experiencing known 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. Only known classical lesions will be included in this analysis. 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.

#### **10.7.7 Duration of Pain (subject assessed)**

Duration of 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: none (1), mild (2), moderate (3), and severe (4). For each subject, 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.

#### **10.7.8 Severity of Lesion Pain**

The maximum severity (over time) of lesion pain will be summarized.

#### **10.7.9 Sample Size Determination**

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 arm and we can be highly 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.

## **11 ADMINISTRATIVE REQUIREMENTS**

### **11.1 Good Clinical Practice**

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master Files should be established at the beginning of the study, maintained for the duration of the trial and retained according to the appropriate regulations.

### **11.2 Ethical Considerations**

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted when IRB/IEC approval has been obtained. The protocol, Investigator Brochure, informed consent, recruitment advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

### **11.3 Subject Information and Informed Consent**

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with GCPs and all applicable regulatory requirement(s).

## **11.4 Subject Confidentiality**

In order to maintain subject privacy, all CRFs, study clinical trial material accountability records, study reports and communications will identify the subject only by initials and the assigned study-specific Randomization Number. The Investigator will grant monitor(s) and auditor(s) from Topical Remedy, LLC, or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The Sponsor, or designee of the Sponsor, also may observe the study in progress. The subject's confidentiality, per HIPAA regulations, will be maintained except as required by the applicable laws and regulations.

## **11.5 Protocol Compliance**

The Investigator will conduct the trial in compliance with the protocol provided by Topical Remedy, LLC, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without written agreement of both the Investigator and Topical Remedy, LLC. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC. Topical Remedy, LLC will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact Topical Remedy, LLC, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be approved by Topical Remedy, LLC and fully documented in the CRF and source documentation.

## **11.6 Study Monitoring**

Monitoring and auditing procedures developed by Topical Remedy, LLC, or its designee, will be followed, in order to comply with GCP guidelines. On-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Topical Remedy, LLC, or its designee. Monitoring will be done by personal visits from a representative of the sponsor (site monitor) who will review the CRFs and source documents. The site monitor will verify that the investigation is conducted according to protocol design and regulatory requirements and will document their findings in frequent communications (email, letter, telephone, and fax).

All unused study materials that have not already been returned during the course of the clinical study, as per instructions from Topical Remedy, LLC, are to be returned to Topical Remedy, LLC, or their designee, after the clinical phase of the trial has been completed.

### **11.7 On-site Audits**

Regulatory authorities, the IEC/IRB, and/or Topical Remedy, LLC.'s Vice President of Clinical Research, or designee may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support for these activities.

### **11.8 Case Report Form Completion and Data Management**

Topical Remedy, LLC, or its designee, will provide the study sites with a CRF for each subject. A subject screening log will be used to document any reason for screen failure. For each subject who has given informed consent, meets the study enrollment eligibility criteria, and is randomized into the trial, a CRF will be completed. The Principal Investigator will certify that the subjects were seen and evaluated by qualified site staff and that he/she has delegated responsibilities for subject evaluation as identified in the Study Site Roles and Responsibilities Log maintained in the study master file.

As appropriate, all source documents or CRF pages should be filled out during (or immediately after) a subject assessment. The text should be written with a black or blue ballpoint pen and must be legible. If a source document or CRF entry needs correction, the error should be crossed out with a single line (not obliterated or covered with correction fluid) and the correct information should be written next to the original entry. The change must be initialed and dated by the Investigator or designee.

The study monitor at the study site will review source documents, CRFs and any queries will be highlighted to the Investigator or designee enabling the errors to be addressed prior to collection of the CRF pages. Errors detected by subsequent in-house CRF review may necessitate clarification or correction.

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. This includes maintenance of documentation to support any changes or corrections applied to the CRFs.

Data collected on the CRFs will be entered into Topical Remedy, LLC designee's database by a dual entry system. The database will be checked for internal consistency, and the critical data will be compared with the original CRFs.

Queries arising during data processing/consistency checking will either be provided to the site for clarification and approval by the Investigator, or handled by the designee's Data Managers.

## **11.9 Clinical Trial Material Accountability**

Accountability for the clinical trial materials at the trial site is the responsibility of the Investigator. The Investigator will ensure that the clinical trial materials are used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the clinical trial material accountability responsibilities to a pharmacist or other appropriate individual. Clinical trial material accountability records indicating the clinical trial material delivery date to the site, inventory at the site, use by each subject, return of used or unused clinical trial material by the subject to the site, and return to Topical Remedy, LLC (or disposal of the drug, if approved by Topical Remedy, LLC) will be maintained by the clinical site. These records will adequately document that the subjects were provided the clinical trial materials as specified in the protocol and should reconcile all study clinical trial materials received from Topical Remedy, LLC. Accountability records will include dates, quantities, and Randomization Numbers. The sponsor or its designee will review clinical trial material accountability at the site on an ongoing basis during monitoring visits. Accountability records must be current and up to date.

All unused and used study clinical trial materials will be retained at the site until they are inventoried by the monitor. All unused study drug will be returned to Topical Remedy, LLC, or if authorized, disposed of at the study site and documented.

## **11.10 Premature Closure of the Study**

This study may be prematurely terminated, if in the opinion of the FDA or Topical Remedy, LLC, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator by Topical Remedy, LLC.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enter subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of Merlin

Should the study be closed prematurely, all study materials (completed, partially completed, and blank CRFs, study clinical trial materials, etc.) must be returned to Topical Remedy, LLC.

## **11.11 Record Retention**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory

requirement(s). The Sponsor will notify the Investigator when these time periods have elapsed. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Topical Remedy, LLC must be notified in writing if a custodial change occurs.

## 11.12 Liability and Insurance

Topical Remedy, LLC has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

## 12 USE OF INFORMATION

All information regarding the Merlin solution supplied by Topical Remedy, LLC to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Topical Remedy, LLC. Any manuscript, abstract, or other publication or presentation of results or information arising in connection with the study must be prepared in conjunction with Topical Remedy, LLC. It is understood that there is an obligation to provide Topical Remedy, LLC with complete data obtained during the study. The information obtained from the clinical trial will be used towards the development of the Merlin solution and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

## 13 REFERENCES

1. Spruance SL, Kriesel JD. Treatment of herpes simplex labialis. *Herpes* 2002; 9:64-69.
2. Spruance SL, Wenerstrom G. Pathogenesis of herpes simplex labialis. IV. Maturation of lesions within 8 hours after onset and implications for antiviral treatment. *Oral Surg Oral Med Oral Path* 1984; 58:667-71.
3. Spruance SL, Crumpacker CS, Schnipper LE, et al. Early, patient initiated treatment of herpes labialis with topical 10% acyclovir. *Antimicrob Agents Chemother*. 1984;25:553-555.
4. Raborn GW and Grace M. Recurrent Herpes Labialis: Selected Therapeutic Options. *J Can Dent Assoc*. 2003;5569(8): 498-503.
5. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother*. 2002;46:2238-2243.

6. Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R, Spruance SL. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc.* 2002;133:303–309.
7. Sailer CA, Spruance SL, and Hull CM. Acyclovir and hydrocortisone cream for the early treatment of recurrent cold sores. *Virus Adaption and Treatment* 2001; 3:1-6.

#### **14. INVESTIGATOR AGREEMENT**

I have read 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

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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Principal Investigator printed name

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Principal Investigator signature

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Date

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Investigational site or name of institution and location (printed)