A Multi-Center, Double-Blind, Randomized Vehicle-Controlled, Parallel- Group Study to Compare Perrigo UK FINCO's Acyclovir Cream, 5% with ZOVIRAX® (Acyclovir) Cream 5%, and both Active Treatments to a Vehicle Control in Treatment of Recurrent Herpes Simplex Labialis

NCT02265913

04-22-2016

A Multi-Center, Double-Blind, Randomized Vehicle-Controlled, Parallel- Group Study to Compare Perrigo UK FINCO's Acyclovir Cream, 5% with ZOVIRAX® (Acyclovir) Cream 5%, and both Active Treatments to a Vehicle Control in Treatment of Recurrent Herpes Simplex Labialis

Protocol No.: PRG-NY-14-008

[redacted]

Confidential

The confidential information provided in this document is for use by parties directly involved in this investigation. By accepting this document, you agree that the information contained herein will not be disclosed to any person not directly involved in this investigation without written authorization from Perrigo.

Protocol No: PRG-NY-14-008
[redacted]

PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: PRG-NY-14-008

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Acyclovir Cream, 5% with ZOVIRAX® (Acyclovir) Cream 5%, and both Active Treatments to a Vehicle Control in Treatment of Recurrent Herpes Labialis

[redacted]

TABLE OF CONTENTS

STUDY SYNOPSIS

Title:	A Multi-Center, Double-Blind, Randomized Vehicle-Controlled, Parallel- Group Study to Compare Perrigo UK FINCO's Acyclovir Cream, 5% with ZOVIRAX® (Acyclovir) Cream 5%, and both Active Treatments to a Vehicle Control in Treatment of Recurrent Herpes Labialis
Study Medication:	1. Acyclovir Cream, 5%, Perrigo 2. Zovirax® (Acyclovir) Cream 5%, Valeant Pharmaceuticals 3. Vehicle of Acyclovir Cream, 5%, Perrigo
Study Objectives:	To compare the safety and efficacy profile of Perrigo's Acyclovir Cream, 5% to Zovirax® Cream 5% and to demonstrate the bioequivalence to the reference product as well as superior efficacy of the two active formulations over that of the vehicle in the treatment of herpes labialis (cold sores) in adults and adolescents 12 years of age and older.
Study Design:	Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study will be admitted into the study only after written informed consent/assent (as applicable) has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects, 12 years of age and older, with recurrent herpes simplex labialis will be eligible for enrollment.
Study Population:	[redacted] subjects 12 years of age and older, who meet the inclusion/exclusion criteria, will be enrolled.
Dosing:	Subjects will be randomized [redacted] to either the test product, reference product or vehicle treatment group, respectively, and will apply study medication 5 times daily for 4 days. [redacted]
Study Visits:	The clinical trial will consist of the following visits: • Screening Visit- once the subject meets inclusion/exclusion criteria; they will be randomized and given the study medication. [redacted] • Treatment Days: 1 (Visit 2), 2 (Visit 3), 3 (Visit 4), and 4 (Visit 5) • Follow-up Days: 5 (Visit 6), 6 (Visit 7), 7 (Visit 8), 8 (Visit 9),10 (Visit 10), 12 (Visit 11), 14 (Visit 12), 21 (Visit 13) • [redacted]. If healing occurs in-between scheduled study days, the subject should return to the clinic as soon as possible and not wait till the next scheduled visit.

Efficacy Assessments:	The primary efficacy endpoint will be: Time to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary), measured in days/hours from the time of first dosing. [redacted]
Safety Assessments:	The incidence of all adverse events reported during the study will be summarized by treatment group. Equivalence of the two active formulations with regard to safety will be evaluated by comparing the nature, severity and frequency of their adverse event profiles. In addition, the frequency and distribution of application site reactions of dry lips, cracked lips, desquamation, dry skin, burning skin, pruritus, flakiness of skin, and stinging of the skin will be summarized for the two active formulations.
Statistical Methods:	Efficacy The primary efficacy endpoint will be the time to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary), measured in days/hours from the time of first dosing. [redacted] Equivalence of Clinical Endpoint Analysis: The mean time to complete healing of the lesion for the test and reference treatments will be estimated using analysis of Variance (ANOVA) with treatment and center as fixed effects in the model. The 90% confidence interval for the ratio (Test/Reference) of mean time-to-**complete healing** will **be obtained by Fieller's** method. A plot for the ratio (Test/Reference) of mean time-to-complete healing and associated 90% CI will be presented. [redacted]. For the time to complete healing of lesion, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the calculated 90% confidence interval of the ratio of the means (Test/Reference) falls within the interval of 0.80 to 1.25.

	Analysis of Superiority between active formulation and vehicle: For the time to complete healing of the lesion, subjects who received active treatment will be compared to those who received the Vehicle as treatment in order to determine if superior efficacy has been attained. The time-to-complete healing of both the active products and Vehicle will be analyzed using Analysis of Variance (ANOVA) evaluations with treatment and center as fixed effects in the model. Each active treatment group will be compared to the Vehicle group using a -two-sided test and tested at an alpha level of 0.05. The mean and its 95% confidence interval will be reported. Superiority will be considered demonstrated if the means for both active treatments are statistically different from ($p<0.05$), and smaller than, that for the Vehicle Safety All adverse events (AEs) will be classified with respect to system organ class (SOC) and preferred term using MedDRA. A treatment-emergent AE is an event that occurs or worsens after the administration of first dose of study medication. The AE profile will be characterized with severity and attribution (unrelated and related) to study medication. Related AEs will be events that are possibly or probably related to treatment in the investigator's judgment. The number and percent of patients who report treatment-emergent AEs will be summarized for each treatment group. Additional summaries by severity and relationship to study medication will be presented for each treatment group. In addition, the number and percent of patients who reported treatment-emergent AEs of interest and serious AEs will be summarized for each treatment group.
Sample Size Considerations:	[redacted]

ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CMH	Cochran–Mantel–Haenszel test
CRF	Case Report Form
DCF	Data Clarification Form
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent to Treat population
mITT	Modified Intent to Treat population
LPN	Licensed Practical Nurse
LVN	Licensed Vocational Nurse
NP	Nurse Practitioner
OTC	Over the Counter
PA	Physician's Assistant
PI	Principal Investigator
PP	Per Protocol Population
RN	Registered Nurse
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

1. BACKGROUND

[redacted]

Zovirax® Cream 5% is indicated for the topical treatment of herpes labialis. Perrigo has developed a generic formulation of Acyclovir Cream, 5%.

2. STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy profile of Perrigo's Acyclovir Cream, 5% to Valeant's Zovirax® Cream 5% and to demonstrate the bioequivalence of the test product to the reference product as well as superior efficacy of the two active formulations over that of the vehicle in the treatment of herpes labialis in adults and adolescents 12 years of age and older.

2.1 Efficacy Endpoints

The primary efficacy endpoint will be the time to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary), measured in days/hours from the time of first dosing.

[redacted]

2.2 Safety

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles.

3. STUDY DETAILS

3.1 Study Overview

Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study will be assigned [redacted] to test product, reference product, or vehicle, respectively. Subjects will apply study medication 5 times daily for 4 days.

3.2 Study Population

[redacted] immunocompetent males/females, ≥ 12 years of age with a clinical diagnosis of non-life-threatening recurrent herpes simplex labialis who meet the inclusion-exclusion criteria, will be enrolled in the multicenter study.

3.3 Study Design

Screening Visit:

During Visit 1, once the subject meets inclusion-exclusion criteria, they will be randomized and given the study medication. [redacted]

[redacted]

[redacted]

[redacted]

Treatment Visits:

Subjects will come in for Day 1 (Visit 2) [redacted]. At this visit, they will be questioned regarding onset of the episode. The investigator will identify a target area and mark it in the source document.

Clinic visits will take place on Days 2 (Visit 3), 3 (Visit 4) and 4 (Visit 5).

All subjects must be treated with the study medication for 4 days even if the lesion has healed before treatment ends.

Follow-up visits:
The subjects will return their study medication on Day 5 (Visit 6).

Subsequent follow up visits will take place on:

- Days 6 (Visit 7), 7 (Visit 8), 8 (Visit 9), 10 (Visit 10) and 12 (Visit 11).
- Day 14 (Visit 12) will have a window +/- 1 day (i.e. Day 13-15).
- Day 21 (Visit 13) will have a window of +/- 2 days (i.e. Day 19-23).

[redacted]

Note:
If the subject's lesion has healed prior to Day 5 (Visit 6), the subject will continue to apply the study medication as proposed for 4 days, and return for all study Visits up to Day 5 (Visit 6), which will be their End of Study Visit.

If the lesion is healed after Day 5 (Visit 6) but before Day 21 (Visit 13), the subject will return for their End of Study visit as directed by protocol upon healing and will not have to continue coming to the clinic for the remaining study visits.

[redacted]

[redacted]

If a subject arrives to the clinic for an unscheduled visit, the subject will go through the same procedures as a scheduled follow-up day. If the subject has not healed by this unscheduled visit, the subject will return to the clinic for the subsequent previously planned follow-up visits.

The use of the study medication should be discontinued after Day 4; however the investigator will continue to monitor the lesion until Day 21 if not healed by then.

[redacted]

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Inclusion Criteria

Subjects **must** meet all of the following criteria:

1. Immunocompetent (defined as not having underlying disease and/or the administration of immunosuppressant medication) male or nonpregnant females, 12 years of age and older, with non-life-threatening recurrent herpes simplex labialis.
2. Subjects must have [redacted] recurrences of herpes simplex labialis per year for the past [redacted] years.
    a. [redacted] recurrences preceded by recognizable prodromal symptoms [redacted]
    b. [redacted] prodromes followed by classical lesions.
3. Subject must sign an Institutional Review Board (IRB) approved written informed consent for this study prior to study related procedures being performed. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative.

4. Subjects must be willing and able to understand and comply with the requirements of the study, apply the study medication as instructed, refrain from use of all other topical medication or topical antibiotics near the area of the cold sore during the treatment and follow up periods of the study, return for the required study visits and comply with therapy prohibitions.

5. Subjects must be in general good health and free from any clinically significant disease that might interfere with the study evaluations in the opinion of the investigator.

6. [redacted].

4.2 Exclusion Criteria

Subjects may **not** be selected if any of the following criteria exist:

1. Females who are pregnant, breast feeding, or planning a pregnancy.

2. Females of childbearing potential who do not agree to utilize an adequate form of contraception.

3. The use of any topical prescription or any over the counter antivirals [redacted] prior to screening visit, [redacted] prior to treatment initiation and throughout the treatment and follow up periods of the study.

4. Candidate for or previous use of parenteral antiviral treatment or prophylactic antiviral therapy for their recurrent herpes simplex labialis.

5. Recent organ transplant.

6. Subjects who are immunocompromised or HIV positive or who have any immune-system disorders including auto-immune diseases.

7. Recent major change in immune system status that could seriously affect the clinical manifestations of herpes simplex labialis and need for treatment in the opinion of the investigator.

8. Subjects with known or suspected history of a clinically significant systemic diseases (i.e., immunological deficiencies), unstable medical disorders (i.e., unstable diabetes), life-threatening disease or current malignancies.

9. Subjects with current episode of herpes simplex labials that is not completely healed (Once current lesion is healed, the subject may return for screening and enroll in the study.)

10. Excessive facial hair (e.g. beards, moustaches, etc.) that would interfere with the direct area for diagnosis or assessment of herpes labialis.

11. Presence of any other facial skin condition that might interfere with herpes labialis diagnosis, assessment, and/or healing ability [redacted]

12. History of herpes keratitis.

13. Contraindication to antiviral therapy or known hypersensitivity to any component of acyclovir therapy. This includes subjects who have a known hypersensitivity to any of the following (in any dosage form): Acyclovir [redacted].

14. History of unresponsiveness to topical acyclovir therapy.

15. Use of any prescription or over the counter antivirals [redacted] prior to screening, 30 days prior to treatment initiation and throughout the treatment and follow up periods of the study.

16. Participation in any other clinical study or who have received treatment with any investigational drug or device within 30 days prior to screening. If the investigational product used in the prior clinical study is believed to have lasting effects beyond 30 days, the investigator should deem an appropriate washout out period prior to screening.

17. Subjects who have previously been enrolled in this study.

18. Subjects who have received any local medication, including topical corticosteroids, in the target area throughout the treatment and follow up periods of the study.

19. Subjects who have been treated with immunosuppressive therapy [redacted] prior to Day 1 (Visit 2) study visit for indications such as:

    a. To prevent the rejection of transplanted organs and tissues (e.g., bone marrow, heart, kidney, liver).

b. To treat autoimmune diseases or diseases that are most likely of an autoimmune origin (e.g., rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, sarcoidosis, focal segmental glomerulosclerosis, Crohn's disease, Behcet's Disease, pemphigus, and ulcerative colitis).

c. To treat other non-autoimmune inflammatory diseases.

20. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements in the investigator's opinion.

21. Use of tanning booths, sun lamps, sunbathing or excessive exposure to the sun [redacted] from initiating study medication.

22. Subjects using immunostimulators (BCG, levamisole, etc.), dye-light therapy, or psoralen therapy [redacted] prior to study medication initiation.

23. [redacted]

24. [redacted].

4.3 Precautions

The following precautions are to be taken during treatment and follow up periods of the study:

1. Subjects should avoid contact of the study medication inside the eyes, mouth, and nose. In case of accidental exposure, rinse with plenty of water.
2. Subject should be told that treatment does not prevent them from being contagious.
3. Subjects should avoid lip/oral contact with other individuals (including kissing) during treatment to avoid transmission of infection.
4. The study medication is not to be shared with any other persons or used in any other manner than instructed by the clinic.
5. [redacted].
6. [redacted]
7. [redacted]
8. [redacted]

[redacted]

9. Subjects should consult the investigator with any questions regarding concomitant medications.
10. Subjects should wash hands before and after applying study medication.
11. [redacted]
12. [redacted].
13. [redacted]
14. [redacted]
15. Subjects should not eat or drink [redacted] prior to or after dosing to avoid irritation and maintain cleanliness of affected area when applying study medication.
16. Study medication should be kept in room temperature at all times (at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)) and kept away from extreme hot/cold environments (i.e. left in the car on a hot/cold day).
17. [redacted]

5. PROCEDURES

5.1 Subject Screening and Enrollment

The study personnel will review the IRB approved informed consent form and assent form, as applicable, with each subject and give the subject an opportunity to have all questions answered before proceeding. The consent/assent form must be signed by each subject and witnessed before the subject is enrolled into the study. A copy of the signed consent/assent will be given to every participant and the original will be maintained with the participant's study records. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative. Once a subject has been screened and meets the inclusion/exclusion criteria, subjects will receive the study medication.

[redacted]

5.2 Assignment of Subject Number

Once the subject has consented, met inclusion/ exclusion criteria, they will be assigned a subject number. The subject number will be taken from the study medication kit dispensed to the subject at each site.

5.3 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study medication. The medical history will include a complete review of all current diseases and their respective treatments.

5.4 Concomitant Medications

Concomitant medications and any medications taken [redacted] prior to signing informed consent/assent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications as well as dietary supplements. All medications taken on either a regular or "prn" basis, including vitamins, aspirin and acetaminophen, should be recorded on this page.

5.5 Physical Examination

The investigator, sub-investigator or appropriately delegated and qualified designee will perform a brief physical examination on Visit 1 (Screening) and Visit 2 (Day 1). The exam will include ENT, heart, lung, abdomen evaluation as well as recording vital signs. Vital signs are to include sitting blood pressure, oral temperature, heart rate, and respiratory rate.

5.6 Urine Pregnancy Test

Females of childbearing potential (excluding women who are surgically sterilized (verified tubal ligation or bilateral oophorectomy or hysterectomy) or post-menopausal for at least 2 years), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study. An investigator could repeat the pregnancy test at any time during the study if there is any suspicion or possibility that the subject is pregnant. [redacted]

[redacted]

5.7 Assessments

Lesion healing assessment and Application Site Reaction Assessment must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated these tasks by the PI. [redacted]

[redacted]

5.7.1 Lesion Healing Assessment

At Day 1 (Visit 2) and at each subsequent visit, the investigator will assess lesion healing.

[redacted].

The primary efficacy endpoint will be the time to complete healing of lesions [redacted] measured in days/hours from the time of first dosing.

[redacted]

5.7.2 Application Site Reaction Assessment

At Day 1 (Visit 2) and at each subsequent visit, application site reactions such as dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin and stinging on the skin (if any) will be recorded.

[redacted]

Site Reaction	DESCRIPTION
Dry Lips	[redacted]
Desquamation	
Dryness of Skin	
Cracked Lips	
Burning skin	
Pruritus	
Flakiness of Skin	
Stinging of the skin	

SCORE	ASSESSMENT	DESCRIPTION
0	None	[redacted]
1	Mild	
2	Moderate	
3	Severe	

5.8 Study Medication Use, and Diary Instructions

At the Screening Visit (Visit 1), each subject will be screened for inclusion/exclusion criteria. The subjects who qualify will be randomized and dispensed the study medication along with the diary including the study instructions.

[redacted]

The study staff will instruct the subject how to apply the study medication. [redacted]

[redacted]

[redacted].

The study staff will also instruct the subject on how to complete the diary. The subjects will record the time and date of each application and healing time in the diary. Subjects will be asked to record the stage of their herpes lesion as well as record their symptoms (i.e. pain, burning, stinging, itching, tingling, etc.) twice a day. [redacted]

The subject will be instructed to bring the diary and study medication with them at all visits for staff review of compliance. The study staff must confirm that the subject is recording all relevant information in a proper manner.

5.9 Visit Specific Procedures

The following sections outline the procedures required at each visit.

5.9.1 Screening Visit (Visit 1)

Prospective subjects will visit the study site and undergo the following procedures:

[redacted]

5.9.2 Day 1 ([Visit 2] within 24 hours of initial study medication application)

[redacted]

[redacted]

5.9.3 Day 2 (Visit 3)

[redacted]

5.9.4 Day 3 (Visit 4)

[redacted]

5.9.5 Day 4 (Visit 5 [End of study medication therapy])

[redacted]

5.9.6 Day 5 (Visit 6)

[redacted]

[redacted]

5.9.7 Day 6, 7, 8, 10, 12, 14 (Visit 7, 8, 9, 10, 11, 12)

[redacted]

5.9.8 Day 21 (Visit 13)

[redacted]

Day 14 (Visit 12) will have a window of +/- 1 day (i.e. Day 13-15).

Day 21 (Visit 13) will have a window of +/- 2 days (i.e. Day 19-23).

5.9.9 Unscheduled Visit

[redacted]

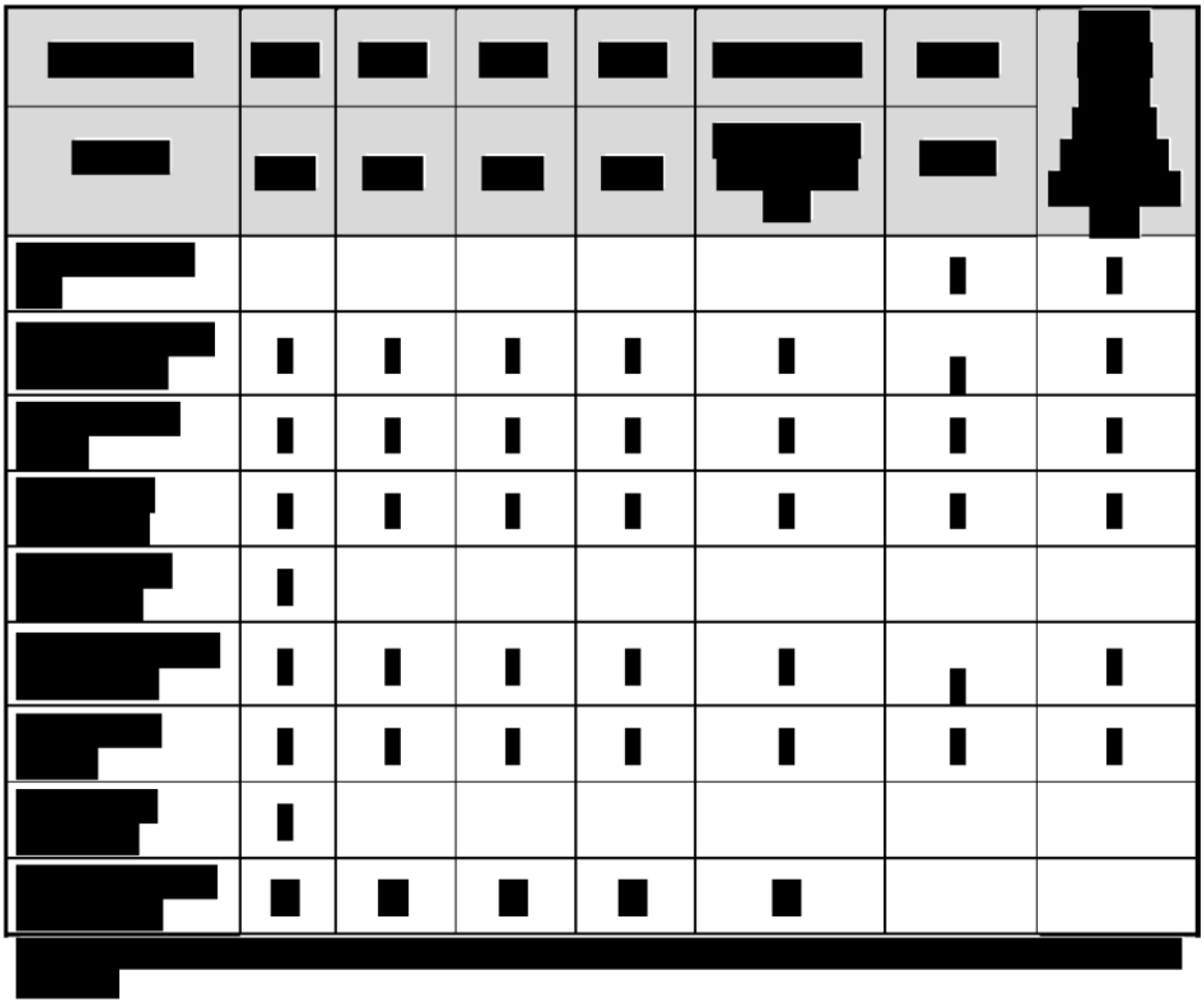
5.9.10 End of Study Visit/Visit after lesion healing within 24 hours of time to complete lesion healing

[redacted]

5.10 Summary of Assessments

The schedule of visits and procedures to be conducted at each visit are summarized in the schedule of study procedures.

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]		[redacted]			
[redacted]		[redacted]			
[redacted]		[redacted]			
[redacted]		[redacted]			
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]



5.11 Screen Failures

Screen failures will not be included in any data analyses. A screen failure is a subject who signed the informed consent/assent and received information about the study, but did not meet the inclusion-exclusion criteria and did not receive the study medication.

5.12 Protocol Deviations/Violations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the

investigator or designee must contact the [redacted] contacts listed in Section 15 (Appendix A) at the earliest possible time.

[redacted]

[redacted]

5.13 Subject Compliance

Subjects will apply the study medication 5 times a day for 4 days. Subject will record the time and date of each application in the diary. The subject will also record any adverse events experienced or medications used during the treatment and follow-up periods of the study.

Study staff will review the diary at each visit to ensure compliance with protocol and to capture all adverse events and use of medication. They will also verify use of study medication by visual inspection of the tube.

[redacted] All used and unused tubes of study medication will be collected by the study site.

5.14 Discontinuation/Withdrawal of Study Subjects

Subjects may be removed from the study for any of the following reasons:

- The subject withdraws his / her consent for any reason.
- The subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study.
- The subject's study medication code is unblinded.
- An adverse event occurs for which the subject desires to discontinue treatment or the

investigator determines that it is in the subject's best interest to be discontinued.

- The subject is lost to follow-up. The study staff will document efforts to attempt to reach the subject at least twice by telephone and will send a certified follow-up letter before considering that subject lost to follow-up. All attempts must be thoroughly recorded.
- The subject becomes pregnant during the course of the trial.

The reasons for a subject being discontinued will be documented in the subject's records, electronic case report form and the enrollment log.

If a subject is discontinued from the study for any reason, the end of study procedures should be completed and any outstanding data and study medication should be collected. Data, in addition to the reason for discontinuation and the date of removal, will be recorded on the End of Study Case Report Form.

In the event that a subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a subject, the investigator must strive to follow the subject until the adverse event has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

Subjects, who significantly worsen (e.g., significant increase in size or number of lesions beyond the subject's usual pattern, progression of lesions after the first few days of therapy, development of severe pain, or evidence of tissue necrosis) during the therapy should be discontinued from the study and may be prescribed standard therapy by the physician.

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by the sponsor will consist of:

Test Product: Acyclovir Cream, 5%- Perrigo [redacted]

Reference Product: Zovirax® Cream 5%, Valeant Pharmaceuticals

Vehicle: Vehicle of Acyclovir Cream, 5%- Perrigo [redacted]

[redacted].

6.2 Medication Management

6.2.1 Labeling, Packaging, Distribution, and Randomization

Randomization will be performed according to a computer generated randomization schematic [redacted] test: reference: vehicle. The treatment group designation has been assigned to the subject number on the study medication kit. Study medication is blinded, labeled and packaged, according to the random code, so that neither the subject nor the investigator can identify the treatment. Each subject will be provided with one of these random kits. An independent third party will hold the randomization code throughout the study.

All study medications will be supplied to the subjects in [redacted] tubes. Each subject's treatment unit will consist of one kit box containing [redacted] study medication.

[redacted]

[redacted]

[redacted]

6.2.2 Procedure for Breaking the Blind

The investigator, staff at the study site, study monitors, and data analysis/management personnel are blinded to the subject assignment. In the event of an emergency, the specific subject treatment may be identified by removing the

overlay of the blinded label, which is attached to the study medication log; however, every effort should be made to maintain the blind. **The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation only and should seek prior authorization by the sponsor or designee when possible.** The reason for breaking the blind must be clearly documented in the source documentation and CRF and the subject must be discontinued from the study. The sponsor must be notified immediately upon all unblinding situations.

6.2.3 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required by Federal Regulations to randomly select and maintain retention samples. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used." The investigator will store the retain sample study medication until such time as notification is received from the sponsor that the samples are no longer required.

6.2.4 Storage and Study Medication Accountability

Study medication used to conduct this study will be maintained under adequate security by the investigator. Study medication will be stored at room temperature at or below 25°C (77°F) not outside the range of 15°C to 30°C (59° to 86°F) in a secured area with limited access. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The study medication should not be frozen, should be protected from heat and kept tightly closed. The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The clinic personnel will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each is dispensed and used. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. At the conclusion of the study all unused, partially used, and empty containers must be inventoried by the monitor and returned to the sponsor, or designee, for destruction.

7. ADVERSE REACTIONS

The potential adverse reactions of generic Acyclovir Cream, 5% are anticipated to be similar to those observed in Zovirax® Cream 5%. Adverse reactions related to treatment with Zovirax® Cream 5% include local application site reactions (dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on the skin) as per the package insert. Each event occurred in less than 1% of subjects receiving Zovirax® Cream 5%. Other adverse reactions (angioedema, anaphylaxis, contact dermatitis, eczema) as well as signs and symptoms of inflammation have been reported with Zovirax® Cream 5% use in clinical practice.

7.1 Deviation from the Protocol for Individual Subjects

When an emergency occurs requiring a deviation from the protocol for a subject for safety reasons, the deviation will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or the sponsor by telephone and follow up with a written description as soon as possible. In such situations, the overseeing IRB should also be notified.

7.2 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes:

- death
- life-threatening event (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- requires in-subject hospitalization or prolongs hospitalization
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- congenital anomaly/birth defect
- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, e.g. allergic bronchospasm requiring intensive treatment in an emergency room or home,

blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse

Immediately Reportable Adverse Events (IRAE): Any serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

Unexpected Adverse Event: An unexpected event is any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study medication, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

Intensity of Adverse Events: The maximum intensity of an AE during a day should be recorded on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.

Moderate - AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication: The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely - The AE:

- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:

- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge).
- cannot be reasonably explained by the known characteristics of the subject's state.

Possible - The AE:

- follows a reasonable temporal sequence from study medication administration but that could readily be produced by a number of other factors.

Unlikely - The AE:

- follows a reasonable temporal sequence from study medication administration.
- could have been produced by either the subject's clinical state or by study medication administration.

Not related - The AE:

- does not have a reasonable temporal association with the administration of study medication
- has some other obvious explanation for the event.

7.3 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. [redacted]

All adverse events (as defined in Section 7.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness/ causal relationship of the event to the study medication or procedure. Serious or unexpected adverse events must be reported to Perrigo ***within 24 hours*** of when the Investigator first learns of the occurrence of the event.
Adverse events will be documented in source and recorded in a timely manner on case report forms. Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE case report form (CRF) with the status of the AE noted.

Adverse events will be recorded and reported during treatment and follow-up period
Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the CRF.

7.3.1 Expedited Reporting Responsibilities of the Study Center

For any serious adverse event, the sponsor must be notified ***within 24 hours*** of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to the sponsor. The adverse event term on the AE case report form and

the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Subjects with unresolved adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs within 30 days after the last assessment, and are determined by the investigator to be reasonably associated (definite, probable & possible) with the use of the study medication, should be reported to the sponsor within 24 hours of when the Investigator first learns of the occurrence of the event.

When reporting a serious adverse event (SAE) the Investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy to [redacted] mmediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier [redacted] within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow up information should be sought (hospital discharge summaries, operative reports etc.) and a follow up SAE report form submitted. A designation of causality from the study medication should always be included with a follow up report. Assess and report the causality of the event.

7.3.2 Submitting an Expedited Safety Report to the IRB

Once [redacted] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with the sponsor, will determine if the safety report is eligible for expedited review. [redacted] will log the initial event and will notify the sponsor that an event has been reported within 1 business day after initial receipt. [redacted] will complete the review of the event, enter information into their safety database and generate the report. This form, as well as other supporting documentation, will be forwarded to [redacted] Medical Monitor for review. [redacted] will finalize the report and distribute it to the sponsor within 2 days after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended [redacted], the sponsor, or study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required

reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

When a Principal Investigator receives an expedited safety report from [redacted] or the sponsor detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center's IRB. The Principal Investigator must retain a copy of such reports as submitted to their IRB in the site's study Regulatory Binder.

7.4 SAE & AEs Requiring Discontinuation of Study Medication, including Pregnancies

ANY SAE, WHICH OCCURS AFTER A SUBJECT HAS INITIATED THE STUDY MEDICATION, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED TO [redacted] IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO [redacted].

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported to the sponsor immediately and within 3 working days. Subjects who discontinue due to experiencing adverse events should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

A subject who experiences a severe adverse event related to study medication will be discontinued from the study.

The notification about any serious adverse event should be directed to:

[redacted]

7.4.1 Pregnancy

At the time a Principal Investigator or site personnel becomes aware that a study participant became pregnant following study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and by faxing a completed Pregnancy Report to [redacted] within one working day of being notified of the pregnancy report.

The report will include the following elements:

- Participant (mother's) coded study identifier;
- Date of participant's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study medication administration.

The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or designee must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus to the [redacted] including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy **meets the criteria for immediate classification of an SAE** (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE report form to [redacted] within one working day of being notified of the pregnancy report.

If [redacted] responsibilities for the trial are completed before the outcome of the pregnancy is known, the sponsor will assume the responsibility for following up on the pregnancy.

7.5 Post Study Adverse Events

7.5.1 Non-serious Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE case report form (CRF) with the status of the AE noted.

7.5.2 Serious Adverse Events

Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE case report form (CRF) page and reported to the sponsor according to the procedures outlined above. Subjects with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs after the last assessment, and are determined by the investigator to be reasonably associated with the use of the study medication, should be reported to Perrigo Pharmaceuticals.

8. STATISTICAL CONSIDERATIONS

8.1 General Considerations

Statistical analyses will be conducted by the Sponsor's designee. The mITT and PP populations will be used in the analysis of efficacy endpoints and the safety population for safety endpoints. Subjects will be analyzed as treated. Summary displays will be presented by treatment group.

Hypotheses will be tested at the 5% statistical significance level, unless otherwise specified. No interim analysis is planned. Efficacy and safety analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC), or comparable software.

All censored data will be accounted for using appropriate statistical methods. See Section 8.4.1 for details.

All data collected on the eCRF will be listed. Routine data listing or tabulation review of blinded data during the study conduct will be performed to identify missing data, anomalies, outliers, etc. A complete description of data handling rules and planned statistical analyses will be described in a separate statistical analysis plan (SAP) prior to data lock and unblinding procedures are completed at the end of the study.

8.2 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) Population/Safety Population: Any subject who was randomized, and received study medication. Subjects will be included in the analysis as randomized.

- Modified Intent-to-Treat (mITT) Population: Any subject, who meet the inclusion/exclusion criteria, was randomized, received and used at least one dose of the study medication, and returned for at least one post-screening efficacy assessment.

- Per Protocol (PP) Population: Any subject:
  - Who met inclusion/exclusion criteria
  - Who was randomized, and received and used study medication.
  - Who met the protocol criteria for compliance [redacted]
  - Without significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

Subjects taking any of the following actions will be considered as having discontinued due to treatment failure:

- Discontinued from the study with reason stated as, "Subject's condition worsened, the investigator feels it is unsafe for the subject to continue in the study", or
- Discontinuation reason listed as "lack of efficacy (treatment failure)", or
- Defined as a treatment failure in the PV/PD log

[redacted].

8.3 Sample Size Considerations

[redacted]

[redacted]

[redacted]

8.4 Measures and Analysis

8.4.1 Efficacy Endpoint and Analysis

The primary efficacy endpoint will be the time to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary), measured in days/hours from the time of first dosing.

[redacted]

[redacted].

Equivalence of Clinical Endpoint Analysis

The mean time to complete healing of the lesion for the test and reference treatments will be estimated using analysis of Variance (ANOVA) with treatment and center as fixed effects in the model. The 90% confidence interval for the ratio (Test/Reference) of mean time-to-complete healing will be obtained by Fieller's method. A plot for the ratio (Test/Reference) of mean time-to-complete healing and associated 90% CI will be presented. For the time to complete healing of lesion the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the calculated 90% confidence interval of the ratio of the means (Test/Reference) falls within the interval of 0.80 to 1.25. Therapeutic equivalent evaluations in the per-protocol (PP) population will be considered the definitive analysis. This analysis will be repeated in the mITT population and will be considered the supportive analysis. Refer to the statistical analysis plan for analysis details.

Analysis of Superiority between active formulation and vehicle

For the time to complete healing of the lesion, subjects who received active treatment will be compared to those who received the Vehicle as treatment in order to determine if superior efficacy has been attained.

The time-to-complete healing of both the active products and Vehicle will be analyzed using Analysis of Variance (ANOVA) evaluations with treatment and center as fixed effects in the model.

Each active treatment group will be compared to the Vehicle group using a -two-sided test and tested at an alpha level of 0.05. The mean and its 95% confidence interval will be reported.

Superiority will be considered demonstrated if the means for both active treatments are statistically different from ($p<0.05$), and smaller than, that for the Vehicle

The analysis of superiority using the mITT population will be considered the definitive analysis. This analysis will be repeated using PP population and will be considered as supportive analysis. Refer to the statistical analysis plan for analysis details.

8.4.2 Safety Endpoints and Analysis

The safety population will be used in the safety analyses.

All AEs will be classified with respect to system organ class (SOC) and preferred term using MedDRA. A treatment-emergent AE is an event that occurs or worsens after the administration of first dose of study medication. The AE profile will be characterized with severity and attribution (unrelated and related) to study medication. Related AEs will be events that are definitely, possibly or probably related to treatment in the investigator's judgment.

The number and percent of patients who report treatment-emergent AEs will be summarized for each treatment group. Additional summaries by severity and relationship to study medication will be presented for each treatment group. In addition, the number and percent of patients who reported treatment-emergent AEs of interest and serious AEs will be summarized for each treatment group.

8.5 Characteristics of Subjects at Screening

Demographic and baseline characteristics will be summarized using Intent-to-Treat (ITT) Population by treatment groups.

Age (years), height at screening (cm), body weight at screening (kg), and body mass index (BMI) at screening in kg/m2 will be summarized using descriptive statistics and gender, race, and ethnicity will be summarized using frequencies and percentages.

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES

It will be made clear to the subject that, for the purposes of the study, they are consenting only for topical application of medication or vehicle. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed consent/assent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by the sponsor, prior to study commencement.

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB must be sent to the sponsor.

The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent/assent form, which shall be approved by the same IRB responsible for approval of this protocol. Each informed consent/assent form shall include the elements required by FDA regulations in 21 CFR Part 50. The investigator agrees to obtain approval from the sponsor of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB-approved written informed consent/assent form shall be signed by the subject and/or their parent/legally authorized representative and the person obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from screening. In the event that the subject is re-screened for study participation, a new informed consent/assent form must be signed.

9.1 Subject Confidentiality

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the sponsor, it is required that the investigator permit the study monitor, any Sponsor authorized representative, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by the sponsor or their authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, the sponsor or their authorized representative and possibly the FDA.

All reports and communications relating to the subject in the study will identify each subject only by the subject's initials and by the subject number. The investigator agrees to furnish the sponsor with complete subject identification, if necessary on a confidential follow-up form, which will be used for the purpose of a long-term follow-up, if needed. This will be treated with strict adherence to professional standards of confidentiality and will be filed at the sponsor under adequate security and restricted accessibility.

10. CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all events and the times at which they occur.

10.1 Completion of Study

The investigational site will complete the study and complete all documentation required in satisfactory compliance with the protocol. It is agreed that, for reasonable cause, either

the investigator or the sponsor may terminate this study before completion provided written notice is submitted at a reasonable time in advance of intended termination. Any extension of this study must be mutually agreed upon in writing by both the investigator and the sponsor.

10.2 Protocol Amendments

The Investigator will not make any changes to this protocol without prior written consent from the sponsor and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed between [redacted] and Perrigo. If agreement is reached regarding the need for an amendment, the amendment will be written by the sponsor. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for 'administrative amendments', investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days. The sponsor will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or the sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

11. RECORDS MANAGEMENT

11.1 Data Collection

All data collected in this study will be entered into eCRFs, verified by monitoring, and submitted for statistical evaluation as described below. Edit checks will be run on the data and queries issued as needed. Once all data is cleaned, full quality control verification will be done prior to breaking the blind. After all data are correctly entered, the database will be locked and submitted for appropriate Quality Assurance verifications before the treatment assignment code is broken. All data collected in the CRFs will be documented in subject data listings and summarized in tables, as appropriate.

During each subject's visit to the clinic, a designee participating in the study will record progress notes to document all significant observations. At a minimum, these notes will contain:

a) Documentation of the informed consent process;
b) The date of the visit and the corresponding Visit in the study schedule;
c) General subject status remarks, including any *significant* medical findings. The severity, frequency, and duration of any adverse events and the investigator's assessment of relationship to study medication must also be recorded.
d) Any changes in concomitant medications or dosages;
e) A general reference to the procedures completed; and
f) The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the study progress notes and other source documents, will be entered in **black or blue ink**, **initialed** and **dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

For transmission to the sponsor, information from the study progress notes and other source documents will be promptly entered into the database. The database also contains a complete audit trail to capture all regulatory components of data corrections (e.g. initial entry, new value, initials and date of the change).

11.2 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

11.3 File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

11.4 Records Retention at the Study Site

FDA regulations require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

a) A period of at least two years following the date on which a New Drug Application is approved by the FDA;
b) A period of two years after the sponsor notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from [redacted]. Such documentation is subject to inspection by the sponsor and the FDA.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

The sponsor has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of eCRFs. Monitors must be given direct access to either original or certified copies of the medical records.

12.2 Auditing

The sponsor (or representative) may conduct audits at the study center(s). Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the sponsor immediately if notified of such an audit, and

must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

13. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, Declaration of Helsinki, the United States Food and Drug Administration (FDA) regulations, any other countries regulations, and ICH GCP Guidelines

14. USE OF INFORMATION AND PUBLICATION

All information supplied by the sponsor in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e. the clinical protocol, case report forms), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by the sponsor in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of the sponsor, and shall not be used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential, and will be used by the sponsor in connection with the development of the drug. The information may be disclosed as deemed necessary by the sponsor to allow the use of the information derived from this clinical study, the investigator is obliged to provide the sponsor with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of the sponsor. [redacted]

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-14-008

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Acyclovir Cream, 5% with ZOVIRAX® (Acyclovir) Cream 5%, and both Active Treatments to a Vehicle Control in Treatment of Recurrent Herpes Labialis

Protocol No: PRG-NY-14-008

[redacted]

I have carefully read the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____

Principal Investigator's Printed Name

_____

Principal Investigator's Signature

_____

Date

15. APPENDICES

15.1 [redacted]

[redacted]

Protocol No: PRG-NY-14-008

[redacted]

15.2 [redacted]

Date: _____

SUBJECT INITIALS: _____ SUBJECT NUMBER: _____

SITE NUMBER: _____

[redacted]

Protocol No: PRG-NY-14-008

[redacted]

5. [redacted]

Please report any side effects or problems you have with the study medication to your study coordinator or the study physician at the subsequent visit

Your initial treatment day is: _____ (Day 1, Visit 2)
(Date)

You are scheduled to return at:

_____on _____ (Day 2, Visit 3)
(Time) (Date)

_____on _____ (Day 3, Visit 4)
(Time) (Date)

_____on _____ (Day 4, Visit 5)
(Time) (Date)

_____on _____ (Day 5, Visit 6)
(Time) (Date)

_____on _____ (Day 6, Visit 7)
(Time) (Date)

_____on _____ (Day 7, Visit 8)
(Time) (Date)

_____on _____ (Day 8, Visit 9)
(Time) (Date)

_____on _____ (Day 10, Visit 10)
(Time) (Date)

_____on _____ (Day 12, Visit 11)
(Time) (Date)

Protocol No: PRG-NY-14-008

[redacted]

_____on _____ (Day 14, Visit 12)
(Time) (Date)

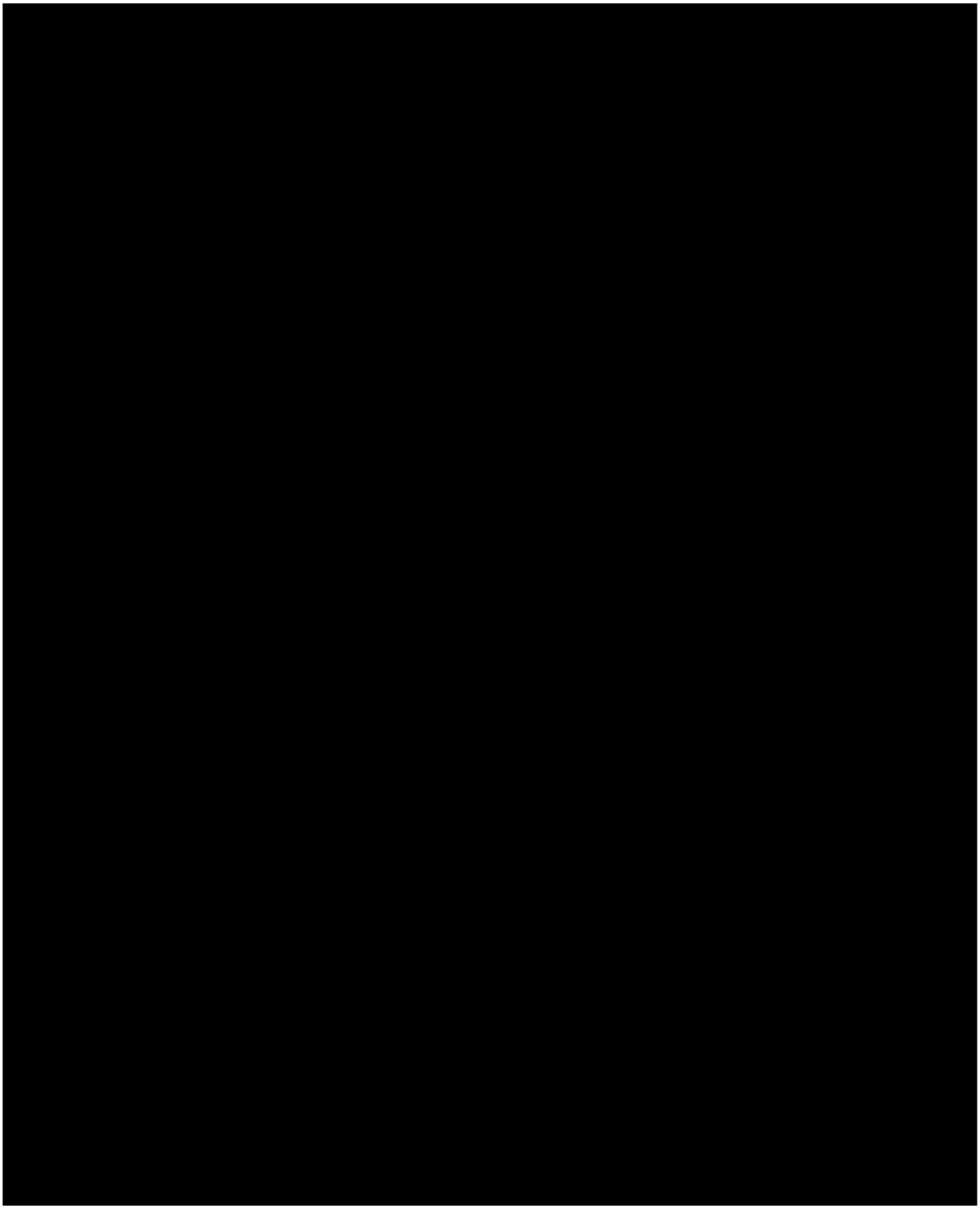
_____on _____ (Day 21, Visit 13)
(Time) (Date)

ALL APPOINTMENTS ARE IMPORTANT! IF YOU NEED TO RE-SCHEDULE YOUR APPOINTMENT, PLEASE CALL YOUR DOCTOR'S OFFICE IMMEDIATELY.

_____
Name and Telephone Number of Study Coordinator/Study Site

15.3 [redacted]

[redacted]



16. REFERENCES

1. James, William D.; Berger, Timothy G.; et al. (2006). Andrews' Diseases of the Skin: clinical Dermatology. Saunders Elsevier
2. FDA Approves Non-Prescription Cold Sore Topical Treatment Docosonal 10%
3. Summary Basis of Approval Zovirax®, Cream (Acyclovir Cream, 5%)
4. Package insert Zovirax® Cream (Acyclovir) dated Oct 2010.
5. www.Zovirax®.com
6. OGD Draft Guidance on Acyclovir March 2012
7. Summary Basis of Approval Xerese® (Acyclovir and Hydrocortisone) Cream 5%/1%
8. Spruance, SL, et. al. Antimicrobial Agents & Chemotherapy 46; 7:2238-2243
9. Summary Basis of Approval for Abreva® (docosanol) Cream 10% (GlaxoSmithKline), NDA # 20-941.