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

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Protocol/CIP No. PRG-NY-14-008[redacted]

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Statistical Analysis Plan

Prepared for:
Perrigo Company plc

[redacted]

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

[redacted]

Table of Contents

[redacted]

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AE(s)	Adverse event(s)
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
CIP	Clinical investigation plan
cm	Centimeters
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
eCRF	Electronic case report form
ENT	Ear, nose, and throat
H_0	Null hypothesis
H_1	Alternative hypothesis
HSV	Herpes simplex virus
ICF	Informed consent form
IRAE	Immediately reportable adverse events
ITT	Intent-to-Treat
kg	Kilogram
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-to-Treat
N	Number of subjects
PP	Per-Protocol
PT	Preferred term
RHL	Recurrent herpes labialis
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical analysis software
SOC	System organ class
SD	Standard Deviation
SOP	Standard operating procedures
TCR	Theorem Clinical Research
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
UNIX	UNiplexed Information and Computing Service

2 INTRODUCTION

[redacted]

[redacted]

[redacted]

An aborted episode is defined as a typical, recurrence-associated localized, site-specific [redacted]

[redacted] Perrigo has developed a generic formulation of Acyclovir Cream, 5%.

[redacted]

[redacted]

[redacted]

3 STUDY OBJECTIVES

The objectives of this study are:

1. To compare the safety and efficacy profile of Perrigo's Acyclovir Cream, 5% to Valeant's Zovirax® Cream 5%.
2. To demonstrate the bioequivalence of Perrigo's Acyclovir Cream 5% (test product) to Valeant's Zovirax® Cream 5% (reference product).
3. To demonstrate the superiority of efficacy of Perrigo's Acyclovir Cream, 5% and Valeant's Zovirax® Cream 5% over Perrigo's Vehicle of Acyclovir Cream, 5%.

4 STUDY DESIGN

4.1 General Design

This is a multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study, conducted in subjects with recurrent herpes simplex labialis.

The subjects will be randomized to one of the following treatment groups [redacted]

1) Acyclovir Cream, 5% - Perrigo
2) Zovirax® (Acyclovir) Cream 5% - Valeant Pharmaceuticals
3) Vehicle of Acyclovir Cream, 5% - Perrigo

The objective of the study is to demonstrate bioequivalence of Perrigo's Acyclovir Cream, 5% and Valeant's Zovarax® (Acyclovir) Cream, 5% based on the primary clinical endpoint of time-to-complete healing of lesions. As a parameter for determining adequate study sensitivity, statistical superiority ($p<0.05$) of active formulations over vehicle control needs to be demonstrated with regard to the primary endpoint.

Subjects will be immunocompetent males and females, ≥ 12 years of age, with a clinical diagnosis of non-life-threatening recurrent herpes simplex labialis.

When a subject meets the inclusion/exclusion criteria, the subject will be randomized to one of the above mentioned study treatment arms. Subjects will apply the study medication at 5 times a day for 4 days. [redacted]

[redacted]

[redacted] At this visit, the investigator will identify a target area and mark it in the source document.

Subjects will maintain a diary in which they will record each time and date of study medication application in addition to recording any adverse events experienced or medication used.

Visits to the study site are scheduled at screening visit (Visit 1), treatment visits on Days 2 (Visit 3), 3 (Visit 4) and 4 (Visit 5) and follow-up visits on Days 5 (Visit 6), 6 (Visit 7), 7 (Visit 8), 8 (Visit 9), 10 (Visit 10), 12 (Visit 11), 14 (Visit 12) and 21 (Visit 13).

[redacted]

[redacted]

[redacted]

If healing occurs in-between scheduled study days, the subject should return to the clinic

[redacted]

4.2 Discussion of Study Design

This study is designed to demonstrate the bioequivalence of Perrigo's Acyclovir Cream, 5% to Valeant's Zovirax® Cream 5% and will also demonstrate the superiority of efficacy of Perrigo's Acyclovir Cream, 5% and Valeant's Zovirax® Cream 5% over Perrigo's Vehicle of Acyclovir Cream, 5%. This study has the following design characteristics:

- Randomized: This is done in order to eliminate the allocation bias and balancing both known and unknown prognostic factors, in the assignment of treatments.
- Vehicle control (Placebo): This study involves a Vehicle group that will be used to demonstrate the superiority of the test and reference formulations.
- Bioequivalence: To establish bioequivalence between Perrigo's Acyclovir Cream, 5% (test) and Valeant's Zovirax® Cream 5% (reference), the 90% confidence interval of the test/reference ratio for the primary endpoint, time-to lesion healing, must be contained within [0.80, 1.25]
- Superiority: As per the FDA guidelines, if bioequivalence is demonstrated for test and reference formulations, this will only be accepted if the study had adequate sensitivity to detect true differences between formulations if they existed. Hence, this study is designed to demonstrate the superiority of Perrigo's Acyclovir Cream, 5% and Valeant's Zovirax® Cream 5% over Perrigo UK FINCO's Vehicle of Acyclovir Cream, 5%.

4.3 Method of Assignment of Subjects to Treatment Groups

Eligible subjects will be randomized to one of the following treatment groups in a 1:1:1 allocation ratio:

- Test Formulation: Acyclovir Cream, 5% - Perrigo
- Reference Formulation: Zovirax® Cream 5% - Valeant Pharmaceuticals
- Vehicle: Vehicle of Acyclovir Cream, 5% - Perrigo

Randomization will be performed according to a computer-generated randomization scheme where the treatment group designation has been assigned to the subject number. The treatment designation will remain blinded until the final database is locked. An

independent third party will hold the randomization code throughout the study. The randomization scheme will be a block randomization.

4.4 Blinding

Being a double-blind study, the subject, investigator, staff at the study site, study monitors, and data analysis/management personnel are blinded to treatment assignments. Study medication is blinded, labeled and packaged, according to the randomization code, so that neither the subject nor the investigator can identify the treatment. Each subject's treatment unit will consist of one kit box containing [redacted] study medication. One tube will be distributed to the subject and the second will remain at the site as a back-up sample to be distributed if necessary only. The tear-off portion of the kit label contains the identity of the study medication in the kit. In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label, which should be attached to the study medication dispensing 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 and should seek prior authorization by the sponsor or designee when possible. If the occluded portion of the label is removed, each involved subject(s) will be discontinued from the study and the reason for breaking the blind will be clearly documented in the source documentation and electronic case report form (eCRF). The sponsor must be notified immediately about any unblinding situation.

Unblinding of individual subject treatment assignments will occur following database hard lock by the Theorem Clinical Research Biometrics department.

4.5 Determination of Sample Size

[redacted]

[redacted]

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

[redacted]

5.2 Changes from the Analyses Planned in the Protocol/CIP

[redacted]

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

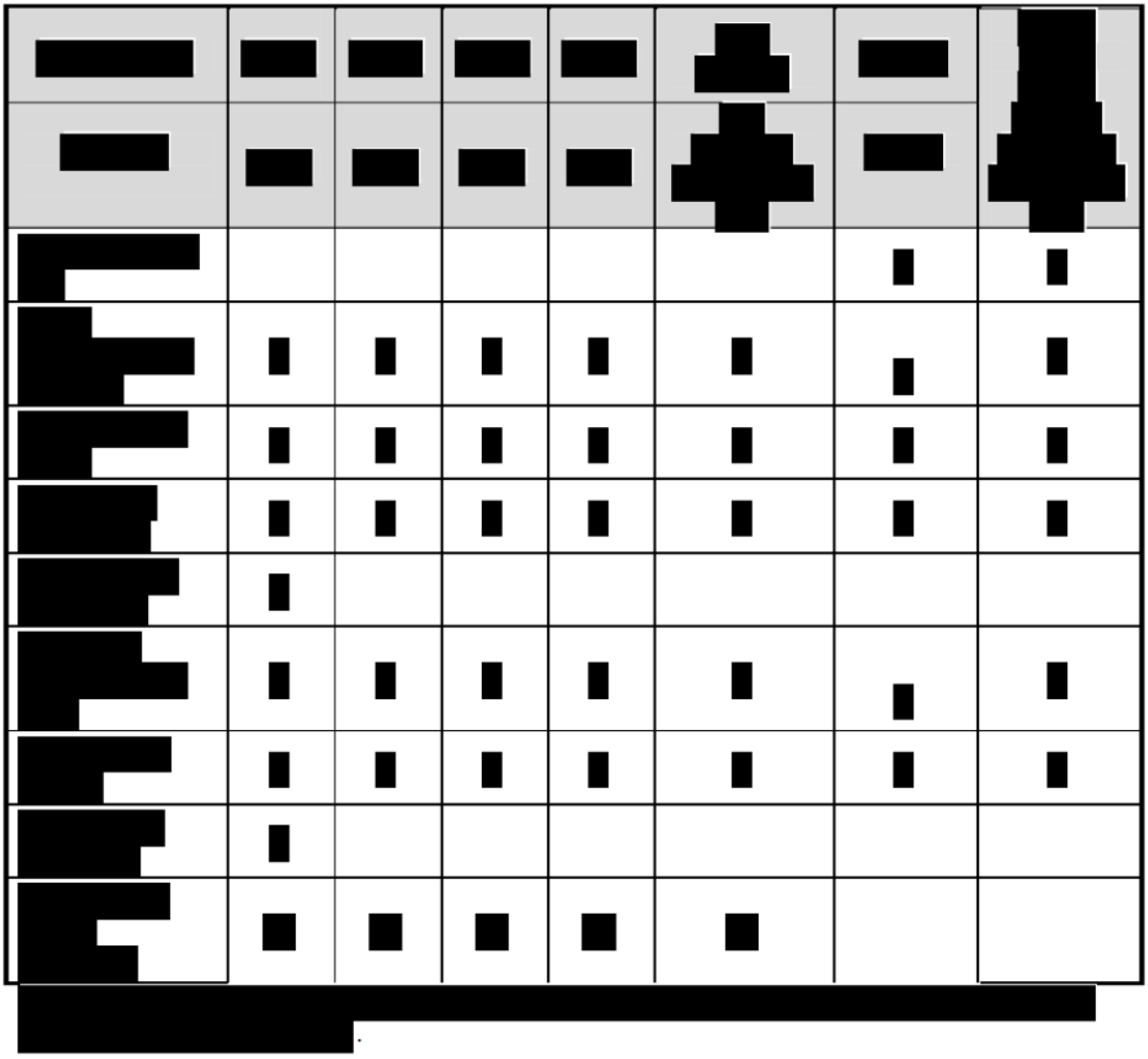
6.1 Schedule of Evaluations

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

Table 2: Assessments Conducted at each Scheduled Visit

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

Table 2: Assessments Conducted at each Scheduled Visit (cont.)



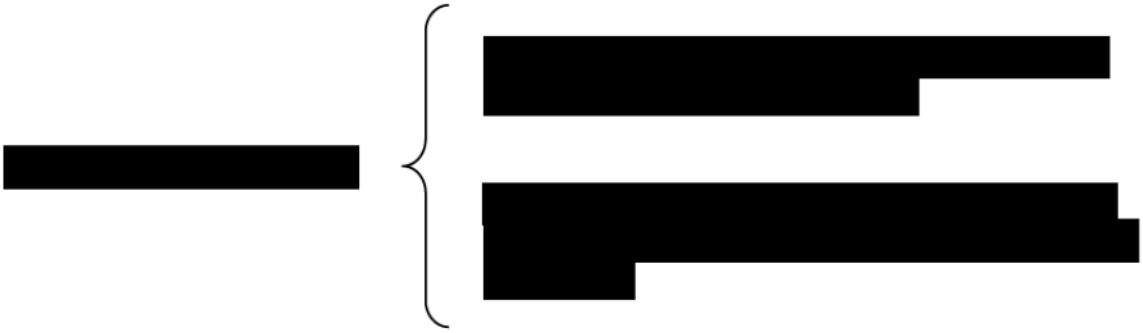
6.2 Time Point Algorithms

6.2.1 Relative Day

[redacted]

6.2.2 Length of Time-to-Event Parameters

[redacted]



Please note, the hours maybe converted to days (24 hours in 1 day),

6.2.3 Windows

The clinic visits will be scheduled as per the following visit window:

If a subject arrives on an unscheduled visit, then the same assessment procedures will be performed as a scheduled follow-up visit.

Data will be summarized as per scheduled study visits only. No windowing of visits will be performed for data analysis.

Table 3: Clinic Visit Window

Visit	Scheduled Study Day	Protocol Visit Window
Visit 2 (Day 1)	The date of initial application	Day 1
Visit 3 (Day 2)	Day 2 (within 24 hours of treatment initiation)	Day 2 (within 24 hours of treatment initiation)
Visit 4 (Day 3)	Day 3	Day 3
Visit 5 (Day 4)	Day 4	Day 4
Visit 6 (Day 5)	Day 5	Day 5
Visit 7 (Day 6)	Day 6	Day 6
Visit 8 (Day 7)	Day 7	Day 7
Visit 9 (Day 8)	Day 8	Day 8
Visit 10 (Day 10)	Day 10	Day 10
Visit 11 (Day 12)	Day 12	Day 12
Visit 12 (Day 14)	Day 14	Day 13 - 15
Visit 13 (Day 21)	Day 21	Day 19 - 23

6.3 Baseline Assessments

Baseline assessments will be the last assessment prior to the date of the initial application of the study medication. [redacted]

[redacted]

6.4 Efficacy Variables

The primary efficacy endpoint is the time of complete healing of lesion. Complete healing (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) is measured in days from the time of first dosing. Time-to-complete lesion healing

will also be reported in hours, as a supplemental analysis for informational purposes only. The primary analysis will use time-to-complete lesion healing in days.

[redacted]

6.4.1 Primary Efficacy Endpoint – Time-to-Complete Healing of Lesions

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) is measured in days/hours from the time of first dosing. The hours will be converted to days for use in the analysis.

Subjects will fall into categories of:

- Complete healing occurred
- Complete healing did not occur

Subject's report their healing of the lesion in the diary. The investigator reviews the diary to confirm the healing. Complete healing occurs when the subject reported healing with date and time of healing. The subject reported healing time will be used in the analysis.

[redacted]

The time until event or censoring will be calculated as described in section 6.2.2.

[redacted]

6.4.2 Other Efficacy Endpoint – Lesion Stages

Lesion stages will be collected via subject diaries. The protocol states lesion stages may include the following categories: stage 0 (no signs), stage 1 (early signs - prodrome), stage 2 (redness), stage 3 (small blister), stage 4 (ulcer), stage 5 (crust) and stage 6 (healed lesion). Stage 0 (no signs) was not collected. The collection of lesion stage was included in the updated version of the diary, so these data are not available for all study subjects.

6.5 Safety Assessments

6.5.1 Extent of Exposure and Compliance to Study Treatment

The extent of exposure to study medication will be quantified for total number of applications applied during the course of the study.

Compliance percentage will be calculated as follows:

> Compliance = (total number of applications applied) / (the number of applications intended during treatment period)*100

Subjects should apply study medication five (5) times daily for four (4) days. Therefore, the number of applications intended during treatment period is 20.

[redacted]

[redacted]

6.5.2 Adverse Events

All adverse events (AEs) occurring after signing the informed consent are to be recorded on the AE pages of the eCRF. All AEs will be classified with respect to system organ class and preferred term using MedDRA version 19.0.

6.5.2.1 Definitions

Adverse event (AE)
An adverse event (AE) is 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.

Serious adverse event (SAE)
Any untoward medical occurrence that meets any of the following criteria:

- Results in death
- Life-threatening event
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Any other adverse events that may be considered serious based upon medical judgment

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.

Treatment emergent adverse event (TEAE)
Treatment-emergent adverse events (TEAE) are any AEs that occur or worsen (increase in severity and/or frequency) during or after the initial application of the study medication.

For treatment-emergent status regarding events with partial or missing dates, please refer to Section 7.3.

6.5.2.2 Classifications of adverse events assessments

Intensity of adverse events
The maximum intensity of an AE during a day will be recorded on the eCRF. The intensity of an AE will be graded as follows:

- Mild
- Moderate
- Severe

For AEs with unknown or missing severity, a value of "Severe" will be imputed for summary analyses.

Causal Relationship to Study Medication
Causal relationship of AE to study medication will be classified by the Investigator and will be reported as following:

- Definitely related
- Probably related
- Possibly related
- Unlikely related
- Not related

An AE will be considered related to study medication if the relationship is definitely related, probably related, or possibly related. Any missing (unknown or missing) causal relationship of an AE to study medication will be summarized as related.

6.5.3 Clinical Laboratory Evaluations – Urine Pregnancy Test

Females of childbearing potential will have a urine pregnancy test at Visit 1(Screening), Visit 2 (Day 1), Visit 13 (Day 21) and at the End of Study visit.

6.5.4 Other Observations Related to Safety

6.5.4.1 Physical Examination

The physical examination includes ear, nose and throat (ENT), heart, lung and abdomen evaluation, and will be performed at Visit 1 (Screening) and Visit 2 (Day 1).

6.5.4.2 Vital Signs

The vital signs include sitting blood pressure, oral temperature, heart rate, respiratory rate, height and weight, and will be performed at Visit 1 (Screening) and Visit 2 (Day 1).

6.5.4.3 Application Site Reaction Asessment

The application site reaction such as dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin and stinging of the skin will be assessed as None, Mild, Moderate and Severe at Visit 2 (Day 1) and at each subsequent visit.

Application site reactions will not to be considered as adverse events unless they warrant temporary discontinuation of the study medication, discontinuation from the study or treatment with new concomitant medication.

6.5.4.4 Lesion Symptoms

Lesion symptoms will be collected via subject diaries.

7 STATISTICAL METHODS

7.1 General Methodology

All analysis will be performed after the database is locked and access has been removed from the database and the study treatment codes are unblinded.

All statistical tests will be two-sided with a significance level of α=0.05, unless specified otherwise.

Data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency and percentage for discrete variables.

For the purpose of display, the summary results will be rounded as follows:

- Min and Max same number of decimals as the raw data.
- Mean and Median one more decimal place than the raw data.
- SD two more decimal places than the raw data.
- Percentages will be displayed with one decimal precision

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Subject listings of all data from the case report forms (eCRFs) as well as any derived variables will be presented.

7.2 Adjustments for Covariates

Not applicable to this study.

7.3 Handling of Dropouts or Missing Data

All available data from subjects who discontinue from the study will be used. Subjects who discontinue the study prior to or after the initiation of the study medication will not be replaced.

[redacted]

For AEs with missing severity, the most severe assessment will be imputed for summary analyses. Any missing causal relationship of an AE to study medication will be summarized as related.

For analyses, partial and completely missing start dates for adverse events and concomitant medications should be imputed as follows:

[redacted]

[redacted]

7.4 Interim Analyses and Data Monitoring

No interim analysis is planned for this study.

7.5 Multi-center Studies and Pooling of Centers

Data from all centers will be pooled for descriptive statistics; pooled data will be used for summary tables and descriptive analyses.

For analysis of variance, center will be included as a fixed effect. [redacted]

[redacted]

7.6 Multiple Comparisons/Multiplicity

Not applicable to this study.

7.7 Use of an "Efficacy Subset" of Subjects

The Intent-to-Treat (ITT), Modified Intent-to-Treat (mITT) and Per-Protocol (PP) populations are defined in section 8.3.

7.8 Active-Control Studies Intended to Show Equivalence

The objective of this study is to demonstrate the bioequivalence of Perrigo's Acyclovir Cream, 5% (Test) to Valeant's Zovirax® Cream 5% (Reference), assessed by mean time-to-complete healing of the lesion. For the purpose of bioequivalence testing, the 90% confidence interval (CI) of the ratio of the means (Test/Reference) must fall within the interval of 0.80 to 1.25.

In addition to testing bioequivalence, the superiority of efficacy of Perrigo's Acyclovir Cream, 5% (Active) and Valeant's Zovirax® Cream 5% (Active) over Perrigo's Vehicle of Acyclovir Cream, 5% (Vehicle) will be demonstrated by comparing the mean time-to-complete healing of lesion of the active treatments to that for the vehicle control. 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

7.9 Examination of Subgroups

Not applicable to this study.

8 STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The disposition of all subjects who sign an informed consent form (ICF) will be provided. The number of subjects screened and the number of screening failures overall will be presented. The frequencies and percentage of subjects randomized, treated, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations, will be summarized by treatment group.

All disposition data will be presented in a subject listing.

Screen failures will not be summarized. A listing of the subjects not meeting the eligibility criteria along with the criteria not met will be presented.

8.2 Protocol Deviations/Violations

Protocol deviations and protocol violations will be evaluated based on the investigators' judgment. These will be identified prior to database lock. The total list of all protocol deviations and protocol violations will be provided to the sponsor after database lock.

[redacted]

[redacted]

The frequencies and percentages of protocol deviations and protocol violations will be presented by treatment group.

A subject listing will be also be presented for all protocol deviations and violations.

8.3 Analysis Populations

Table 5: Population Descriptions

Population	Definition	Displays
Intent-to-Treat (ITT)	Subjects who were randomized, and dispensed the study medication regardless if the medication was used or not by the subject. Subjects will be summarized by randomized (assigned) treatment.	Displays related to subject population, demographics and baseline characteristics, disposition status, medical history, concomitant medication, major protocol deviations etc.
Modified Intent-to-Treat (mITT)	Subjects who met the following criteria will be considered: • met Visit 2 inclusion/exclusion criteria; • randomized, dispensed and used at least one dose of the study medication; • returned for at least one post-screening efficacy assessment. Subjects will be summarized by randomized (assigned) treatment.	The analysis of superiority between active and vehicle will use this population which will be considered the definitive analysis. The bioequivalence of clinical endpoint analysis will be repeated in this population and will be considered as a supportive analysis.
Per-Protocol (PP)	Subjects who met the following criteria will be considered: • met Visit 2 inclusion/exclusion criteria; • randomized, dispensed and met the protocol criteria for treatment compliance, [redacted] • had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy; - had Visit 2 investigator assessment within +2 days of first treatment; - did not take any prohibited	The bioequivalence of clinical endpoint analysis will use this population which will be considered the definitive analysis. The analysis of superiority between active and vehicle will be repeated in this population and will be considered as a supportive analysis.

	medications; - subject-reported healing and had investigator-healing assessment within +2 days of subject-reported healing time Subjects who do not have subject-reported healing, but met the other criteria for PP, can be included in PP population per the following: • [redacted] • [redacted] • Subjects who did not experience a prodrome, but initiated study treatment, completed the study, and met all the above criteria will be included in the PP population. Subjects will be summarized by the actual treatment dispensed.	
Safety	Subjects who were randomized, and dispensed the study medication regardless if the medication was used or not by the subject. Subjects will be summarized according to the actual treatment dispensed.	The safety displays will use this population which includes (Exposure, AE, application site reaction, physical examinations and vital signs)

8.4 Demographic and Other Baseline Characteristics

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/m^2 will be summarized using descriptive statistics and gender, race, and ethnicity will be summarized using frequencies and percentages.

Medical history will be summarized by frequencies and percentages of subjects by system organ class (SOC) and preferred term (PT), within SOC and PT sorted by descending frequencies. Subjects with multiple events for the same SOC or PT, will be counted only once for that SOC or PT. Medical history will be coded using MedDRA version 19.0.

Birth control methods will be summarized by frequencies and percentages.

All demographic and baseline characteristics described within this section will be presented in subject listings.

8.5 Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary (March 2016) will be used to classify prior and concomitant medications by Preferred Name and WHO anatomical therapeutic chemical (ATC) classification of ingredients.

Prior medications are defined as any medication given prior to and stopped before the initial application of study medication. Concomitant medications are defined as any medication given to the subject starting on or after the day of the initial application of study medication or started prior to the initial application of study medication and continuing during the study.

If the start date of medication is unknown and the end date is known, then the medication will be considered:

- Prior to study medication if the end date is prior to the initial application of the study medication
- Concomitant to study medication if the end date is either on or after the initial application of study medication or the end date is unknown.

If both the start and end dates are unknown, then the medication will be considered to be "concomitant on-treatment". The partial and completely missing dates for prior and concomitant medications will be imputed as mentioned in section 7.3.

Prior and concomitant medication will be summarized by frequencies and percentages of subjects by preferred name within each ATC, with ATC and preferred names sorted by descending frequency.

ATC classification level 2 will be used in summary tables and listings. If ATC classification level 2 is missing, then ATC classification level 1 will be used.

A subject listing of prior and concomitant medications will be presented.

8.6 Analysis of Efficacy Parameters

8.6.1 Equivalence of Clinical Endpoint Analysis

The primary efficacy analysis is to demonstrate that Acyclovir Cream, 5% - Perrigo (Test) is bioequivalent to Zovirax® Cream 5% - Valeant Pharmaceuticals (Reference).

The hypothesis to test bioequivalence of Test formulation to Reference formulation will be:

H_0 (null hypothesis): $\mu_T / \mu_R \leq 0.80$ or $\mu_T / \mu_R \geq 1.25$

versus

H_1 (alternative hypothesis): $0.80 < \mu_T / \mu_R < 1.25$

Where, μ_T: The mean time-to-complete healing of the lesion in the test treatment (i.e. Acyclovir Cream, 5% - Perrigo)

μ_R: The mean time-to-complete healing of the lesion in the reference treatment (i.e. Zovirax Cream 5% - Valeant Pharmaceuticals)

The test formulation (i.e. Acyclovir Cream, 5% - Perrigo) will be considered as bioequivalent to the reference formulation (i.e. Zovirax® Cream 5% - Valeant Pharmaceuticals) if the 90% confidence interval (CI) for the ratio of the means or medians (Test/Reference) falls within the interval of 0.80 to 1.25.

The mean time-to-complete healing of Test and Reference product will be analyzed 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].

8.6.1.1 Sensitivity Analysis Using Secondary Censoring Rule for Aborted Lesions

[redacted]).

[redacted].

8.6.1.2 Sensitivity Analysis Exclusion of Sites/Subjects

[redacted]

[redacted]

8.6.2 Analysis of Superiority between Active Formulation and Vehicle

The test for superiority will be performed to show each of the active formulations (i.e. Acyclovir Cream, 5% - Perrigo and Zovirax® Cream 5% - Valeant Pharmaceuticals) is superior in efficacy over Vehicle of Acyclovir Cream, 5% - Perrigo.

The hypothesis to test the superiority of active formulations over vehicle will be:

H_{0t}: $\mu_T \geq \mu_P$ vs H_{1t}: $\mu_T < \mu_P$
H_{0r}: $\mu_R \geq \mu_P$ vs H_{1r}: $\mu_R < \mu_P$

Where,

μ_T: The mean time-to-complete healing of the lesion in the test i.e. Acyclovir Cream, 5% - Perrigo

μ_R: The mean time-to-complete healing of the lesion in the reference i.e. Zovirax Cream 5% - Valeant Pharmaceuticals

μ_P: The mean time-to-complete healing of the lesion in the Vehicle

Two separate superiority analyses will be conducted, Test vs. Vehicle and Reference vs. Vehicle. The mITT Population will serve as the definitive analysis, and analysis based on the PP Population will be considered as the supportive one for the superiority analysis.

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.

The statistical significance (p-value) of mean time-to-complete healing of Test vs. Vehicle and Reference vs. Vehicle will be determined identically using separate ANOVA tests. The difference in adjusted mean (LS means) time-to-complete healing between active products and Vehicle, and the associated 95% CIs of the difference will be presented.

8.6.2.1 Sensitivity Analysis Using Secondary Censoring Rule for Aborted Lesions

[redacted]

8.6.2.2 Sensitivity Analysis Exclusion of Sites/Subjects

[redacted]

8.6.3 Subgroup Analyses

No subgroup analyses of efficacy data are planned.

8.6.4 Exploratory Analyses

The elapsed time, in hours, between the subject-reported lesion healing date/time and the investigator-assessed lesion healing date/time will be summarized.

The elapsed time is calculated as investigator date/time minus subject date/time.

[redacted]

8.6.4.2 Analysis of Superiority between Active Formulation and Vehicle in Time-to-Event

If the residuals diagnostic from the ANOVA (section 8.6.2) does not demonstrate homogeneity of variance, non-parametric analyses will be performed. A non-parametric ANOVA controlling for Center (Stoke, 2000[10]), will be done to test the superiority of the Reference vs. Vehicle and of the Test vs. Vehicle ($p<0.025$).

8.6.5 Other Efficacy Analyses

[redacted]

8.7 Analysis of Safety

All safety analyses will be performed using the safety population and will be summarized by treatment groups. No statistical inference will be drawn on safety analyses.

Due to the nature of the safety population (all subjects dispensed medication), analyses will be based on all subjects who were dispensed medication. For example, TEAE percentages are based on all subject dispensed medication (includes dosed and not dosed subjects).

8.7.1 Extent of Exposure and Compliance to Study Treatment

8.7.1.1 Extent of Exposure

The exposure to study medications will be summarized descriptively for the following:

- Total number of applications applied during the study
- Total number of applications missed during the study

A subject listing will be presented which includes:

- Date/time of first application
- Total number of applications applied during the study
- Total number of applications missed during the study
- Whether subject missed more than five consecutive doses? (Yes/No)
- Whether all subject diaries were collected? (Yes/No)

[redacted]

[redacted]

Also, the frequencies and percentages of subjects who missed more than five consecutive applications of study medications will be summarized.

8.7.1.3 Study Medication Dispensation

A subject listing will be presented which will include:

- Whether subject was randomized and study medication was dispensed? (Yes/No)
- Date of randomization
- Kit number
- Whether tear-off label was affixed to the study medication dispensing log? (Yes/No)
- Number of tubes dispensed? (1 or 2)
- Whether all the dispensed tubes were collected? (Yes/No)
- Whether the subject diary and instructions were dispensed/reviewed with the subject? (Yes/No)

8.7.2 Adverse Events

All AE summary tables will include only TEAEs unless otherwise noted.

Adverse events will be summarized by system organ class and preferred term. A subject will only be counted once per system organ class and preferred term. AE's will also be presented by severity grades. In the case of multiple experiences with the same AE, the subject will be counted only once under the worst reported severity.

Adverse events will be presented in decreasing order of the incidences at SOC level and within each SOC, in decreasing order of the incidences at the preferred term level.

An overall summary of adverse events will be presented and will include:

- at least one TEAE
- any severe TEAE
- any treatment-related TEAE
- any serious TEAE
- any serious treatment-related TEAEs
- any TEAE resulting in death
- any TEAE resulting in study medication interruption/discontinuation
- any unexpected adverse event
- any TEAEs of interest

The subjects' frequencies and percentages will be presented by system organ class and preferred term for the following:

- All TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- TEAEs leading to study medication interruption/discontinuation
- Treatment-related TEAEs leading to study medication interruption/discontinuation
- Serious TEAEs
- Serious treatment-related TEAEs
- Unexpected adverse events
- TEAEs of interest

The overall event counts will also be presented for the above mentioned adverse event parameters.

The following subject listings will be presented:

- all AEs
- SAEs
- AEs leading to study medication interruption/discontinuation
- AEs leading to death

8.7.3 Clinical Laboratory Evaluations – Urine Pregnancy Test

Females of childbearing potential will have a urine pregnancy test at Visit 1(Screening), Visit 2 (Day 1), Visit 13 (Day 21) and at the End of Study. This will be presented in a subject listing.

8.7.4 Other Observations Related to Safety

8.7.4.1 Physical Examination

The physical examination will be performed at Visit 1 (Screening) and Visit 2 (Day 1). A subject listing will be presented which will include:

- Whether physical examination was performed? (Yes/No)
- Examination date
- Were there any abnormal findings? (Yes/No)

8.7.4.2 Vital Signs

Vitals signs will be performed at Visit 1 (Screening) and Visit 2 (Day 1). [redacted]

[redacted]

[redacted].

8.7.4.3 Application Site Reaction Asessment

The severity (none, mild, moderate and severe) of application site reaction will be summarized by frequencies and percentages by visit.

9 COMPUTER SOFTWARE

All analyses will be performed by Theorem Clinical Research using Version 9.2 of SAS® software or higher within a UNiplexed Information and Computing Service (UNIX) environment. All summary tables and data listings will be prepared using SAS® software.

10 REFERENCES

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