A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/3.75% to Valeant Pharmaceuticals North America, LLC Onexton™ Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/3.75%), and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

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STATISTICAL ANALYSIS PLAN

Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/3.75%
Protocol PRG-NY-15-003

[redacted]

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[redacted]

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List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
CI	Confidence Interval
CMH	Cochran-Mantel Haenszel Test
IGA	Investigator's Global Assessment
ITT	Intent-to-Treat (Population)
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat (Population)
PD	Protocol Deviation
PP	Per-Protocol (Population)
PV	Protocol Violation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
WHO Drug	World Health Organization Drug Dictionary

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol PRG-NY-15-003 [redacted]

2 Study Objectives

To compare the safety and efficacy profiles of Perrigo UK FINCO Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/3.75% to Valeant Pharmaceuticals Onexton™ Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/3.75%) and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of acne vulgaris.

3 Study Design

For the purpose of exploring the above objectives, the study will be conducted as a double-blind, randomized, parallel-group, vehicle-controlled, multicenter trial.

Approximately [redacted] healthy males and females, 12 to 40 years of age, inclusive, who meet the inclusion/exclusion criteria, will be enrolled to obtain approximately [redacted] modified-Intent-To-Treat (mITT) and [redacted] per-protocol (PP) subjects. [redacted]

The actual number of subjects enrolled in the study will be based on blinded review of subject status (related to the per-protocol definition, section 4) to determine that the number of subjects expected to meet the PP criteria is sufficient [redacted]). If this number is expected to be met prior to enrolling [redacted] subjects, the enrollment will be closed.

Each subject will be randomly assigned to one of following treatment groups in a [redacted] ratio:

(1) Test: Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/3.75%, [redacted]

(2) Reference: Onexton™ Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/3.75%), Valeant Pharmaceuticals North America, LLC
(3) Vehicle of test product Perrigo UK FINCO, [redacted]

Subjects will be admitted into the study only after written informed consent has been obtained and all of the inclusion and none of the exclusion criteria have been met. 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 closed. An independent third party generator will generate and hold the randomization code throughout the study. Randomized subjects will apply [redacted] study medication onto six areas of the face (chin, left cheek, right cheek, nose, left forehead and right forehead) [redacted] avoiding contact with the eyes, lips, mouth, broken areas of the skin and mucous membranes at approximately the same time once daily for 12 weeks.

Subjects will be scheduled for an office visit for Visit 1/Day 1 (Baseline), Visit 2/Week 4/Day 28 (±4 days)(Interim, Visit 3/Week 8/Day 56 (±4 days)(Interim), and Visit 4/Week 12/Day 84 (±4 days) (End of treatment/End of study). Safety will be assessed by monitoring adverse events at each visit and at the Week 2/Day 15 (±4 days) Telephone Contact.

4 Populations To Be Analyzed

Three subject populations are defined as follows:

(1) Intent-to-Treat (ITT) (safety population): Any subject that was randomized, received and used study medication;
(2) Modified Intent-to-Treat (mITT): Any subject, who met the inclusion/exclusion criteria, was randomized, received and used the study medication, and returned for at least one post-baseline efficacy assessment;
(3) Per-Protocol (PP): Any subject:

- Who met inclusion/exclusion criteria,
- Who was randomized and received and used study medication,
- Who met the protocol criteria for compliance [redacted] and
- Who completed Visit 4/Week 12/Day 84 (End of Treatment/Early Termination Visit) within window OR was dropped from the study due to treatment failure [redacted] treatment [redacted]
- Without significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[redacted]

[redacted]

[redacted]

5 Planned Analyses

5.1 Methodological Considerations

The study will be conducted under the same protocol across all the sites. No formal statistical analyses are planned to evaluate the consistency of efficacy results across the multiple clinical sites. These results, however, will be tabulated and if a site's efficacy data are obviously inconsistent with the results across all sites, this will be explored and addressed in the final study report.

Two-sided hypothesis testing will be conducted for all the tests. Resulting p-values less than 0.05 will be considered statistically significant unless noted otherwise. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned. SAS software will be used for all data analyses and tabulations.

5.2 [redacted]

[redacted]

[redacted]

5.3 Demographics and Baseline Characteristics

Baseline variables (e.g., sex, age, ethnic origin) will be evaluated, adjusting for site, to identify differences between treatment groups, which were not eliminated by randomization. Any significant baseline differences will be reviewed for their potential impact on the efficacy findings.

Continuous variables at baseline will be examined by two-way analysis of variance (ANOVA) with treatment and site as fixed effects when normal error and homogeneous variance assumptions are satisfied, or by the nonparametric rank based ANOVA when they are not, to compare treatment group differences.

Categorical variables such as gender, race, etc., will be examined by Cochran-Mantel-Haenszel test, stratified by site.

Summary tables by treatment group will be presented. For each continuous variable, the summary will include the mean, standard deviation, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

5.4 Subject Accountability

A summary of subject disposition will be provided for all subjects. Descriptive summaries of subject disposition, reason for discontinuation, and analyses population will be provided by treatment group. The data will also be presented in subject data listings.

5.5 Efficacy Variables and Analyses

5.5.1 Primary Endpoints

The primary efficacy endpoints are the mean percent change from baseline to Week 12 (Visit 4/Day 84) in the inflammatory (papules and pustules) lesion counts AND the mean percent change from baseline to Week 12 (Visit 4/Day 84) in the non-inflammatory (open and closed) lesion counts.

Equivalent Efficacy

For the mean percent change from baseline in the inflammatory lesion counts, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the Test-to-Reference ratio of means, calculated by Fieller's Method, falls within the interval 0.80 to 1.25. The compound hypothesis to be tested for therapeutic equivalence between test and reference is:

$H_0: \mu_T/\mu_R \leq 0.80$ or $\mu_T/\mu_R \geq 1.25$ versus

$H_A: 0.80 < \mu_T/\mu_R < 1.25.$

Where μ_T and μ_R are the mean percent change from baseline to Week 12 (Visit 4/Day 84) in inflammatory lesions counts for the test treatment and the reference treatments, respectively. The null hypothesis is rejected when the two-sided 90% confidence interval (CI) for the ratio of means between test and reference products is between 0.80 and 1.25. Rejection of the null hypothesis supports the conclusion of therapeutic equivalence between test and reference products for the primary efficacy variable.

The two-sided 90% confidence interval will be constructed using an ANOVA model adjusting for the effects of treatment and site. [redacted]

The same analysis will be applied to the mean percent change from baseline in the non-inflammatory lesion count.

Therapeutic equivalence evaluations in the per-protocol (PP) population will be considered definitive and those in the mITT will be considered supportive.

Superiority

For the percent change from baseline in the inflammatory lesion counts, each active treatment will be evaluated to determine if it has superior efficacy to that of the Vehicle at Week 12 (Visit 4/Day 84) via ANOVA model containing terms for treatment and site. The compound hypothesis to be tested for superiority of test and reference over Vehicle is:

$H_0: \mu_T \leq \mu_V$ or $\mu_R \leq \mu_V$ versus

$H_A: \mu_T > \mu_V$ and $\mu_R > \mu_V$

Where μ_T, μ_R and μ_V are the mean percent change from baseline to Week 12 (Visit 4/Day 84) in inflammatory lesions counts for the test, the reference and the vehicle treatments, respectively. The null hypothesis is rejected when both p-values from the ANOVA are less than 0.05 (two-sided test). Rejection of the null hypothesis supports the conclusion of superiority of test and reference products over the vehicle product for the primary efficacy variable.

[redacted]

5.5.2 Secondary Endpoint

The secondary efficacy endpoint is the proportion of subjects with clinical success on the Investigator's Global Assessment (IGA) at Week 12 (Visit 4/Day 84), where success is defined as an IGA score that is at least 2 grades less than the baseline assessment.

Equivalent Efficacy

The Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% Wald confidence interval with Yates' continuity correction on the difference in their success proportions is contained within the interval of -20% to +20%.

Superiority

The proportion of subjects with clinical success for each active treatment will be compared separately between each of the active treatments and the Vehicle using two-sided, $\alpha = 0.05$, continuity-corrected Z-tests.

Equivalence and superiority analyses will be conducted in both the PP and mITT populations.

5.5.3 [redacted]

5.6 Safety Variables and Analyses

Duration of Treatment and Medication Compliance

Number of applications, days of exposure, and compliance rate will be summarized by treatment group using descriptive statistics. For each subject, the overall duration of treatment (days) will be calculated using the following formula:

(Date of last application of study medication) - (Date of first application of study medication) + 1.

Medication compliance rate (%) will be calculated for each subject as follows:

(Total number of applications used) / (Expected number of applications) *100%.

[redacted]

Adverse Events

Adverse events (AEs) will be coded in MedDRA, version 15.1. Treatment-Emergent Adverse Event (TEAE) is defined as any AE occurs on or after applying the first dose of study drug. Number and percent of subjects reporting TEAEs will be tabulated by treatment group. Summaries will be presented by body system and preferred term for the ITT population. Similar tables will be presented by severity and relationship to study drug. TEAEs reported by more than 5% subjects for any treatment group will also be summarized. In summaries of incidence rates (frequencies and percentages), severity and relationship to study drug, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly. The difference between Test and Reference treatments with regard to the severity and frequency of their dermatological adverse events wil be statistically evaluated. Fisher's exact test will be used to compare the proportions of subjects of the two active treatment groups who report any TEAE.

Treatment-Emergent Serious Adverse Events (TESAEs) and TEAEs that led to treatment interruption or discontinuation will be presented in data listings.

Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary, version September, 2014, and will be presented in data listings.

Application Site Reactions

Frequency and distribution of application site reactions of erythema, dryness, scaling/peeling, burning/stinging, erosion, edema, pain and itching will be summarized and compared descriptively by visit.

Safety comparisons will be performed only for the ITT population.

6 Appendices

6.1 Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Adverse Events

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first dose

- the day and month are missing and the start year is the same or greater than the year of the first dose date

- the start date is completely missing

Concomitant Medications

Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose

- the day and month are missing and the stop year is the same or greater than the year of the first dose date

- the stop date is completely missing or the medication is ongoing

6.2 Summary of Assessments

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