# A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo Israel Pharmaceuticals, Ltd. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% to Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), 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%/2.5%
Protocol PRG-NY-12-005

[redacted]

**A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo Israel Pharmaceuticals, Ltd. Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% to Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris**

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## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| CI | Confidence Interval |
| CMH | Cochran-Mantel Haenszel |
| 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-12-005 [redacted]

## 2 Study Objectives

To compare the efficacy and safety profiles of Perrigo Israel Pharmaceuticals, Ltd.; Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5% and Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%) and to show 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.

The actual number of subjects enrolled in the study will be based on blinded review of subject status (related to the per-protocol (PP) definition under 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.

[redacted]

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

(1) Test: Clindamycin Phosphate and Benzoyl Peroxide Topical Gel 1.2%/2.5%, [redacted]
(2) Reference: Acanya® Topical Gel (Clindamycin Phosphate and Benzoyl Peroxide Gel 1.2%/2.5%), Valeant Pharmaceuticals (Dow Pharmaceutical Sciences, Inc)
(3) Vehicle of test product [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] to the affected areas of the face avoiding contact with the eyes, mouth, lips, inside and on angles of the nose, and mucous membranes 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 14 (±4 days) Telephone Contact.

## 4 Populations To Be Analyzed

Three subject populations are defined as follows:

(1) An intent-to-treat (ITT) subject is any individual who: (a) was randomized into the study, received and (b) applied at least one dose of study medication;

(2) A modified intent-to-treat (mITT) subject is any individual who: (a) met inclusion/exclusion criteria, (b) was randomized into the study, (c) received and applied at least one dose of study medication, and (d) had at least one post-baseline efficacy assessment for the two lesion types;

(3) A per-protocol (PP) subject, consistent with the protocol, is one that: (a) met inclusion/exclusion criteria, (b) was randomized into the study, received and used study medication, (c) [redacted] (d) returned for Visit 4/ Week 12 (End of Treatment/Early Termination Visit) within the specified window (+/- 4 days) and had data on lesion count, OR was discontinued early due to treatment failure [redacted] and (e) took no concomitant medications prohibited by the protocol or had any other significant protocol violations, and

[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 Handling of Dropouts or Missing Data

[redacted]

For demographic and baseline characteristics and the safety profile, each variable will be analyzed using all available data. Subjects with missing data will be excluded only from the analyses for which data are not available.

## 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 for the study 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 $\mu_T$ and $\mu_R$ 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. A skewness test (SAS® PROC UNIVARIATE) will be performed using the residuals from the ANOVA of the primary efficacy variable. If the skewness statistic is less than -2, the analysis will be performed on the ranked mean percent change from baseline to Week 12 (Visit 4/Day 84) in inflammatory lesion counts.

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

[redacted]

Superiority

Evaluation of superiority will be conducted separately for the Test versus Placebo products and for the Reference versus Placebo products comparing their difference in the percent change from baseline in the inflammatory lesion counts using ANOVA with treatment and site as fixed effects. If the mean percent change for an active treatment is greater and statistically different (two-sided, $p<0.05$) than that of the Placebo, then the active treatment will be considered superior to the Placebo. 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 $\mu_T$, $\mu_R$ and $\mu_V$ 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 active product over the vehicle product for the primary efficacy variable.

[redacted]

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

[redacted]

5.5.2 Secondary Endpoint

The secondary efficacy measure 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.

[redacted].

5.5.3 Additional Efficacy Variables

The following efficacy variables at Week 12 (Visit 4/Day 84) will be tabulated descriptively for both the PP and mITT populations: (1) inflammatory (papules and pustules) lesion counts, (2) non-inflammatory (open and closed) lesion counts, and (3) IGA.

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] For prematurely discontinued subjects, expected number of applications will be determined based on the expected number of applications by the time of discontinuation, i.e. the overall duration of treatment. Descriptive summaries of exposure and medication compliance rate will be provided by treatment group for the ITT subjects

Adverse Events

Adverse events (AEs) will be coded in MedDRA, version 14.0 or higher. 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 5% or more subjects for any treatment group will also be summarized. In summaries of incidence rates (frequencies and percentages), severity and relationship to study drug of individual, 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 will 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 March, 2011 or higher, and will be presented in data listings.

Application Site Reactions

Frequency and distribution of application site reactions of erythema, dryness, 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.

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