A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Brimonidine Topical Gel 0.33% to Mirvaso® (Brimonidine) Topical Gel 0.33%, and Both Active Treatments to a Vehicle Control in the Treatment of Persistent (nontransient) Facial Erythema of Rosacea

NCT02385240

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STATISTICAL ANALYSIS PLAN

Brimonidine Topical Gel 0.33%

[redacted]

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[redacted]

[redacted]

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[redacted]

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
CEA	Clinician's Erythema Assessment
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)
PSA	Patient Self-Assessment
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-14-022 [redacted]

2 Study Objectives

To compare the safety and efficacy of Perrigo UK FINCO's Brimonidine Gel 0.33% to Mirvaso® (Brimonidine) Topical Gel 0.33% and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of persistent (nontransient) facial erythema of rosacea.

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.

[redacted]

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

(1) Test: Brimonidine Topical Gel 0.33%, Perrigo Israel Pharmaceuticals, Ltd.
(2) Reference: Mirvaso® (Brimonidine) Topical Gel 0.33%, Galderma Laboratories, L.P.
(3) Vehicle of test product, Perrigo Israel Pharmaceuticals, Ltd.

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 after the final database is closed from editing. An independent third party generator will generate and hold the randomization code throughout the study. Randomized subjects will apply the study medication once daily in the morning for 15 days.

Subjects will be scheduled for an office visit for Visit 1/Day 1 (Baseline) and Visit 2/Day 15 (End of Study/Treatment). Safety will be assessed by monitoring adverse events at each visit.

4 Populations To Be Analyzed

Three subject populations are defined as follows:

(1) An intent-to-treat (ITT) subject is any individual who was randomized, received and used study medication;

(2) A modified intent-to-treat (mITT) subject is any individual 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) A per-protocol (PP) subject, consistent with the protocol, is one that: (a) met eligibility criteria, (b) was randomized into the study, received and used study medication, (c) did not miss the scheduled applications for more than 1 consecutive day (2 or more consecutive doses), (d) did not take any concomitant medications prohibited by the protocol or have any other significant protocol violations, and (e) returned for Visit 2/Day 15 within the designated visit window (± 2 days) with data on the primary efficacy variables [redacted]

[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]

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 Endpoint

The primary efficacy measure is the proportion of subjects with composite success at hour 6 on Day 15, where composite success is defined as at least a 2-grade improvement from Visit 1/Day 1 (Baseline), prior to first study medication application, on both the Clinician's Erythema Assessment (CEA) and the Patient Self-Assessment (PSA) scales.

Equivalent Efficacy

The compound hypothesis to be tested for clinical equivalence between test and reference is:

$H_0: p_T - p_R < -0.20$ or $p_T - p_R > 0.20$ versus

$H_A: -0.20 \leq p_T - p_R \leq 0.20$.

Where p_T and p_R are the proportions of subjects with composite success at hour 6 on Day 15 for the test and reference products, respectively. The test product will be considered to be clinically equivalent to the reference product if the 90% confidence interval (CI) on the difference in their rates of composite success, calculated by the Wald's method with Yates' continuity correction, is contained within the limits -0.20 to +0.20 for the PP population. Rejection of the null hypothesis supports the conclusion of therapeutic equivalence between the test and reference products for the primary efficacy variable.

[redacted]

Superiority

The hypotheses to be tested for superiority of the test and reference products over vehicle are:

$H_0: p_T \leq p_V$ versus $H_A: p_T > p_V$

$H_0: p_R \leq p_V$ versus $H_A: p_R > p_V$

Where p_T, p_R and p_V are the proportion of subjects with composite success at hour 6 on Day 15 for the test, reference and vehicle products, respectively. The tests will be conducted independently for the test product and the reference product using two-sided, $\alpha = 0.05$, continuity-corrected Z-tests for the mITT subjects. Superiority will be established if the proportion of subjects with composite success in the active treatment group is greater and statistically different than that in the vehicle. Rejection of the null hypothesis supports the conclusion of superiority of the test and reference products over the vehicle product for the primary efficacy variable.

[redacted]

5.5.2 Secondary Endpoints

The secondary efficacy endpoints will be the proportions of subjects with composite success at hours 3 and 9 on Day 15, proportion of subjects with composite success at all three hours 3, 6 and 9 on Day 15 and the proportion of subjects with composite success at all three hours: 3, 6 and 9 on Day 1. The same analysis from the primary efficacy endpoint will be applied to second endpoints.

5.5.3 Other Endpoint

Investigator's Global Assessment (IGA) will be evaluated on Visit 1/ Day 1 (Baseline) and Visit 2/Day 15 (End of Study/Treatment) prior to each visits' application of study medication. They will be summarized descriptively.

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%.

Subjects who complete the study are expected to have 15 applications. 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 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, and further by severity and relationship to study medication. [redacted] In the 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. 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) will be discussed within the clinical study report. 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.

[redacted].

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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