A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Ingenol Mebutate Topical Gel 0.015% to Leo Pharma Inc. Picato® Topical Gel 0.015% (Ingenol Mebutate Topical Gel 0.015%), and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis on the Head Region (Face or Scalp)

Protocol No.: PRG-NY-14-019

NCT02385318

04-15-2015

STATISTICAL ANALYSIS PLAN

Ingenol Mebutate Topical Gel 0.015%
Protocol PRG-NY-14-019

[redacted]

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO Ingenol Mebutate Topical Gel 0.015% to Leo Pharma Inc. Picato® Topical Gel 0.015% (Ingenol Mebutate Topical Gel 0.015%), and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis on the Head Region (Face or Scalp)

Perrigo Pharmaceuticals, Ltd.

1701 Bathgate Ave.
Bronx, NY 10457

[redacted]

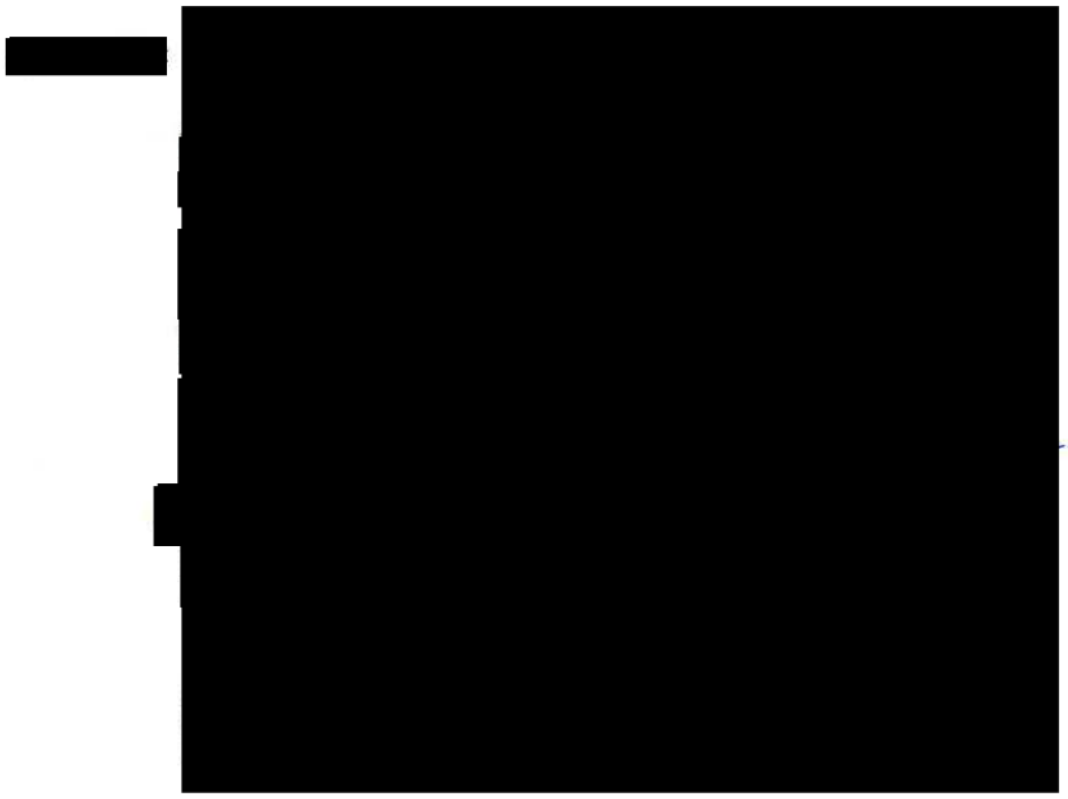

Table of Contents

[redacted]

List of Abbreviations

AE	Adverse Event
AK	Actinic Keratosis
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-14-019 [redacted]

2 Study Objectives

To compare the safety and efficacy profiles of Perrigo UK FINCO Ingenol Mebutate Topical Gel 0.015% to Picato® Topical Gel 0.015% (Ingenol Mebutate Topical Gel 0.015%) and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of Actinic Keratosis.

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 modified intent-to-treat (mITT) definition and the per-protocol (PP) definition under Section 4 to determine that the size of enrollment is adequate to obtain a sufficient number of subjects meeting the mITT criteria [redacted] and a sufficient number of subjects meeting the PP criteria [redacted] If this number is expected to be met prior to enrolling [redacted] subjects, the enrollment will be closed.

[redacted]

[redacted]

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

(1) Test: Ingenol Mebutate Topical Gel 0.015%, Perrigo [redacted].
(2) Reference: Picato® Topical Gel 0.015% (Ingenol Mebutate Topical Gel 0.015%), Leo Pharma Inc.

(3) Vehicle of test product, Perrigo [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 assigned treatment medication topically by spreading evenly [redacted] to the designated treatment area (up to one contiguous skin area of approximately 25cm^2 on the head region (face or scalp) once daily for three (3) consecutive days, avoiding contact with the eyes, mouth and other body areas during and after gel application.

Subjects will be scheduled for an office visit for Visit 1/Day 1 (Baseline), Visit 2/Day 4 (+1 days) (Post-Treatment Interim), Visit 3/Day 29 (±3 days) (Interim), and Visit 4/Day 57 (±2 days) (End of Study). Safety will be assessed by monitoring adverse events at each visit and during a Follow-Up Phone Call/Day 15 (±3 days).

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, and (b) received and applied at least one dose of study medication;

(2) A modified intent-to-treat (mITT) subject is any individual who: (a) was randomized into the study, (b) met eligibility criteria, (c) received and applied at least one dose of study medication, and (d) had 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) applied the study medication on Days 1-3 [redacted] (d) completed Visit 4/Day 57 (End of Study/Early Termination Visit) within the ±2 days visit window OR was discontinued from the study due to treatment failure [redacted] and (e) without significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[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

The primary efficacy measure is the proportion of subjects with clinical response of success defined as complete clearance (absence) of all clinically visible Actinic Keratosis lesions identified at the baseline visit and no new Actinic Keratosis lesions in the treatment area at Visit 4/Day 57.

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 clinical success at Visit 4/Day 57 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 clinical 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 clinical success at Visit 4/Day 57 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 clinical 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]

5.6 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 3 applications. Subjects will only be considered compliant if they apply all three daily doses on study Days 1-3. For prematurely discontinued subjects, expected number of applications will be determined based on the overall duration of treatment by the time of discontinuation. 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.

Application Site Reactions

The severity of application site reactions such as erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration will be summarized by treatment group and visit using frequencies and percentages of subjects.

[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.