An Evaluation of the Reduction in Erythema by RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1% (Allergan) in Adult Patients with Moderate to Severe Persistent Facial Erythema Associated with Rosacea, [redacted]

Protocol Number: PRG-NY-17-013

NCT03352323

09-13-2017

[redacted]

STATISTICAL ANALYSIS PLAN

An Evaluation of the Reduction in Erythema by RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1% (Allergan) in Adult Patients with Moderate to Severe Persistent Facial Erythema Associated with Rosacea, [redacted]

Protocol Number: PRG-NY-17-013

[redacted]

Sponsor:

Perrigo [redacted]
1701 Bathgate Ave.
Bronx, NY 10457

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN

RHOFADE™ (oxymetazoline hydrochloride) Cream, 1% Protocol No. PRG-NY-17-013

SAP Final Version Approvals

An Evaluation of the Reduction in Erythema by RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1% (Allergan) in Adult Patients with Moderate to Severe Persistent Facial Erythema Associated with Rosacea[redacted]

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

[redacted]

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

List of Abbreviations and Definition of Terms

ADaM	Analysis Dataset Model
AE	Adverse Event
ANOVA	Analysis of Variance
[redacted]	[redacted]
C	Celsius
CDISC	Clinical Data Interchange Consortium
[redacted]	[redacted]
CRO	Clinical Research Organization
eCRF	electronic Case Report Form
eCTD	electronic Common Technical Document
F	Fahrenheit
FDA	Food and Drug Administration
g	Gram
ICF	Informed Consent Form
ICH	International Conference on Harmonization
LOCF	Last Observation Carried Forward
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mL	Milliliter
PD	Protocol Deviation
PP	Per-Protocol
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model

[redacted]

STATISTICAL ANALYSIS PLAN

RHOFADE™ (oxymetazoline hydrochloride) Cream, 1% Protocol No. PRG-NY-17-013

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[redacted]

[redacted]

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol PRG-NY-17-013 [redacted]. The SAP provides details on the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Study Protocol PRG-NY-17-013 [redacted]
- Case Report Form Booklet Version 1.0 [redacted]

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

2. OBJECTIVES

The objectives of this study are to:

1. Evaluate [redacted] the marketed formulation RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1% in the treatment of moderate to severe persistent (non-transient) facial erythema associated with rosacea [redacted].
2. Estimate the between-patient variability [redacted]
3. [redacted]

3. OVERALL STUDY DESIGN

This open-label, single-product, single-site, multiple-dose study has been designed to evaluate the reduction in erythema by RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1%

(Allergan) in patients with moderate to severe persistent (non-transient) facial erythema associated with rosacea. [redacted].

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent form (ICF).

Approximately 50 eligible patients, 18 years of age and older, will be enrolled in the study. Eligible patients will complete four clinic visits as follows:

- Visit 1: Screening (Day -28 to -1)
- Visit 2: Baseline (Day 1)
- Visit 3: Interim Visit (Day 7 ± 2)
- Visit 4: End of Study (Day 15 ± 2)

The study product will be applied to the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips. Study product will be applied in the clinic at Visits 2, 3, and 4. Patients will be instructed to apply the study product at home once daily, at approximately the same time of day, on non-visit days. [redacted]. Evaluations will be performed in accordance with the study schematic. Safety assessments will include vital sign measurement and urine pregnancy test (for all women of childbearing potential). [redacted]

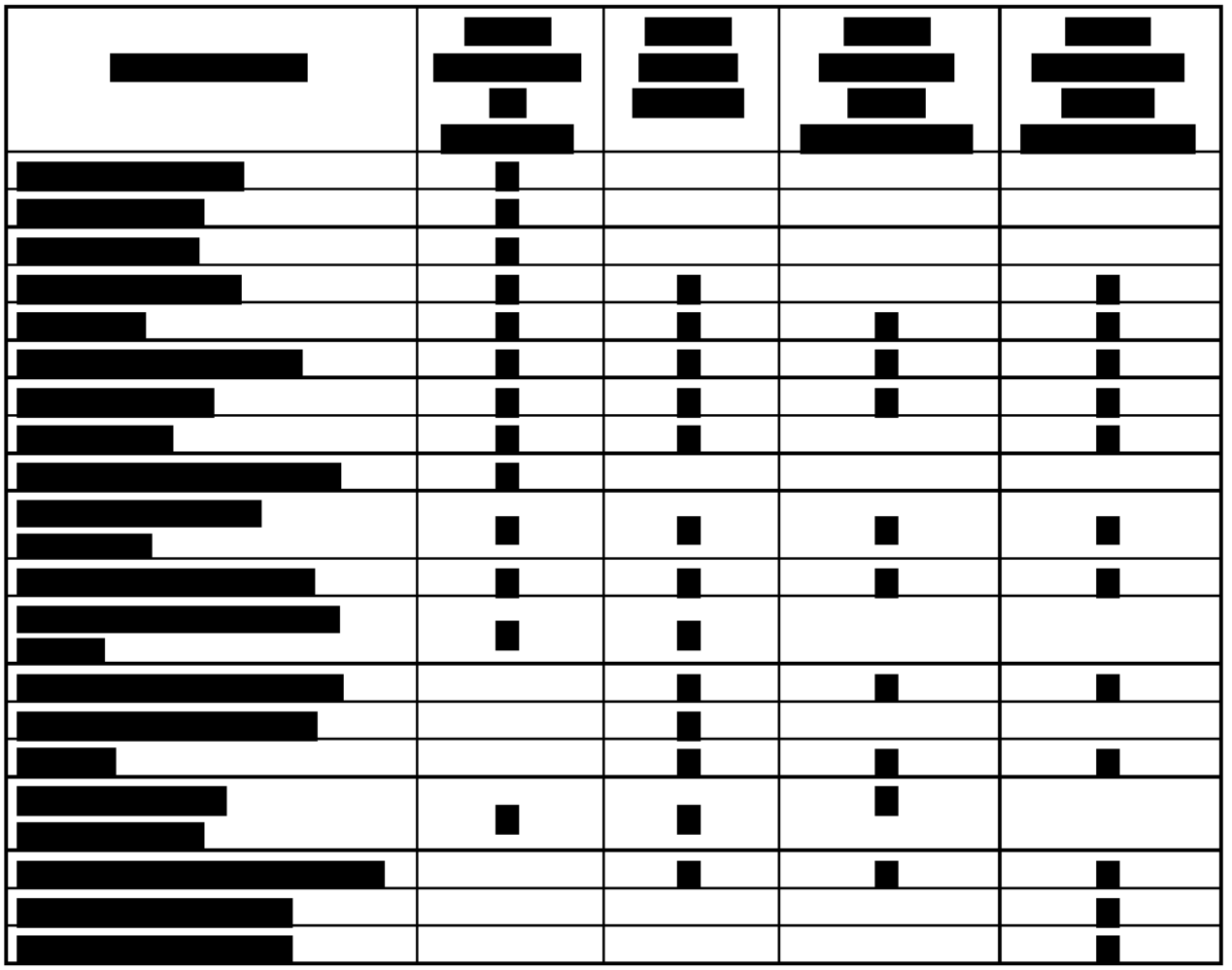
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted].

Figure 1 Study Schematic



4. RANDOMIZATION AND BLINDING

Patients will be assigned to treatment in an open-label fashion. At Visit 2, eligible patients will be assigned a randomization number in ascending sequential order, starting with the lowest number available.

This is an open-label study.

5. SAMPLE SIZE

The sample size of approximately 50 patients was deemed appropriate to meet the objectives of the study.

6. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

7. STUDY POPULATIONS

Per-Protocol (PP) Population

The PP population will include all randomized patients who:

- Meet all inclusion and exclusion criteria.
- Complete the final study visit within the protocol window of Day 15 [redacted]
- Have no significant protocol deviations (PDs) that would affect treatment evaluation.
- Apply the study product appropriately [redacted].
- Do not miss the scheduled applications for more than one consecutive day.

[redacted]

[redacted]

Modified Intent-to-Treat (mITT) Population

The mITT population will include: randomized patients who:

- Meet all inclusion/exclusion criteria.
- Administer at least one dose of assigned product.
- Have at least one post-baseline evaluation.

Patients discontinued early for reasons other than lack of treatment effect or worsening condition will be included in the mITT population using last observation carried forward (LOCF).

Safety Populations

The Safety population will include all patients who are randomized and received study product.

8. STATISTICAL ANALYSIS METHODS

[redacted] Data will be summarized with respect to demographic and baseline characteristics and safety variables.

For categorical variables, the number and percentage of each category within a parameter will be

calculated for non-missing data. For continuous variables, statistics will include n, mean, standard deviation, median, minimum and maximum values.

All statistical analyses will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC), Study Data Tabulation Model (SDTM) implementation for human clinical trials, and ADaM (Analysis Dataset Model).

8.1 Baseline Characteristics

8.1.1 Patient Disposition

The patient disposition information will be summarized. The number of patients randomized, treated with study medication will be tabulated. In addition, completion status and primary reason for withdrawal will be summarized.

8.1.2 Demographic and Other Baseline Characteristics

Baseline characteristics will be evaluated separately for the PP, mITT, and Safety populations.

The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Sex (Male/Female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian, or Alaska Native)
- Baseline number of inflammatory lesions (i.e., papules and pustules)
- [redacted]
- [redacted]
- [redacted]

Summary tables will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean, and SD). Categorical variables will be summarized using frequencies and percentage.

All data will be listed by patient.

8.1.3 Medical History

At Visit 1, patients will be questioned about personal medical history, including rosacea history.

Medical history data will be listed by patient.

8.1.4 Concomitant Medications

At Visit 1, patients will be questioned about medication use [redacted]. At all subsequent visits, patients will be questioned about ongoing or new concomitant medication use.

All prior and concomitant medications taken since screening until the end of the study will be listed by patient.

8.2 Efficacy Analyses

8.2.1 [redacted]

[redacted]

8.2.2 [redacted]

[redacted]

[redacted]

8.2.3 [redacted]

[redacted]

[redacted]

8.3 Safety Analysis

Safety analysis will be conducted on safety population.

8.3.1 Adverse Events

All the adverse events (AEs) reported throughout the study will be coded and classified according to the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary (Version 20.0 or higher). Each adverse event is to be evaluated for date of start and end, seriousness, severity, causal relationship with the study drugs, action taken and outcome.

All AEs will be listed by patient.

A summary table of the number and percent of patients with AEs by system organ class, preferred term will be presented. Each patient will be counted only once within each preferred term.

A frequency summary table of the number of AEs by system organ class, preferred term, severity will be presented. Severity will be classified as "Mild", "Moderate", or "Severe".

Similarly, a frequency summary table of the number of AEs by system organ class, preferred term, and relationship to a study drug will be presented. Relationship to a study drug will be classified as "Not Related", "Unlikely", "Possible", "Probably", "Definitely".

8.3.2 Vital Signs

The patient's vital signs will be recorded [redacted] at each visit.

Descriptive summaries (number of observations, mean, standard deviation, minimum, median and maximum) will be provided by visit.

All data will be listed by patient.

8.3.3 Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at Visits 1, 2, and 4.

Pregnancy test results will be listed by patient.

8.4 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

8.5 Methods for Handling Missing Data

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

8.6 Interim Analyses

There is no interim analysis planned in this study.

[redacted]