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

1.0 TITLE PAGE

Drug Product	RHOFADE™ (oxymetazoline hydrochloride) Cream, 1%
Population	Approximately 50 males and non-pregnant females, 18 years of age and older, with a clinical diagnosis of persistent (non-transient) facial erythema associated with rosacea
Study Design	An open-label, single-product, single-site, multiple-dose study
Sponsor	Perrigo
Protocol Number	PRG-NY-17-013

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor:

Perrigo
1701 Bathgate Ave.
Bronx, NY 10457

SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable FDA regulations, ICH guidelines and Good Clinical Practice standards.

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol PRG-NY-17-013 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Perrigo New York, Inc.) or [redacted], the company managing the study.

_____ _____

Principal Investigator Date

3.0 TABLE OF CONTENTS

4.0 SYNOPSIS

Protocol Number	PRG-NY-17-013
Title	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]
Objectives	The objectives of this study are to: 1. Evaluate the reduction of erythema by 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]
Sponsor	Perrigo New York, Inc.
Study Product	RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1% (Allergan)
Route of Administration	Topical
Dosage Regimen	Patients will be instructed to apply [redacted] once daily at approximately the same time of day for 15 ± 2 days. Patients will apply the first dose of study product at Visit 2 under supervision of the study staff. The last dose should be administered at

	the clinic during Visit 4. Each patient is expected to receive up to 17 doses of study product.
Study Design	An open-label, single-product, single-site, multiple-dose study
Study Population	Approximately 50 males and non-pregnant females, 18 years of age and older, with a clinical diagnosis of persistent (non-transient) facial erythema associated with rosacea
Confinement	Patients will remain confined to the clinic [redacted] at Visits 2, 3, and 4.
Study Conduct	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]
Inclusion Criteria	1. Male or non-pregnant, non-lactating female, 18 years of age or older. 2. Signed informed consent form that meets all criteria of current Food and Drug Administration regulations. 3. Females of childbearing potential must not be pregnant or lactating at Visits 1 and 2 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). 4. Females of childbearing potential must agree to the use of a reliable method of contraception throughout the study (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive) throughout the study. A sterile sexual partner is not considered an adequate form of birth control. If the female is using any estrogen or oral contraceptive therapy, the same product must have been taken for one month before Visit 1. 5. Have clinical diagnosis of rosacea with persistent (non-transient) facial erythema. 6. Have [redacted] inflammatory lesions on the face. 7. [redacted] 8. Willing to minimize external factors that might trigger rosacea flare-ups [redacted] during the study.
Exclusion Criteria	1. Particular forms of rosacea [redacted] that, in the opinion of the Investigator, would interfere with the diagnosis or assessment of study endpoints. 2. Patient has a skin condition that, in the opinion of the Investigator, would interfere with the diagnosis or assessment of rosacea [redacted]

[redacted]

3. Patients with active sunburn or excessive facial hair such as beards, sideburns, moustaches, etc. that would interfere with the diagnosis or assessment of rosacea.
4. Patients with moderate to severe telangiectasial masses in the designated target area that would interfere with study evaluations.
5. History of allergy, hypersensitivity, or intolerance to oxymetazoline or any other component of the study product.
6. History of blood dyscrasia.
7. Significant history or current evidence of any uncontrolled chronic or serious disease or medical condition that would, in the judgment of the Investigator, would put the subject at undue risk or compromise the study assessments.
8. History or current evidence of Raynaud's syndrome, severe, unstable or uncontrolled cardiovascular disease, orthostatic hypotension, uncontrolled hypertension or hypotension, thromboangiitis obliterans, cerebral or coronary insufficiency, renal or hepatic or renal impairment, scleroderma, Sjögren's syndrome, depression, or narrow-angle glaucoma to an extent that, in the opinion of the Investigator, would place the subject at undue risk.
9. Female patients taking hormonal contraceptives or oral estrogen [redacted] or those that plan to change the dosage regimen during the course of the study.
10. Dermatologic or surgical procedures on the face, [redacted] before Visit 1.
11. Use of systemic immunomodulators [redacted] before Visit 1.
12. [redacted]
13. Recent initiation, current use, or planned change in anti-hypertensive regimen with cardiac glycosides, beta blockers, or other anti-hypertensive agents that, in the opinion of the Investigator, would compromise the safety of the patient.
14. Use [redacted] before Visit 1 of oral retinoids or therapeutic Vitamin A supplements of greater than 10,000 units/day.

	15. Use before Visit 1 of 1) topical immunomodulators, 2) systemic antibiotics, 3) systemic corticosteroids, 4) systemic anti-inflammatory agents, 5) systemic treatment for rosacea, or 6) systemic treatment for acne (other than oral retinoids, which require a six month washout). Acetaminophen will be recommended to treat acute and transient conditions (e.g., headaches, menstrual cramps). 16. Use on the face before Visits 1 or 2 of 1) topical corticosteroids, 2) topical retinoids, 3) topical antibiotics, 4) topical anti-inflammatory agents, 5) topical treatment for rosacea, or 6) topical treatment for acne. 17. Use of niacin ≥ 500 mg/day before Visits 1 or 2. 18. Use of antihistamines before Visits 1 or 2. 19. Use of anti-coagulation therapy (e.g., Warfarin) before Visits 1 or 2. 20. Consumption of caffeine or rosacea trigger-foods before Visits 1 or 2. See Appendix C. 21. Patients who have been previously unresponsive to treatment with RHOFADE™. 22. Previous participation in this study. 23. Employees of the Investigator or research center or their immediate family members. 24. Inability to understand the requirements of the study and the relative information and are unable or not willing to comply with the study protocol.

	[redacted]
Safety Analysis	Adverse events (AEs) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 20.0 or higher. Summary tables including the type, date of onset, date of resolution, incidence, severity, relationship to the study product, action taken, and outcome will be prepared for AEs. Concomitant medication use, including medication name, start date, stop date, and reason for use during the randomized treatment period will be tabulated by patient. Signs and symptoms of rosacea will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition. All randomized patients who received study product will be included in the safety analysis.
Sample Size Determination	The sample size of approximately 50 patients was deemed appropriate to meet the objectives of the study.

5.0 STUDY SCHEMATIC

6.0 LIST OF ABBREVIATIONS AND TERMS

ADaM	Analysis Dataset Model
AE	Adverse Event
ANOVA	Analysis of Variance
AUEC	Area-under-the-effect curve
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
GCP	Good Clinical Practices
ICF	Informed Consent Form
IRB	Institutional Review Board
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

7.0 INTRODUCTION

7.1 Disease Being Treated

7.2 Availability and Efficacy of Already Approved Therapies

[redacted]

7.3 Scientific and Statistical Considerations

[redacted]

7.4 Use of Placebo

There will be no placebo used in this study.

7.5 Risks and Benefits

The potential for any drug-related side effects of significance occurring during the study is low.

All patients enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans. In addition, the patient will receive a stipend for participation to cover costs and expenses associated with trips to the medical facility.

8.0 STUDY OBJECTIVES

[redacted]

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

This open-label, single-product, single-site, multiple-dose, three-period 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.

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. . 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]

Wherever possible, the same Investigator should attempt to perform all [redacted] exams at all visits for an individual patient.

9.2 Selection of Study Design

This protocol is designed based on the FDA draft guidance for brimonidine tartrate topical gel released in September 2015.[16]

[redacted]

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating female, 18 years of age or older.
2. Signed ICF that meets all criteria of current Food and Drug Administration (FDA) regulations.
3. Females of childbearing potential must not be pregnant or lactating at Visits 1 or 2 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).
4. Females of childbearing potential must agree to the use of a reliable method of contraception throughout the study (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive) throughout the study. A sterile sexual partner is not considered an adequate form of birth control. If the female is using any estrogen or oral contraceptive therapy, the same product must have been taken for one month before Visit 1.
5. Have clinical diagnosis of rosacea with persistent (non-transient) facial erythema.
6. Have [redacted] inflammatory lesions on the face.
7. [redacted]

8. Willing to minimize external factors that might trigger rosacea flare-ups during the study.

9.3.2 Exclusion Criteria

1. Particular forms of rosacea that, in the opinion of the Investigator, would interfere with the diagnosis or assessment of study endpoints.
2. Patient has a skin condition that, in the opinion of the Investigator, would interfere with the diagnosis or assessment of rosacea
3. Patients with active sunburn or excessive facial hair such as beards, sideburns, moustaches, etc. that would interfere with the diagnosis or assessment of rosacea.
4. Patients with moderate to severe telangiectasial masses in the designated target area that would interfere with study evaluations.
5. History of allergy, hypersensitivity, or intolerance to oxymetazoline or any other component of the study product.
6. History of blood dyscrasia.
7. Significant history or current evidence of any uncontrolled chronic or serious disease or medical condition that would, in the judgment of the Investigator, would put the subject at undue risk or compromise the study assessments.
8. History or current evidence of Raynaud's syndrome, severe, unstable or uncontrolled cardiovascular disease, orthostatic hypotension, uncontrolled hypertension or hypotension, thromboangiitis obliterans, cerebral or coronary insufficiency, renal or hepatic or renal impairment, scleroderma, Sjögren's syndrome, depression, or narrow-angle glaucoma to an extent that, in the opinion of the Investigator, would place the subject at undue risk.
9. Female patients taking hormonal contraceptives or oral estrogen or those that plan to change the dosage regimen during the course of the study.
10. Dermatologic or surgical procedures on the face before Visit 1.
11. Use of systemic immunomodulators before Visit 1.
12. Current use of monoamine oxidase inhibitors (MAOIs), barbitrates, opiates, sedatives, systemic anesthetics, alpha-agonists.

13. Recent initiation, current use, or planned change in anti-hypertensive regimen with cardiac glycosides, beta blockers, or other anti-hypertensive agents that, in the opinion of the Investigator, would compromise the safety of the patient.
14. Use before Visit 1 of oral retinoids or therapeutic Vitamin A supplements of greater than 10,000 units/day.
15. Use before Visit 1 of 1) topical immunomodulators, 2) systemic antibiotics, 3) systemic corticosteroids, 4) systemic anti-inflammatory agents, 5) systemic treatment for rosacea, or 6) systemic treatment for acne (other than oral retinoids, which require a six month washout). Acetaminophen will be recommended to treat acute and transient conditions (e.g., headaches, menstrual cramps).
16. Use on the face before Visits 1 or 2 of 1) topical corticosteroids, 2) topical retinoids, 3) topical antibiotics, 4) topical anti-inflammatory agents, 5) topical treatment for rosacea, or 6) topical treatment for acne.
17. Use of niacin ≥ 500 mg/day before Visits 1 or 2.
18. Use of antihistamines before Visits 1 or 2.
19. Use of anti-coagulation therapy (e.g., Warfarin) before Visits 1 or 2.
20. Consumption of caffeine or rosacea trigger-foods before Visits 1 or 2. See
21. Patients who have been previously unresponsive to treatment with RHOFADE™
22. Previous participation in this study.
23. Employees of the Investigator or research center or their immediate family members.
24. Inability to understand the requirements of the study and the relative safety information and are unable or not willing to comply with the study protocol.

9.3.3 Restrictions During the Study

- Topical and systemic immunomodulators
- MAOIs, barbiturates, opiates, sedatives, systemic anesthetics, alpha agonists
- The use of tanning booths, sun lamps, or excessive sun exposure
- Cosmetic products (i.e., creams, lotions, powders)
- Systemic corticosteroids, systemic retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed), Systemic (oral or injectable) antibiotics, and any systemic or topical product for the treatment of rosacea or acne
- Antihistamines
- Alpha and beta adrenergic receptor blockers
- Anti-coagulation therapy
- Niacin ≥ 500 mg/day
- Systemic anti-inflammatory agents. Acetaminophen will be recommended to treat acute and transient conditions (e.g., headaches, menstrual cramps).
- Consumption of caffeine or rosacea trigger foods before study visits.

Patients should not initiate or change anti-hypertensive therapy with cardiac glycosides, beta blockers or other anti-hypertensive agents during the study.

[redacted]

The use of hormonal contraceptives should not be initiated or changed during the study.

Patients will be questioned about all prescription and over-the-counter concomitant medication use (including vitamins or nutritional supplements) at each study visit. All concomitant medications (including the use of sunscreen) will be recorded in the patient's source documents. Any patient who violates any of the listed restrictions may be dropped the study.

9.3.4 Removal of Patients from the Study

Patients will be advised that they are free to withdraw from the study at any time. If necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. If a patient terminates from the study early, all efforts will be made to complete Visit 4 study procedures. For early termination, the Investigator will fully document the reason for early termination. The clinical report will include all reasons for early withdrawals.

Reasons for removal may include the following:

- Patient withdrew consent.
- Significant adverse event (AE) that led the Investigator or patient to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Pregnancy
- Significant worsening of rosacea such that the Investigator and/or patient believes it is in the best interest of the patient to withdraw from the study and be provided alternative treatment.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial.

Patients who withdraw or are removed from the study will not be replaced. All patients who are randomized will be included in the safety monitoring tabulating all AEs experienced after dosing.

9.4 Treatments

9.4.1 Identity of Study Product

RHOFADE™ (oxymetazoline hydrochloride) Topical Cream, 1% (Allergan) will be used in this study.

9.4.2 Treatment Administration

At Visit 2, eligible patients will receive [redacted] tubes of RHOFADE™ Topical Cream, 1%. 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,

for a total of 15 ± 2 days. The last dose should be applied during Visit 4. Patients should not to dose within approximately 24 hours before any study visit.

The cleanser should not be shared with others (i.e., the cleanser should only be used by the patient who receives it from the investigative site). Patients will also be instructed not to apply the study product to cuts, abrasions, eczematous skin and sunburned skin and not to use "waxing" as a depilatory method on skin treated with the study product.

Each patient will be provided with a dosing diary in which they will be required to record dosing dates and times. These diaries should be brought to Visits 2, 3, and 4 so that the study staff may check compliance and file it in the patient's source documentation. At the end of the study, they will be retained in the patient's file as source documentation.

9.4.3 Study Blind

This is an open-label study.

9.4.4 Study Product Shipment, Storage, and Retention

The study products will be shipped in bulk to the Investigator's site from a centralized location. The Principal Investigator is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations.

The label will include the following information:

- Protocol number
- Randomization number
- Space for patient's initials
- Statement that the study product is for Investigational Use only
- Space for dispensing date and the Sponsor's name

In addition all patients will be provided with written instructions on how to use the study product.

Each patient will receive tubes of study product. This quantity will suffice for the entire study duration.

Storage Conditions

While at the research site, the study product is to be stored in a secure, locked location, at controlled room temperature of 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F). Any excursions from the above temperature range will require prompt notification to ; thereafter will notify the Sponsor.

Retention

As this is not a bioanalytical or bioequivalence study, no retention samples are needed.

9.4.5 Method of Assigning Patients to Treatment Groups

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.

9.4.6 Compliance

Patients will be provided with a diary to record the time and date of dosing, other concomitant medications, and AEs. . Compliance with dosing will be verified by the use of the patient diaries. Compliance criteria are as outlined in the table below:

For patients who have completed the study:

Study Design				
Visit 4	Treatment Duration	Required Doses		
Day 13-17	13-17 Days	15		

For patients who are early terminated, compliance will be based off their duration in the study, up to the time they are considered early terminated. For example, if a patient is dropped after 10 days of participation and doses 8 times, their percent compliance is 80%.

9.5 Study Conduct

9.5.1 Visit 1 – Screening/Baseline (Day -28 to -1)

[redacted]

9.5.2 Visit 2 – Baseline (Day 1)

[redacted]

[redacted]

9.5.3 Visit 3 – Interim Visit (Day 7 ± 2 Days)

[redacted]

[redacted]

9.5.4 Visit 4 – End of Study Visit or Early Termination (Day 15 ± 2 Days)

[redacted]

[redacted]

9.6 Study Procedures

9.6.1 Informed Consent

At Visit 1, before performing any study-related procedures, the patient must sign the IRB-approved ICF. The ICF will be reviewed and approved by an IRB before study commencement. No patient will be entered into the study without reading, understanding, and signing an ICF. If any other language is required, translation will be performed by a certified translator.

9.6.2 Medical History

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

9.6.3 Demographics

At Visit 1, each patient will be required to provide basic demographic information (i.e., date of birth, sex, ethnicity, and race).

9.6.4 Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at Visits 1, 2, and 4. The test must be negative at Visits 1 and 2 for the patient to be eligible for inclusion in the study. If the patient is female and not considered of childbearing potential, then the reason must be documented in the patient's source documents.

Any patient who becomes pregnant during the study should be discontinued and end of study procedures (Visit 4) completed. The outcome of the pregnancy should be followed by the Investigator to the conclusion of the pregnancy. The pregnancy will be reported as an AE.

9.6.5 Vital Signs

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

9.6.6 Concomitant Medication Use

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.

At Visit 2, any patient who has used medications restricted by the protocol may be discontinued from the study. If discontinued, all early termination procedures (Visit 4 procedures) should be performed.

9.6.7 Adverse Events

At the end of Visit 1, patients will be questioned about any AEs that occurred during the visit. At Visits 2, 3 and 4, patients will be questioned regarding any changes in their medical status since their previous visit. Any significant health changes observed after enrollment into the study will be reported as AEs, as deemed appropriate by the Investigator.

9.6.8 Lesion Count

At Visits 1, 2, and 4, the number of inflammatory lesions (i.e., papules and pustules) on the facial area, including the nose, will be counted and recorded. Wherever possible the same individual should attempt to perform lesion counts at all visits for an individual patient.

9.6.9 [redacted]

9.6.10 [redacted]

9.6.11 [redacted]

9.6.12 Inclusion/Exclusion Criteria Review

At Visits 1 and 2, inclusion/exclusion criteria will be reviewed to ensure patients' eligibility for participation in the study.

9.6.13

9.6.14 Dispense Study Product

The site will dispense one tube of study product at Visit 2 along with dosing instructions. The site will ensure the study product logs are reported correctly.

9.6.15 Dosing

Patients will dose at the site during Visits 2, 3, and 4. After pre-dose assessments are complete, patients will wash and dry their face with the supplied cleanser and apply the study product according to the dosing instructions.

9.6.16 Dispense Patient Diary/Supplies

Patients will be provided with a dosing diary at Visits 1, 2, and 3 along with instructions on how to complete the diary. Patients will be asked to record AEs and concomitant medications throughout the study. Starting at Visit 2, patients will also be asked to record the time and date of each dose.

At Visit 1, the patient will be provided with the mild non-medicated cleanser (e.g., Dove® Sensitive Skin or similar) and sunscreen (e.g., Neutrogena SPF 45 or similar). The use of the sunscreen should be documented on the concomitant medication page on the source documents

and eCRFs. Additional cleanser and sunscreen may be provided during the study at the request/need of the patient.

9.6.17 Collect/Review Patient Diary

At Visits 2, 3, and 4, patient diaries will be collected and reviewed for compliance with the protocol.

9.6.18 Collecting Study Product

The study product will be collected by the site at Visit 4. The site will ensure the study product logs are reported correctly.

9.7 Adverse Reactions

In studies with RHOFADE™ (oxymetazoline hydrochloride) Topical Gel treated for 29 days, adverse reactions related to treatment reported by at least 1% of subjects treated included erythema, flushing, skin burning sensation, contact dermatitis, dermatitis, warm skin, parasthesia, acne, skin pain, blurred vision, and nasal congestions.

9.7.1 Deviation from the Protocol for Individual Patients

When an emergency occurs requiring a patient's departure from the protocol, this shall apply only for that patient. In such circumstances, the Investigator or other physician in attendance shall notify the Medical Monitor or Perrigo by telephone and follow up with a written description within one day. The overseeing IRB should also be notified.

9.7.2 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally of the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an AE that results in any of the following outcomes:

- Death
- Life-threatening event (i.e., the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires in-patient hospitalization or prolongs hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other AEs that may be considered serious based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent

one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

Immediately Reportable Adverse Events (IRAE): Any SAE or any AE that necessitates discontinuation of study product, including pregnancy.

Unexpected Adverse Event: Any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study product, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

9.7.3 Intensity of Adverse Events

The maximum intensity of an AE during a day should be recorded on the eCRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity. The intensity of the AE will be graded by the Investigator using the following criteria as guidelines:

- Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.
- Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

9.7.4 Causal Relationship to Study Product

The following criteria should be used in assessing the apparent causal relationship of an AE to study product:

Definitely - The AE:

- Follows a reasonable temporal sequence from study product administration.
- Abates upon discontinuation of the study product (de-challenge).
- Is confirmed by reappearance of the reaction on repeat exposure.

Probably - The AE:

- Follows a reasonable temporal sequence from study product administration.
- Abates upon discontinuation of the study product (de-challenge).
- Cannot be reasonably explained by the known characteristics of the patient's state.

Possible - The AE:

- Follows a reasonable temporal sequence from study product administration but that could readily be produced by a number of other factors.

Unlikely - The AE:

- Follows a reasonable temporal sequence from study product administration.
- Could have been produced by either the patient's clinical state or by study product administration.

Not related - The AE:

- Does not have a reasonable temporal association with the administration of study product.
- Has some other obvious explanation for the event.

9.7.5 Eliciting and Reporting of Adverse Events

The Investigator will periodically assess patients for the occurrence of AEs. To avoid bias in eliciting AEs, the patient or parent/legally authorized representative should be asked a non-specific question (e.g., "How have you been feeling since your last visit?") to assess whether any AE has been experienced since the last visit. All AEs (as defined in Section 9.7.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the patient spontaneously or in response to direct questioning, will be reported and documented in the source and eCRF. When reporting an AE, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study product or procedure.

Adverse events will be documented in source and recorded in a timely manner on eCRF. Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE page of the eCRF with the status of the AE noted.

Adverse event reporting begins from the signing of informed consent/assent. Worsening of erythema of rosacea from baseline may be expected, however, if the conditions worsens to the degree that it requires alternative treatment or results in discontinuation from the study, it shall be recorded as an AE and will be documented on the patient's source documents and on the eCRF. Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, SAEs that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the Investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the eCRF.

9.7.6 Expedited Reporting Responsibilities of the Study Center

For any serious or unexpected AE, Perrigo must be notified within 24 hours of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for SAEs are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to the sponsor. The AE term on the AE eCRF and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Patients with unresolved AEs or SAEs should be followed by the Investigator until the events are resolved, events determined to be chronic, or the patient is lost to follow-up according to Section 9.7.5. Resolution means the patient has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the AE. The Investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved.

All SAEs will be reported as per applicable regulations. All SAEs encountered during the study will be reported on the appropriate form and summarized in the final report.

Any SAEs should be reported [redacted] within 24 hours. Following is the contact information:

[redacted]

[redacted] will report any SAE to Sponsor:

Documentation of serious or unexpected AEs and follow-up information should be sent to the Sponsor within 24 hours from [redacted] being made aware of the SAE. Following is the contact information:

[redacted]

The sponsor will be responsible for notifying the FDA of any SAEs. The sponsor must notify FDA of fatal or life-threatening SAE as soon as possible, but no later than seven calendar days from reporting the event by the Investigator.

9.7.7 Submitting an Expedited Safety Report to the IRB

Once [redacted] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with Perrigo, will determine if the safety report is eligible for expedited review. [redacted] will log the initial event and will notify Perrigo that an event has been reported within one business day after initial receipt. [redacted] will complete the review of the event, enter information into their safety database, and generate the report. This form, as well as other supporting documentation, will be forwarded to [redacted] Medical Monitor for review. [redacted] will finalize the report and distribute it to Perrigo within two days after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended by [redacted], Perrigo, or study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

9.7.8 Serious Adverse Events and Adverse Events Requiring Discontinuation

Non-serious events that require discontinuation of study product (including laboratory abnormalities) should be reported to Perrigo within one working day from reporting of the event by the Investigator.

Patients who discontinue due to AEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal. It is expected that the Investigator will provide or arrange appropriate supportive care for the patient.

A patient who experiences a severe AE related to study product will be discontinued from the study.

The notification about any SAE should be directed to the contact information provided in Section 9.7.6.

9.7.9 Pregnancy

[redacted]

A negative result of a urine pregnancy test having a minimum sensitivity of at least 50 mIU/mL for hCG should be obtained, before study participation. Pregnancy testing will be performed at Visits 1, 2, and 4 and the results of all pregnancy tests (positive or negative) will be documented.

At the time an Investigator or site personnel becomes aware that a patient became pregnant following study participation, the Investigator or designee will report the pregnancy immediately by phone and by faxing a completed Pregnancy Report to [redacted] within one working day after being notified of the pregnancy report.

The report will include the following elements:

- Patient's (mother's) coded study identifier;
- Date of patient's last menstrual period;
- Total accumulated dose of study product administered to date;
- Date of study product administration.

The pregnancy will be reported as an AE. The Investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Investigator or designee must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus to the [redacted], including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE report form to [redacted] within one working day after being notified of the pregnancy report.

If [redacted] responsibilities for the trial are completed before the outcome of the pregnancy is known, they must have a plan in place to conduct pregnancy outcome follow-up and notify Perrigo.

9.7.10 Post-Study Adverse Events

9.7.10.1 Non-Serious Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted.

9.7.10.2 Serious Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted.

Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE eCRF and reported to Perrigo according to the procedures outlined above. Patients with unresolved previously reported SAEs, or any new SAEs identified on the last assessment visit, should be followed by the Investigator until the events are resolved, or the patient is lost to follow-up according to Section 9.7.5. Resolution means the patient has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the AE. The Investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any SAE reported by the patient to the Investigator that occurs after the last assessment, and are determined by the Investigator to be reasonably of the use of the study product, should be reported to Perrigo.

10.0 STATISTICAL METHODS

10.1 Statistical Plan

A Statistical Analysis Plan (SAP), including study data report format, detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused, and spurious data will be included in the SAP.

If not otherwise specified, statistical significance is defined as $p < 0.05$, two-sided. Data will be summarized with respect to demographic and baseline characteristics, efficacy variables, and safety variables. For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, statistics will include number of observations, mean, standard deviation, median, minimum, and maximum values.

All statistical analysis will be conducted using Statistical Analysis Software (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 Analysis Dataset Model (ADaM).

10.2 Sample Size Determination

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

10.3 Protocol Deviations/Violations

This study will be conducted as described in this protocol except for an emergency situation in which the protection, safety, and well-being of the patient requires immediate intervention, based on the judgment of the Investigator or a responsible, appropriately trained and credentialed professional(s) designated by the Investigator. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the Investigator or designee must contact Perrigo at the earliest possible time.

10.4 Study Populations

10.4.1 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 ± 2 days (Day 13 to Day 17 inclusive).
- Have no significant protocol deviations (PDs) that would affect treatment evaluation.
- Apply the study product appropriately .
- Do not miss the scheduled applications for more than one consecutive day.

10.4.2 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).

10.4.3 Safety Populations

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

10.5 Baseline Comparability

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 by treatment group 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. Baseline treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel tests for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and patient.

10.6 Efficacy Variables

[redacted]

10.7 Efficacy Endpoints

Primary Efficacy Endpoints

[redacted]

10.8 Efficacy Analysis

[redacted]

[redacted]

10.9 Safety Analysis

Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 20.0 or higher. Summary tables including the type, date of onset, date of resolution, incidence, severity, relationship to the study product, action taken, and outcome will be prepared for AEs.

Concomitant medication use, including medication name, start date, stop date, and reason for use during the randomized treatment period will be tabulated by patient.

11.0 REGULATORY OBLIGATIONS

11.1 Institutional Review Board

The study protocol, ICF, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an IRB before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

11.2 Study Documentation

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs) and all applicable regulations, including the Federal Food, Drug, and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.[17-20] The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

11.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page.

11.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and local state regulations will be provided to each prospective study patient before being screened into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient.

11.2.3 Protocol and Informed Consent Changes

Sponsor approved changes to the protocol or the ICF will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

11.2.4 Source Documents and Case Report Forms

All patients will be identified by initials, date of birth, and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete eCRFs. A set of eCRFs will be completed for each patient randomized in the study. All data and eCRFs will be reviewed, evaluated, and signed by the Investigator.

The original source documents and a copy of the corresponding eCRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 4 (End of Study) source/eCRF completed.

11.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing, and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study (after the database has been locked) all used and unused study product will be returned to Sponsor or designee.

11.2.6 Drug Storage

Study product will be stored at controlled room temperature of 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F) in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of drug

receipt, dispensing, and return. After finalizing the study report, all partially used and unused study product will be returned to Sponsor or designee.

11.2.7 Retention of Reserve Samples

No reserve samples are required for this study.

11.2.8 Return of Clinical Supplies

All unused kits of study product will be returned to .

11.2.9 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.[21]

11.2.10 Record Retention

All study product accountability records, eCRFs, source data, and related regulatory documents must be retained according to 21 CFR 312.62(c) for a period of 2 years following the date the marketing application is approved for the study product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. The Sponsor will be notified before any destruction of records.

11.2.11 Study Monitoring and Auditing

 will be responsible for monitoring the study according to GCP and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to representative during such visits and audits.

The study may be subject to audit by the Sponsor, Sponsor Representative, or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

11.2.12 End of the Trial

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study product will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

11.2.13 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as

may be appropriate. The report will be in electronic format according to eCTD and International Conference on Harmonisation formatting standards and guidelines.[22]

12.0 REFERENCES

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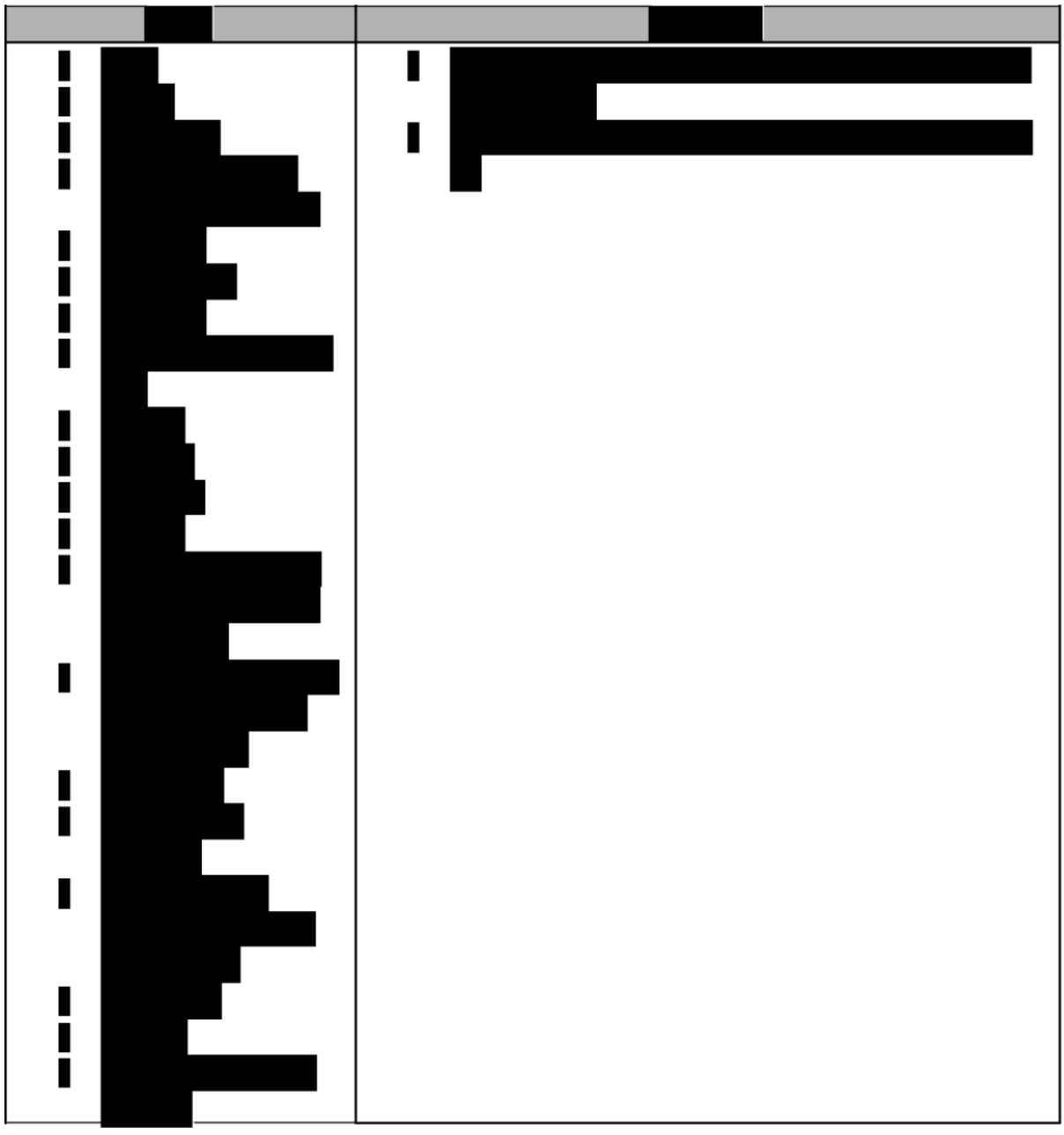
13.0 APPENDICES

13.1

13.2

13.3



13.4 Appendix D: RHOFADE™ Product Insert