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

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Protocol No.: PRG-NY-14-022

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PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: PRG-NY-14-022

PROTOCOL TITLE: 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

Signatures of representati[redacted] indicate this is the agreed upon final version of the protocol:

[redacted]

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STUDY SYNOPSIS

Title:	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
Study Period:	15 Days
Study Medication:	1. Brimonidine Topical Gel 0.33%, Perrigo Israel Pharmaceuticals, Ltd. 2. Mirvaso® (Brimonidine) Topical Gel 0.33%, Galderma Laboratories, L.P. 3. Vehicle of test product, Perrigo Israel Pharmaceuticals, Ltd.
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.
Study Design:	Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be admitted into the study only after written informed consent has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects ≥ 18 years of age with persistent (nontransient) facial erythema of rosacea will be eligible for enrollment.
Study Population:	[redacted] healthy males and females, ≥ 18 years of age who meet the inclusion/exclusion criteria, will be enrolled to obtain [redacted] modified intent-to-treat (mITT) subjects and [redacted] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized [redacted] to either the test product, reference product or vehicle treatment group, respectively, and will apply [redacted] to each of the five areas of the face avoiding contact with the eyes and lips once daily for 15 days.
Study Visits:	Clinical Evaluations will be performed at: 1. Visit 1/Day 1 (Baseline) 2. Visit 2/Day 15 (±2 days)(End of Study/Treatment) Safety will be assessed by monitoring adverse events at each visit.
Evaluations:	• The Clinician's Erythema Assessment (CEA) will be administered at Visit 1/Day 1 and Visit 2/Day 15. • The Patient Self-Assessment (PSA) will be performed at Visit 1/Day 1 and Visit 2/Day 15. • Investigator's Global Assessment (IGA) will be administered on Visit 1/Day 1 and Visit 2/Day 15 prior to study medication application. • The Fitzpatrick Classification Scale will be administered on Visit 1/Day 1 prior to study medication application.

Endpoints:	The primary efficacy endpoint will be the proportion of subjects with composite success on Day 15 at hour 6 post study medication application, where composite success is defined as at least a 2-grade improvement from Visit 1/Day 1 prior to the first application of study medication on both the Clinician's Erythema Assessment (CEA) and the Patient Self-Assessment (PSA) scales. The secondary endpoints will be: • The proportions of subjects with composite success on Day 15 at hours 3 and 9 post study medication application.
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Equivalence of the test and reference with regard to safety will be evaluated by comparing the nature, severity and frequency of their adverse event profiles.

ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CEA	Clinician‘s Erythema Assessment
CMH	Cochran–Mantel–Haenszel Test
CRF	Case Report Form
DCF	Data Correction Form
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IGA	Investigator‘s Global Assessment
IRB	Institutional Review Board
ITT	Intent to Treat Population
IUD	Intra-Uterine Device
LPN	Licensed Practical Nurse
LVN	Licensed Vocational Nurse
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat population
NP	Nurse Practitioner
OTC	Over the Counter
PA	Physician‘s Assistant
PI	Principal Investigator
PP	Per Protocol Population
PSA	Patient Self-Assessment
RN	Registered Nurse
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPF	Sun Protection Factor

1. BACKGROUND

[redacted]

Perrigo UK FINCO has developed a generic formulation of Brimonidine Topical Gel 0.33%.

2. STUDY OBJECTIVES

The objectives of this study are to compare the safety and efficacy of Perrigo UK FINCO's Brimonidine Topical 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.

2.1 Endpoints

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

The secondary endpoints will be the proportions of subjects with composite success at Day 15 hours 3 and 9 post study medication application

2.2 Safety

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles. All adverse events that occur during the study will be recorded. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, relationship to study medication, treatment and the outcome. Comparisons between the treatment groups will be made by tabulating the frequency of Subjects with one or more adverse events (classified into MedDRA terms) during the study. Pearson's Chi-Square test or Fisher's Exact test, whichever is most appropriate, will be used to compare the proportion of subjects in each treatment group with any adverse event. The adverse events reported by at least five percent of the subjects in any treatment group will be summarized descriptively.

3. STUDY DESIGN

3.1 Type/Design of Study

Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be assigned [redacted] to either test product, reference product, or vehicle product. Subjects will apply the study medication once daily in the morning for 15 days.

Visits to the study site are scheduled at Visit 1/Day 1 (Baseline) and Visit 2/Day 15 (End of Study/Treatment).

3.2 Study Population

Male and female subjects, ≥ 18 years of age, with persistent (nontransient) facial erythema of rosacea.

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Inclusion Criteria

Subjects **must** meet all of the following criteria:

1. Subject must sign an Institutional Review Board (IRB) approved written informed consent for this study. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative.
2. Subjects must be healthy male or non-pregnant female, ≥ 18 years of age.
3. Subjects must have a definite clinical diagnosis of rosacea with moderate to severe erythema on the face defined as: a score of ≥ 3 on the Clinician's Erythema Assessment (CEA) and a score of ≥ 3 on the Patient's Self-Assessment (PSA) on Visit 1/Day 1 (Baseline) prior to the first application of study medication
4. Subjects must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, refrain from use of all other topical rosacea medication or topical antibiotics during the 15 day treatment period, comply with therapy prohibitions, [redacted] return for the required study visits, and complete the study.
5. Subjects must be in general good health and free from any clinically significant disease, other than rosacea, that might interfere with the study evaluations.
6. [redacted]

7. [redacted]

4.2 Exclusion Criteria

Subjects do not qualify if any of the following criteria exist:

1. Subjects, who are pregnant, breast feeding, or planning a pregnancy within the study participation period.
2. Presence of [redacted] facial inflammatory lesions of rosacea [redacted]
3. [redacted]
4. Other facial conditions that in the Investigator's opinion might interfere with a rosacea diagnosis and/or assessment [redacted]
5. Any uncontrolled, chronic or serious disease or medical condition that would prevent participation in a clinical trial or, in the judgment of the Investigator, would put the subject at undue risk or might confound the study assessments (such as planned hospitalization during the study).
6. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements.
7. Excessive facial hair [redacted] that would interfere with diagnosis or assessment of rosacea.
8. History of hypersensitivity or allergy to brimonidine tartrate and/or any ingredient in the study medication.
9. Previous enrollment in this study.
10. [redacted].
11. Currently using any product containing brimonidine tartrate or oxymetazoline.
12. [redacted]
13. Start or change of dose of;
    - [redacted]
    - [redacted]

14. [redacted]
15. Use [redacted] prior to baseline or during the study of oral retinoids (such as Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
16. Use [redacted] prior to baseline or during the study of systemic immunomodulators
17. Use of medicated make-up throughout the study and/or significant change in the use of consumer products [redacted] study entry and throughout the study.
18. Participation in any clinical study involving an investigational product or device in the 4 weeks (28 days) prior to baseline or throughout the study.
19. Use [redacted] prior to baseline or during the study of

[redacted]

20. Use of following topicals on the face [redacted] prior to baseline or during the study of
    - antibiotics
    - prescription anti-inflammatory agents including ophthalmic
21. Use of over the counter (OTC) topical anti-acne medications (e.g. Benzoyl peroxide, salicylic acid, etc.) [redacted]
22. Chronic, daily use of OTC anti-inflammatory medications (e.g. ibuprofen, naproxen) [redacted] prior to baseline and throughout the study. Subjects may use acetaminophen for pain relief, as needed throughout the study.
23. Use of tanning booths, sun lamps, sunbathing, phototherapy or excessive ultraviolet (UV) exposure to the sun [redacted] prior to baseline and throughout the study.
24. [redacted]
25. [redacted].

26. [redacted]

4.3 Precautions

The following precautions are to be taken during this study:

1. Subjects should avoid contact of the study medication with the eyes, lips or on irritated skin or open wounds.
2. Subjects should minimize sun exposure, refrain from using sunlamps and tanning beds and use protective apparel such as hats when outdoors during the study.
3. [redacted].
4. [redacted]
5. Subjects should wash hands before and after applying study medication.
6. Study medication should not be applied to cuts, abrasions, eczematous or sunburned skin.
7. Study medication should not be applied more than once daily and subjects should not use more than the recommended amount.
8. [redacted]

5. PROCEDURES

5.1 Subject Screening and Enrollment

The study staff will review the IRB approved informed consent form and assent form, if applicable, with each subject and give the subject an opportunity to have all questions answered before proceeding. The consent/assent form must be signed by each subject and witnessed before the subject is enrolled into the study. A copy of the signed consent/assent will be given to every participant and the original will be maintained with the participant's records. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative.

5.2 Assignment of Subject Number

Once the subject has consented and met inclusion/exclusion criteria, they will be assigned a subject number. The subject number will be taken from the respective study medication kit dispensed to the subject at each site.

5.3 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study medication. The medical history will include a complete review of all current diseases and their respective treatments.

5.4 Concomitant Medications

Concomitant medications and any medications taken [redacted] prior to signing informed consent/assent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications

taken on either a regular or ~~–prn~~" basis, including vitamins, aspirin and acetaminophen, should be recorded on this page prior to commencing the use of the study medication. A record of medication taken by the subject during the study is to be obtained at each study visit.

5.5 Physical Examination

The investigator, sub-investigator or appropriately delegated and qualified designee will perform a brief physical examination, prior to the subject starting study medication. [redacted]

5.6 Urine Pregnancy Test

[redacted]

An investigator could repeat the pregnancy test at any time during the study if there is any suspicion or possibility that the subject is pregnant.

5.7 Investigator Assessments

All investigator assessments must be conducted by qualified study staff listed on the Form FDA 1572 who have been delegated these tasks by the PI. [redacted]

[redacted].

5.7.1 Investigator's Global Assessment (IGA) of Lesions

The investigator's global assessment will be performed at Visit 1/Day 1 and Visit 2/Day 15 prior to the application of study medication to assess the overall disease of the subject. This will be done for inclusion and exclusion criteria and to ensure that the treatment of erythema does not worsen other manifestations of the disease. The following scale will be used for the IGA:

Grade	Score	Description
Clear	0	[redacted]

Almost Clear	1	[redacted]
Mild	2	[redacted]
Moderate	3	[redacted]
Severe	4	[redacted]

5.7.2 Clinician's Erythema Assessment (CEA)

Each subject's initial condition and course of erythema of rosacea will be assessed using the CEA. The investigator will evaluate the subject's facial erythema by performing a static evaluation of erythema severity using the CEA and record the number that best describes overall severity. The CEA will be performed at Visit 1/Day 1 (Baseline) and Visit 2/Day 15 (End of Study/Treatment) prior to the application of study medication and at hours 3 (+15 minutes), 6 (+15 minutes) and 9 (+15 minutes) post study medication application for each visit.

The following scale will be used for the CEA:

Grade	Description
0	Clear skin with no signs of erythema
1	Almost clear, slight redness
2	Mild erythema, definite redness
3	Moderate erythema, marked redness
4	Severe erythema, fiery redness

5.7.3 Fitzpatrick Classification Scale

The Fitzpatrick skin scale classifies a person's complexion and their tolerance of sunlight. It is commonly used by many practitioners to determine how someone will respond or react to facial treatments, and how likely they are to get skin cancer.

The Fitzpatrick Classification Scale will be performed at Visit 1/Day 1 (Baseline) prior to the first application of study medication and will be recorded in the subject's source document and CRF.

Skin Type	Skin Color	Characteristics
I	White; [redacted]	[redacted]
II	White; [redacted]	[redacted]
III	Cream white; [redacted]	[redacted]
IV	Brown; [redacted]	[redacted]

V	Dark Brown; [redacted]	[redacted]
VI	Black	[redacted]

5.8 Patient Self-Assessment (PSA)

Each subject's initial condition and course of erythema of rosacea will be assessed using the PSA. The patient will evaluate their facial erythema by performing a static evaluation of erythema severity using the PSA and report the number that best describes overall severity of their facial redness as seen in a mirror at the time of the evaluation. The PSA will be performed at Visit 1/Day 1 (Baseline) and Visit 2/Day 15 (End of Study/Treatment) prior to the application of study medication and at hours 3 (+15 minutes), 6 (+15 minutes) and 9 (+15 minutes) post study medication application for each visit. [redacted]

Study staff will instruct the subject on how to correctly perform the PSA at Visit 1/Day 1 (Baseline) prior to the first application of study medication and as needed thereafter.

Grade	Description
0	No redness
1	Very mild redness
2	Mild redness
3	Moderate redness
4	Severe redness

5.9 Diagnosis/ Enrollment Eligibility

At Visit 1/Day 1 (Baseline), prior to the first application of study medication, the investigator will examine the subject to establish the clinical diagnosis of persistent (nontransient) facial erythema of rosacea using the CEA scale. Each subject will also evaluate their facial erythema of rosacea using the PSA scale.

Both the investigator (CEA) and subject (PSA) assessments should each yield a score of at least 3 (moderate erythema) or 4 (severe erythema) in order for the subject to be enrolled in the study.

5.10 Study Medication Use, Subject Instructions and Diary

At Visit 1/Day 1 (Baseline), study staff will dispense one [redacted] tube of study medication from the subject kit box to eligible subjects along with a diary card. Each subject will also receive a copy of usage instructions and study precautions (Appendix B).

The initial/first application on Visit 1/Day 1 (Baseline) will be applied by the subject at the site under the supervision of study staff not conducting clinical evaluations. The time of first application will be noted as Hour 0. The study staff will instruct the subject to apply all subsequent doses of the study medication (starting on Day 2 of study treatment period) similarly and to record each application in their study diary. On Visit 2/Day 15 (End of Study/Treatment)

the study medication will be applied by the subject at the site after completion of all assessments required. The time of application will be noted as Hour 0.

The study medication tube is to be examined by the study staff at Visit 2. If, at any time, additional study medication is required, [redacted] tube from the subject medication kit is to be dispensed to the subject. The study medication must be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] at all times (at the investigator site and when dispensed to the subject).

The subjects will apply the study medication once daily in the morning for 15 days. On study visit days, study medication will be applied by the subject at the site after completion of all assessments required prior to the application. [redacted] the study medication should be applied to **each** of the five areas of the face (forehead, chin, nose, each cheek) [redacted] avoiding contact with the eyes and lips. Subjects will be instructed to wash hands immediately after applying the study medication. Subjects will be instructed to not use any other topical treatments on the treatment area.

The subject will capture daily, the time of application in the diary card. They will also record any new medications that they took during the study.

The study staff will collect and review the diary card at Visit 2 for compliance. Each subject will be reminded to bring with them all study medication tube(s) (regardless of content) and the completed diary card to Visit 2. Study staff will schedule the subject's Visit 2 prior to the subject's departure at Visit 1.

5.11 Visit Specific Procedures

The following sections outline the procedures required at each visit.

5.11.1 Visit 1/Day 1 (Baseline)

[redacted]

[redacted]

5.11.2 Visit 2/End of study /treatment / Early Termination Visit /Day 15 (±2 days)

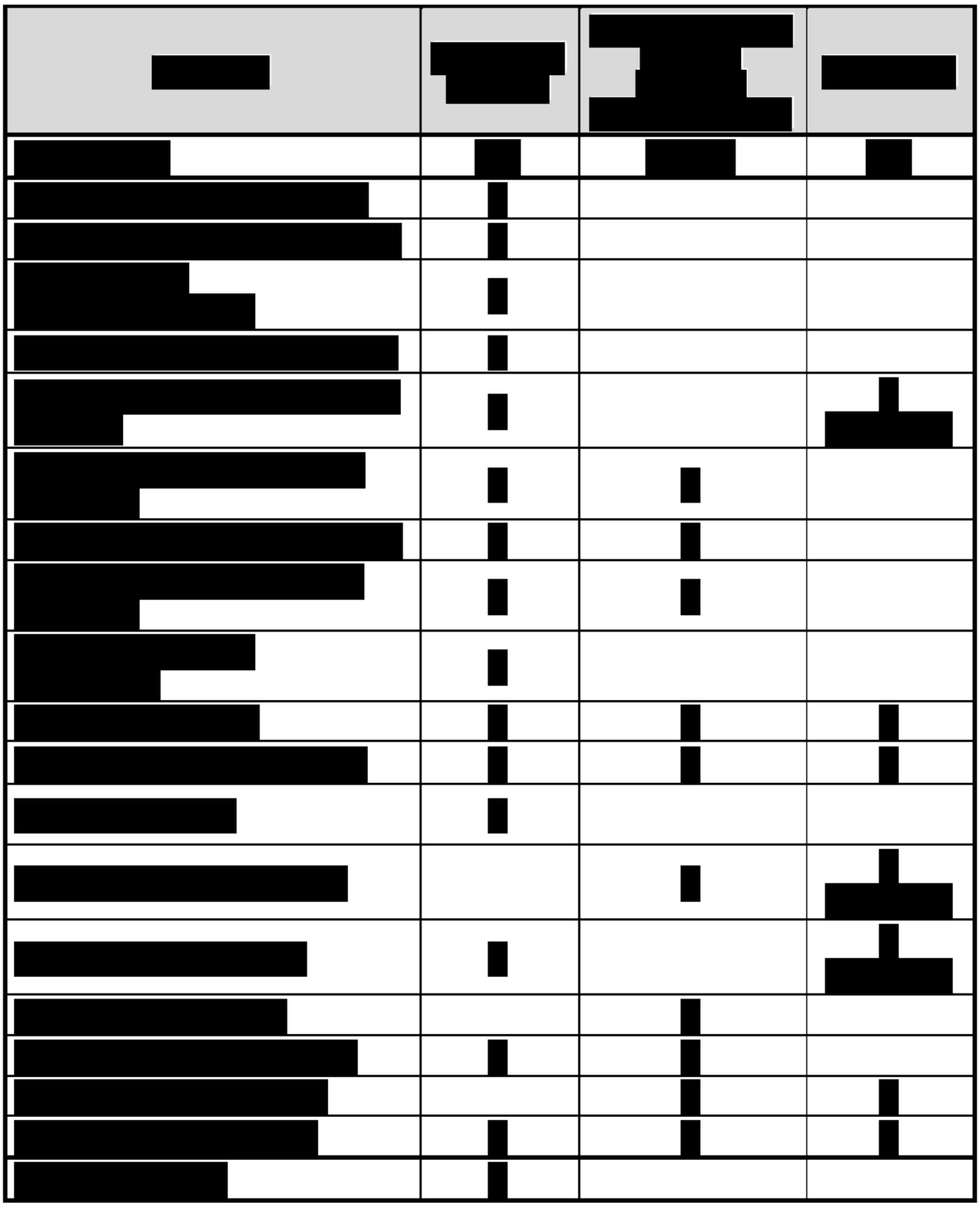
[redacted]

5.11.3 Unscheduled Visit

[redacted]

5.12 Summary of Assessments

The schedule of visits and procedures to be conducted at each visit are summarized in the Schedule of Study Procedures.



5.13 Screen Failures

Screen failures will not be included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent, but never received study medication. All screen failures will be collected on a Subject Screening Log.

5.14 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 subject 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 CRO contacts in Section 15 (Appendix A) at the earliest possible time.

[redacted]

[redacted]

5.15 Subject/Treatment Compliance

[redacted]

5.16 Discontinuation/Withdrawal of Study Subjects

Subjects may be removed from the study for any of the following reasons:

1. The subject withdraws his or her consent for any reason.
2. The subject‘s condition has worsened to the degree that the study staff feels it is unsafe for the subject to continue in the study.
3. Subject did not meet entry criteria.

4. The subject‘s medication code is unblinded.
5. An adverse event occurs for which the study staff determines that it is in the subject‘s best interest to be discontinued.
6. The subject is lost to follow-up. The study staff will document efforts to attempt to reach the subject twice by telephone and will send a certified follow-up letter before considering that subject lost to follow-up. All attempts must be thoroughly recorded.
7. The subject becomes pregnant during the course of the trial.
8. Non-compliant use of the study medication
9. Significant protocol violation or non-compliance with the study protocol that could interfere with the effect or accurate assessment of the assigned study treatment.

After a subject has been enrolled, he/she will not be allowed to re-enroll in the study.

In the event that a subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a subject, the investigator must strive to follow the subject until the adverse event has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

If the investigator assesses the subject‘s condition and determines that the subject‘s condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure, and a standard of care treatment may be advised at the investigator‘s discretion.

The reason for a subject‘s discontinuation will be documented in the subject‘s source documents, case report form and the enrollment log.

If a subject is discontinued from the study for any reason, the Day 15/End of Study Visit/Early Termination Visit procedures should be completed and any outstanding data and study medication should be collected. Data, in addition to the reason for discontinuation and the date of removal, will be recorded on the End of Study Case Report Form.

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo will consist of:

Test Product: Brimonidine Topical Gel 0.33% - [redacted]

Reference Product: Mirvaso® (Brimonidine) Topical Gel 0.33%, - manufactured by Galderma Laboratories, L.P.

Vehicle: Vehicle of test product - [redacted].

6.2 Medication Management

6.2.1 Labeling, Packaging, Distribution and Randomization

Randomization will be performed according to a computer generated randomization schematic [redacted] of test: reference: vehicle. The treatment group designation has been assigned to the subject number on the study medication kit. Study medication is blinded, labeled and packaged, according to the randomization code, so that neither the subject nor the investigator can identify the treatment. Each subject will be assigned to one of the randomized study medication kits. An independent third party will hold the master randomization code throughout the study.

[redacted]

In order to nullify any potential differences in product packaging, study staff not collecting any clinical evaluations will dispense and collect study medication from the subjects. The study staff will instruct the subject how to apply the study medication, how to complete the diary card, and will oversee the application of study medication during the subject study visits.

The study staff performing the clinical evaluations will not dispense or collect study medication or oversee the application of study medication during the subject study visits.

6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [redacted] block of study medication ([redacted] subject treatment units) to be maintained as retention samples. The investigator will maintain one randomly selected block of study medication from each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), –Each reserve sample shall be stored

under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used." The investigator will store the retention sample study medication until such time as notification is received from Perrigo that the samples are no longer required.

6.2.3 Storage and Study Medication Accountability

Study medication used to conduct this study will be maintained under adequate security by the investigator. Study test articles will be stored between 20-25°C (68-77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] in a secured area with limited access. Each investigative site will ensure that the temperature of study medication is monitored and recorded throughout the study. The medication should not be frozen, should be protected from heat and kept tightly closed. The investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The study staff will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each is dispensed and used. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. At the conclusion of the study all unused, partially used, and empty containers must be inventoried by the monitor and returned to Perrigo, or designee, for destruction.

6.2.4 Procedure for Breaking the Blind

The investigator, staff at the study site, study monitors, and data analysis/management personnel are blinded to the subject assignment. In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label, which is attached to the study medication log; however, every effort should be made to maintain the blind. **The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation only and should seek prior authorization by Perrigo or designee when possible.** The reason for breaking the blind must be clearly documented in the source documentation and CRF and the subject must be discontinued from the study. Perrigo must be notified immediately upon all unblinding situations.

7. ADVERSE REACTIONS

The potential adverse reactions of generic Brimonidine Topical Gel 0.33% are anticipated to be similar to those observed in Mirvaso® (Brimonidine) Topical Gel 0.33%.

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

In an open label study with Mirvaso® (Brimonidine) Topical Gel for one year where other rosacea therapies were allowed, adverse reactions related to treatment included flushing, ertythema, rosacea, nasopharyngitis, burning skin sensation, increased intraocular pressure and headache.

Allergic contact dermatitis to Mirvaso® (Brimonidine) Topical Gel was reported in approximately 1% of subjects across the clinical development program. One subject was found to be sensitive to brimonidine tartrate and one was subject was sensitive to a preservative phenoxyethanol.

7.1 Deviation from the Protocol for Individual Subjects

When an emergency occurs requiring a subject‘s departure from the protocol this shall apply only for that subject. 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.

7.2 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event 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 adverse event that results in any of the following outcomes:

- death
- life-threatening event (i.e., the subject 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-subject 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 adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject 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 serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

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

Intensity of Adverse Events: The maximum intensity of an AE during a day should be recorded on the CRF. 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.

Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.

Moderate - AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication: The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely - The AE:

- follows a reasonable temporal sequence from study medication administration.
- abates upon discontinuation of the study medication (dechallenge).
- is confirmed by reappearance of the reaction on repeat exposure.

Probably - The AE:

- follows a reasonable temporal sequence from study medication administration.
- abates upon discontinuation of the study medication (dechallenge).
- cannot be reasonably explained by the known characteristics of the subject's state.

Possible - The AE:

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

Unlikely - The AE:

- follows a reasonable temporal sequence from study medication administration.
- could have been produced by either the subject's clinical state or by study medication administration.

Not related - The AE:

- does not have a reasonable temporal association with the administration of study medication.
- has some other obvious explanation for the event.

7.3 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. In order to avoid bias in eliciting adverse events, the subject 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 adverse events (as

defined in Section 7.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected adverse events must be reported to Perrigo ***within 24 hours*** of when the Investigator first learns of the occurrence of the event.

Adverse events will be documented in source and recorded in a timely manner on case report forms. Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE case report form (CRF) 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 adverse event and will be documented on the subject's source documents and on the CRF. Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, serious adverse events 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 CRF.

7.3.1 Expedited Reporting Responsibilities of the Study Center

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

Subjects with unresolved adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, events determined to be chronic or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs within 30 days after the last assessment, and are determined by the investigator to be reasonably associated with the use of the study medication, should be reported to Perrigo within 24 hours of when the Investigator first learns of the occurrence of the event.

When reporting a serious adverse event (SAE) the Investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy to [redacted] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to [redacted] within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow up information

should be sought (hospital discharge summaries, operative reports etc.) and a follow up SAE report form submitted. A designation of causality from the study medication should always be included with a follow up report. Assess and report the causality of the event.

7.3.2 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 1 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] s Medical Monitor for review. [redacted] will finalize the report and distribute it to Perrigo within 2 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.

When a Principal Investigator receives an expedited safety report from [redacted] or Perrigo detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center‘s IRB. The Principal Investigator must retain a copy of such reports as submitted to their IRB in the site‘s study Regulatory Binder.

7.3.3 SAE & AEs Requiring Discontinuation of Study Medication, including Pregnancies

ANY SAE, WHICH OCCURS AFTER A SUBJECT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED TO [redacted] AND/OR PERRIGO IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO [redacted].

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported to Perrigo immediately and within 1 working day.
Subjects who discontinue due to experiencing adverse events 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 subject.

A subject who experiences a severe adverse event related to study medication will be discontinued from the study.

The notification about any serious adverse event should be directed to:

[redacted]

[redacted]

7.3.4 Pregnancy

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

The report will include the following elements:

- Participant (mother's) coded study identifier;
- Date of participant's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study medication administration.

The investigator will follow the subject 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 Principal 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 of being notified of the pregnancy report.

If [redacted]s 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.

7.4 Post Study Adverse Events

7.5 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 case report form (CRF) with the status of the AE noted.

7.6 Serious Adverse Events

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

8. STATISTICAL ANALYSIS

8.1 General Considerations

Statistical analyses will be conducted by the Sponsor‘s designee. The sections that follow highlight sample size determination and the planned analyses for this study. A statistical analysis plan (SAP) will be prepared separately from this protocol which gives descriptions of the statistical methods, models, hypotheses and subject populations to be analyzed. The SAP will be completed and finalized / approved before locking the database and unblinding the study and will serve as a companion to the protocol and the *de facto* documentation of the proposed statistical evaluation.

8.2 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject who was randomized, received and used study medication.

- Modified Intent-to-Treat (mITT): Any subject, who met the inclusion/exclusion criteria, was randomized, received and used the study medication, and returned for at least one post-baseline efficacy assessment.

- Per Protocol (PP): Any subject who:
  - met inclusion/exclusion criteria,
  - was randomized, received and used study medication
  - did not miss more than 3 consecutive doses of study medication applications
  - did not take any concomitant medications prohibited by the protocol or have any other significant protocol violations
  - returned for Visit 2/Day 15 within the designated visit window (± 2 days) with data on the primary efficacy variables [redacted]

[redacted]

[redacted]

[redacted]

8.3 Planned Analysis

All subjects who received study medication will be evaluated for safety. The efficacy analysis will be conducted on both the PP and the mITT populations. Summary displays will be presented by treatment group. Hypotheses will be tested at the 5% significance level, unless otherwise specified. 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.

The primary efficacy endpoint will be the proportions 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.

The secondary efficacy endpoints will be the proportions of subjects with composite success at hours 3 and 9 on Day 15

Other Assessment:

- 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 visit‘s application of study medication.

For the efficacy analysis on the mITT population, the Last Observation Carried Forward (LOCF) method will be used to fill in missing data. For the PP subjects who discontinued early due to treatment failure, the efficacy data from their last visit will be carried forward to all subsequent visits.

8.3.1 Sample Size Considerations

[redacted]

[redacted]

8.3.2 Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy measure will be 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.

The secondary efficacy endpoints will be the proportion of subjects with composite success at hours 3 and 9 on Day 15

Equivalent efficacy

For the proportion of subjects with composite success on Day 15 at hour 6 and a 90% confidence interval (CI) will be constructed using Wald‘s method with Yates‘ continuity correction for the difference between the two active treatment groups. The Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% CIs are contained within the interval –20% to +20%.

[redacted]

Superiority

The proportion of subjects with composite success at hour 6 on Day 15 for each active treatment will be compared to that of the Vehicle, using a two-sided Z-test with Yates‘ continuity

correction at a significance level of $\alpha = 0.05$. Each active treatment is demonstrated to be superior to the vehicle if $p<0.05$ is achieved.

[redacted].

The secondary efficacy endpoints at hours 3 and 9 on Day 15 will be analyzed using the same methods as the primary efficacy endpoints.

Other efficacy endpoints will be summarized descriptively.

8.3.3 Safety and Adverse Events Analysis

The frequency and percent of subjects with adverse events will be summarized by MedDRA (Version 15.1 or higher) system organ class and preferred term and by severity and causality to study medication for all three treatment groups. The adverse events reported by at least five percent of the subjects in any treatment group will also be tabulated. The comparable safety of the Test and Reference treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. Safety comparisons will be performed only for the safety intent-to-treat population.

8.4 Comparability of Subjects at Baseline

Treatment group difference in the distribution of categorical variables such as gender and Fitzpatrick Classification will be tested using Cochran–Mantel–Haenszel (CMH) test for general association adjusted for site. Continuous variables, such as age, will be analyzed using a two-way analysis of variance (ANOVA) model with site and treatment as a fixed effect.

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES

It will be made clear to the subject that, for the purposes of the study, they are consenting only for topical application of medication or vehicle. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed consent/assent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research. When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by Perrigo, prior to study commencement.

Periodic status reports must be submitted to the IRB at least annually as required by the site‘s IRB, as well as notification of completion of the study and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB must be sent to Perrigo.

The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be

documented on a written informed consent/assent form, which shall be approved by the same Institutional Review Board (IRB) responsible for approval of this protocol. Each informed consent/assent form shall include the elements required by FDA regulations in 21 CFR Part 50. The investigator agrees to obtain approval from Perrigo of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB-approved written informed consent/assent form shall be signed by the subject (or their parent/legally authorized representative) and the person obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from screening. In the event that the subject is re-screened for study participation, a new informed consent/assent form must be signed.

9.1 Subject Confidentiality

All study participants are concerned for the individual subject‘s privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to sponsor, it is required that the investigator permit the study monitor, any Sponsor authorized representative, and/or FDA representative to review that portion of the subject‘s medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by sponsor or their authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator‘s responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, sponsor or their authorized representative and possibly the FDA.

All reports and communications relating to the subject in the study will identify each subject only by the subject‘s initials and by the subject number. The investigator agrees to furnish Perrigo with complete subject identification, if necessary on a confidential follow-up form, which will be used for the purpose of a long-term follow-up, if needed. This will be treated with strict adherence to professional standards of confidentiality and will be filed at Perrigo under adequate security and restricted accessibility.

10. CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all events and the times at which they occur.

10.1 Completion of Study

The investigational site will complete the study and complete all documentation required, in satisfactory compliance with the protocol.

It is agreed that, for reasonable cause, either the investigator or sponsor may terminate this study before completion provided written notice is submitted at a reasonable time in advance of intended termination. Any extension of this study must be mutually agreed upon in writing by both the investigator and Perrigo.

10.2 Protocol Amendments

The Investigator will not make any changes to this protocol without prior written consent from sponsor and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed between CRO and sponsor. If agreement is reached regarding the need for an amendment, the amendment will be written by sponsor. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for _administrative amendments‘, investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days. Sponsor will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

11. RECORDS MANAGEMENT

11.1 Data Collection

All data collected in this study will be entered onto case report forms (CRFs), verified by monitoring, and submitted for statistical evaluation as described below. Checks will be run on the data and queries issued as needed. Once all data is cleaned, full quality control verification will be done prior to breaking the blind. After all data are correctly entered, the database will be locked and submitted for appropriate Quality Assurance verifications before the treatment assignment code is broken. All data collected in the CRFs will be documented in subject data listings and summarized in tables, as appropriate.

During each subject's visit to the clinic, a designee participating in the study will record progress notes to document all significant observations. At a minimum, these notes will contain:

a) Documentation of the informed consent process;
b) The date of the visit and the corresponding Visit Day in the study schedule;
c) General subject status remarks, including any *significant* medical findings. The severity and duration of any adverse events and the investigator's assessment of relationship to study medication must also be recorded.
d) Any changes in concomitant medications or dosages;
e) A general reference to the procedures completed; and
f) The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the study progress notes and other source documents, will be entered in **black ink**, **initialed** and **dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

For transmission to sponsor, information from the study progress notes and other source documents will be promptly entered into the CRF/database. The database also contains a complete audit trail which will automatically generate a time-stamped audit trail including the date, time, login ID of the initial entry as well as any subsequent change, addition, or deletion of database information.

11.2 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

11.3 File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

11.4 Records Retention at the Study Site

FDA regulations require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

a) A period of at least two years following the date on which a New Drug Application is approved by the FDA;
b) A period of two years after sponsor notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from sponsor or (2) providing an opportunity for sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data correction forms (DCFs) received from CRO. Such documentation is subject to inspection by sponsor and the FDA.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

Perrigo has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of CRFs.

12.2 Auditing

Perrigo (or representative) may conduct audits at the study center(s). Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact sponsor immediately if notified of such an audit, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

13. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, any other countries regulations, and ICH GCP Guidelines.

14. USE OF INFORMATION AND PUBLICATION

All information supplied by the sponsor in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e. the clinical protocol, case report forms), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by sponsor in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of sponsor, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of sponsor, and shall not be

used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential, and will be used by sponsor in connection with the development of the drug. The information may be disclosed as deemed necessary by sponsor to allow the use of the information derived from this clinical study, the investigator is obliged to provide sponsor with complete test results and all data developed in the study. [redacted].

The investigator shall not make any publication related to this study without the express written permission of sponsor.

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-14-022

PROTOCOL TITLE: 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

I have carefully read the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____

Principal Investigator's Printed Name

_____

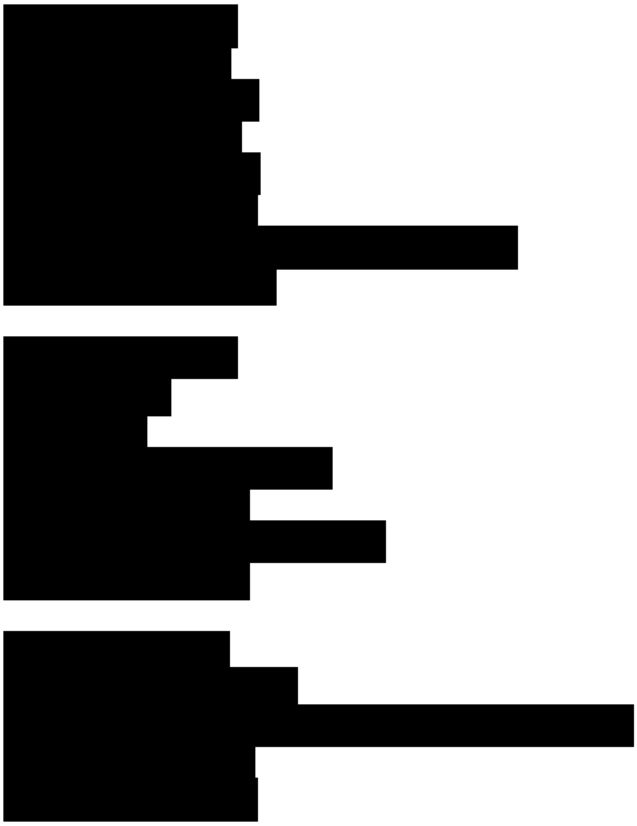
Principal Investigator's Signature

_____

Date

15. APPENDICES

15.1 Appendix A: Study Personnel Contacts



15.2 Appendix B: Instructions for the Subject

Check Visit Dispensed: Visit 1/Day 1: ☐ Unscheduled visit: ☐
Date: _____

SUBJECT INITIALS: _____ SUBJECT NUMBER: _____ SITE NUMBER: _____

[redacted]

1. [redacted]

[redacted]

[redacted]

Call your study coordinator with any questions you may have at telephone #

You are scheduled to return at:

_____on _____ (Day 15)
(Time) (Date)

ALL APPOINTMENTS ARE IMPORTANT! IF YOU NEED TO RE-SCHEDULE YOUR APPOINTMENT, PLEASE CALL YOUR DOCTOR'S OFFICE IMMEDIATELY.

_____
Name and Telephone Number of Study Coordinator/Study Site

16. REFERENCES

1. The Merck Manual - www.merckmanuals.com
2. Summary Basis of Approval Mirvaso® (Brimonidine) Topical Gel, 0.33%
3. Package insert Mirvaso® (Brimonidine) Topical Gel, 0.33% dated August-2013
4. www.mirvaso.com
5. Azelaic Acid Draft Guidance Bioequivalence recommendations: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM212602.pdf