A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Azelaic Acid Foam, 15%, to Bayer Healthcare Pharmaceutical Inc.'s, FINACEA® (AZELAIC ACID) FOAM, 15%, and Both Active Treatments to a Vehicle Control in the Treatment of Inflammatory Lesions of Rosacea

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[redacted]

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[redacted] [redacted]

PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: **PRG-NY-16-009**

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Signatures of representatives below indicate this is the agreed upon final version of the protocol:

Perrigo:

[redacted]

Signature Date

[redacted]

Signature Date

[redacted]

Signature Date

CRO:

[redacted]

Signature Date

[redacted]

Signature Date

Consultant:

[redacted]

Signature Date

[redacted] [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 Azelaic Acid Foam, 15% to Bayer HealthCare Pharmaceuticals Inc., Finacea® (Azelaic acid) Foam, 15%, and Both Active Treatments to a Vehicle Control in the Treatment of Inflammatory Lesions of Rosacea
Study Period:	12 weeks (84 Days)
Study Medication:	1. Azelaic Acid Foam, 15%, owned by Perrigo UK FINCO, manufactured by Perrigo Israel Pharmaceuticals Ltd. 2. Finacea® (Azelaic Acid Foam, 15%) manufactured by Bayer HealthCare Pharmaceuticals Inc. 3. Vehicle of test product, manufactured by Perrigo Israel Pharmaceuticals Ltd.
Study Objectives:	To compare the safety and efficacy profiles of Perrigo UK FINCO's Azelaic Acid Foam, 15%, to Bayer HealthCare Pharmaceuticals Inc., Finacea® (Azelaic Acid) Foam, 15%, in order to prove bioequivalence between them and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of Inflammatory Lesions 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 at least 18 years of age with moderate papulopustular rosacea IGA grade 3 with 12 to 50 facial inflammatory lesions (papules and pustules), at least moderate persistent erythema and presence of telangiectasia will be eligible for enrollment.
Study Population:	Approximately [redacted] healthy males and females, at least 18 years of age, who meet the inclusion/exclusion criteria, will be enrolled to obtain approximately [redacted] modified-Intent-To-Treat (mITT) and [redacted] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized in a [redacted] to either the test product, reference product or vehicle treatment group, respectively, and for a single application will apply the smallest amount of the study medication necessary to adequately cover each area of the face (chin, left cheek, right cheek, nose, forehead) [redacted] and avoiding contact with the eyes (upper and lower eyelids), lips, broken skin, inside the nose/nostrils, and mucous membranes twice daily, morning and evening, ([redacted]) approximately the same time for 12 weeks.
Study Visits:	Clinical Evaluations will be performed at: 1. Visit 1/Day 1 (Baseline) 2. Visit 2/Week 4/Day 28 (±4 days) (Interim) 3. Visit 3/Week 8/Day 56 (±4 days) (Interim) 4. Visit 4/Week 12/Day 84 (±4 days) (End of treatment/End study) Safety will be assessed by monitoring adverse events at each visit and at the Week 2/Day 14 (±4 days) Telephone Contact.

[redacted] [redacted]

Evaluations:	The number of facial inflammatory lesions (papules and pustules) will be recorded at baseline and each subsequent visit (Visits 2, 3 and 4). Erythema severity, the Investigator Global Assessment (IGA) and local irritation will be assessed at Baseline and all subsequent visits. The presence of Telangiectasia will be recorded at Baseline.
Endpoints:	The primary efficacy endpoint will be the mean percent change from baseline to Visit 4/Week 12 (Day 84) in the inflammatory (papules and pustules) lesion count. The secondary endpoint will be the proportion of subjects with clinical success defined as a score of clear or almost clear (score of 0 or 1) on the Investigator Global Assessment (IGA) at Visit 4/Week 12 (Day 84).
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Safety of the test and reference will be evaluated by comparing the nature, severity and frequency of their adverse event profiles.

ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CMH	Cochran–Mantel–Haenszel test
CRF	Case Report Form
DCF	Data Correction Form
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent- to-treat (population)
IU	International Unit
IUD	Intra-Uterine Device
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat (population)
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the counter
PI	Principal Investigator
PP	Per- protocol (population)
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPF	Sun Protection Factor
Sub-I	Sub-Investigator
UPT	Urine Pregnancy Test

1. BACKGROUND

[redacted]

Finacea® (Azelaic Acid foam, 15%) is indicated for the treatment of Inflammatory Lesions of Rosacea.[5] Perrigo UK FINCO has developed a generic formulation of Azelaic Acid foam, 15%.

2. STUDY OBJECTIVES

The objectives of this study are to compare the efficacy and safety profiles of Perrigo UK FINCO, Azelaic Acid foam, 15%, and Finacea® (Azelaic Acid foam, 15%), in order to show bioequivalence between them, and to show the superior efficacy of the two active formulations over that of the vehicle in the treatment of Inflammatory Lesions of Rosacea.

2.1 Endpoints

The primary efficacy endpoint will be the mean percent change from baseline to Week 12 (Day 84) in the inflammatory (papules and pustules) lesion count.

The secondary endpoint will be the proportion of subjects with clinical success defined as a score of clear or almost clear (score of 0 or 1) on the Investigator Global Assessment (IGA) at Visit 4/Week 12.

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

[redacted]

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, 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 in a [redacted] to test product, reference product, or vehicle, respectively. [redacted] will be applied topically as a thin layer to adequately cover each area of the face (chin, left cheek, right cheek, nose, and forehead), avoiding contact with the eyes (upper and lower eyelids), lips, broken skin, inside the nose/nostrils and mucous membranes, twice daily morning and evening ([redacted]) approximately the same time for 12 weeks.

Visits to the study site are scheduled at Baseline (Day 1) and Weeks 4, 8, and 12. A telephone contact will be made at Week 2/Day 14.

3.2 Study Population

Subjects will be males and females, at least 18 years of age, with at least moderate papulopustular facial rosacea with an inflammatory lesion (papules and pustules) [redacted], inclusive, on the face including those present on the nose, at least moderate erythema and presence of telangiectasia.

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. [redacted]
2. Subjects must be healthy males or females at least 18 years of age. Subjects must be in general good health and free from any clinically significant disease, other than rosacea, that might interfere with the study evaluations.
3. Subjects must have a definite clinical diagnosis of moderate facial papulopustular rosacea, defined as the presence of:

   a) A [redacted] inflammatory lesions (papules and pustules) including those present on the nose.

b) At least moderate persistent erythema, AND

c) Telangiectasia.

4. [redacted]
5. [redacted]
6. [redacted]
   - [redacted]
   - [redacted]

   [redacted].
7. Subjects must be willing to minimize controllable external factors that might trigger rosacea flare-ups ([redacted]) throughout their participation in the study.
8. [redacted].

4.2 Exclusion Criteria

[redacted]

Subjects may **not** be selected if any of the following criteria exist:

1. Subjects, who are pregnant, breastfeeding, or planning a pregnancy within the period of their study participation.
2. [redacted].
3. Current or past ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.
4. Subjects with isolated and/or moderate to severe rhinophyma, dense telangiectases or plaque-like facial edema.
5. Presence of any other facial skin condition that might interfere with rosacea diagnosis and/or assessment [redacted].
6. Any uncontrolled, chronic or serious disease or medical condition that would prevent participation in a clinical trial or, in judgment of the Investigator, would put the subject at undue risk or might confound the study assessments (such as planned hospitalizations during the study).
7. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
8. [redacted]
9. [redacted].
10. [redacted]
11. History of hypersensitivity or allergy to azelaic acid, and/or any ingredient in the study medication (e.g., propylene glycol).
12. Use within 6 months (180 days) prior to baseline or during the study of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
13. [redacted]
14. [redacted]
15. [redacted]
16. Use of medicated make-up ([redacted]) throughout the study and significant change in the use of consumer products within 30 days of study entry and throughout the study.

17. [redacted]
18. Use within 30 days (1 month) prior to baseline or during the study of 1) systemic steroids**, 2) topical retinoids to the face, 3) systemic (e.g., oral or injectable) antibiotics known to impact on the severity of facial rosacea (e.g., cyclines and its derivatives, tetracycline and its derivatives, erythromycin and its derivatives, doxycycline and its derivatives, minocycline and its derivatives, macrolides and its derivatives, azithromycin and its derivatives, clarithromycin and its derivatives, metronidazole and its derivatives, sulfamethoxadole, bactrim or trimethoprim); short term treatment of all other antibiotics (not affecting rosacea for) ≤ 14 days for non-rosacea related conditions is acceptable, 4) immunosuppressive agents, or immunomodulators.
    - [redacted]
    - [redacted]
    - [redacted].
    - [redacted]
19. [redacted]
20. [redacted]
21. [redacted].
22. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements and/or have drug or alcohol addiction requiring treatment in the past 12 months.
23. [redacted]
24. [redacted]
25. Participation in *any clinical study involving an investigational product, agent or device* that might influence the intended effects or mask the side effects of study medication in the 1 month (30 days) prior Visit 1/Day 1 (Baseline) or throughout the study.
26. [redacted]

27. [redacted]
28. [redacted]
29. [redacted]
30. [redacted].
31. Subjects who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.

4.3 Prohibited Medications

The following medications/procedures are prohibited during this study:

1. Use of any treatment for rosacea other than the assigned study treatment.
2. [redacted].
   - [redacted].
3. Use of systemic anti-rosacea drugs, systemic retinoids, systemic corticosteroids, or immunosuppressive drugs or immunomodulators, therapeutic vitamin A supplements of greater than 10,000 units/day are prohibited during this study.
4. [redacted]
   - [redacted] d.
   - [redacted].
   - [redacted]
5. Use of systemic antibiotics (e.g., oral or injectable) known to impact on the severity of rosacea including, but not limited to, cyclines and its derivatives, tetracycline and its derivatives, erythromycin and its derivatives, doxycline and its derivatives, minocycline and its derivative, macrolides and its derivatives, azithromycin and its derivatives, clarithromycin and its derivatives, metronizadole and its derivatives, sulfamethoxadole, bactrim and trimethoprim are prohibited during this study. Short term treatment of all other antibiotics ≤ 14 days for non-rosacea related conditions is acceptable.
6. Use of topical antibiotics, other rosacea drugs, retinoids or corticosteroids applied to the face are prohibited during this study.
7. Use of oral retinoids is prohibited during the study.
8. Application of topical astringents or abrasives e.g., rubs, exfoliating cleansers and products [redacted]

containing Salicylic acid and/or alcohol based toners, astringents; topical preparations that contain spices or lime, or medicated topical preparations (prescription and OTC products) to the face.

9. Use of abrasive cleansers or washes (e.g., exfoliating facial scrubs) and adhesive cleansing strips (e.g., Bioré® Pore Strips) on the face.
10. [redacted]
11. [redacted]
12. Use of tanning booths, sun lamps, sauna, sunbathing or other excessive exposure to sunlight should be avoided.
13. Medicines and/or products that may increase sensitivity to sunlight (apart from the study medication) should be used during this study only after consultation with the Investigator.
14. Use of hormonal contraceptives should not be initiated or changed during the study.

4.4 Precautions

The following precautions are to be taken during this study:

1. Subjects should avoid contact of the study medication with the eyes (upper and lower eyelids), inside their nose/nostrils, mucous membranes and lips, or on any cuts or broken skin. In case of accidental exposure, the eyes should be rinsed with plenty of water and a physician should be consulted if eye irritation persists.
2. Avoid fire, flame, or smoking during and immediately following application of the study medication since the propellant in the study medication is flammable.
3. The aerosol canister should not be punctured or incinerated.
4. The product should not be applied to cuts, abrasions, eczematous or sunburned skin, or sites other than the treatment area.
5. Subjects should wash their hands before and immediately after applying study medication.
6. [redacted] s.
7. [redacted]
8. The study medication should be spread smoothly and [redacted] on the face (forehead, chin, and nose, left and right cheek); excessive rubbing must be avoided.
9. The study medication should not be applied more than twice daily and subjects should not use more than the recommended amount on the entire face ([redacted]).

[redacted]

10. [redacted].
11. Subjects should not apply moisturizers ([redacted]), medicated make-up (including new brands), creams, lotions, powders or any topical product other than the study medication to the face.
12. [redacted]
13. Subjects should limit sun exposure, including sunlamps (non-prescription UV light sources); avoid tanning beds/booths/parlors and sauna while using the product.
14. Subject should use any type of sunscreen and protective apparel (e.g., wide-brimmed hat) when outdoors. Weather extremes, such as wind or cold, may be irritating to subjects receiving treatment.
15. [redacted].
16. [redacted]
17. [redacted].
18. Subjects should consult the investigator with any questions regarding concomitant medications.
19. [redacted]
20. [redacted].
21. [redacted].
22. Subject should avoid any foods and beverages that might provoke erythema, flushing, and blushing [redacted] throughout the study.

5. PROCEDURES

5.1 Subject Screening and Enrollment

The study personnel will review the IRB approved informed consent form with each subject and give the subject an opportunity to have all questions answered before proceeding. The consent form must be signed by each subject and witnessed before the subject is enrolled into the study. The witness can be anyone present during the signing of the consent form other than the individual explaining the consent. A copy of the signed consent will be given to every participant (or legally authorized representative) and the original will be maintained with the participant's records.

[redacted]

5.2 Assignment of Subject Number

[redacted] [redacted]

[redacted] The subject number will correspond to a computer-generated randomization schedule assigning the number to one of the three study treatment groups.

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 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 in the [redacted] prior to signing informed consent 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 starting study medication. A record of medication taken by the subject during the study is to be obtained at each study visit including the Week 2/Day 14 (±4 days) telephone contact.

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 on Baseline/Day 1. [redacted]

5.6 Urine Pregnancy Test

A urine pregnancy test will be conducted at Visit 1/Baseline (before the subject applies the first dose of the study medication at the site) and at each subsequent visit. An investigator may repeat the pregnancy test anytime during the study if there is any suspicion or possibility that the subject may be pregnant. [redacted]

[redacted]

5.7 Dermatological Assessment (Diagnosis)

The Investigator or sub-investigator will examine the subject to establish the clinical diagnosis of papulopustular facial rosacea [redacted].

5.8 Investigator's Global Assessment (IGA)

To the greatest extent possible, the same investigator who made baseline (Day 1) assessments will perform a Global Assessment of the subject's overall rosacea condition at each subsequent visit.

At Visit 1/Baseline (Day 1), the investigator should perform the IGA before the subject applies the first dose of the study medication at the site.

[redacted].

The following scale will be used for the Investigator's Global Assessment:

Grade	Category	Description
0	Clear	Clear skin with no inflammatory lesions (papules or pustules) or nodules; at most, mild erythema.
1	Almost Clear	Very few small papules or pustules. Very mild erythema present.
2	Mild Severity	Several small papules or pustules. Mild erythema
3	Moderate Severity	Several small or large papules or pustules, and up to 2 nodules. Moderate erythema.
4	Severe	Numerous small and/or large papules or pustules, up to several nodules. Severe erythema.

5.9 Evaluation of Treatment Area

The investigator should evaluate the treatment area before a subject applies the first dose of study medication. Each subject's initial condition and course of rosacea will be assessed by the following: 1) counting the inflammatory (papules and pustules) and nodules including those present on the nose and documenting on the facial diagram ([redacted] as part of the source documentation, 2) rating the severity of erythema, 3) presence/absence of telangiectasia (evaluated at Visit 1/Baseline only), and 4) evaluation of the application site reaction. [redacted]

[redacted]

[redacted]

5.9.1 Inflammatory Lesion Count (Papules and Pustules)

The numbers of inflammatory lesions (facial papules and pustules) and nodules, located above the jaw line to the hairline including those present on the nose, are to be counted at baseline (before the subject applies the first dose of the study medication at the site) and at each subsequent visit. The type and number of each lesion is to be recorded on the source document at each visit and the total count of papules and pustules recorded (excluding nodules).

Papule = solid palpable inflammatory lesion ≤ 5mm diameter

Pustule = pus-filled inflammatory lesion ≤ 5mm in diameter

Nodule = palpable solid or soft lesion > 5mm in diameter

Counts of nodules should be reported separately and not included in inflammatory lesion counts. Subjects with more than 2 facial nodules at baseline should be excluded from the study.

5.9.2 Erythema Severity Assessment

At Visit 1/Baseline (Day 1), the investigator should perform the erythema assessment before the subject applies the first dose of the study medication at the site.

The severity of erythema is to be rated as follows:

SCORE	ASSESSMENT	DESCRIPTION
0	None	No redness present
1	Mild	Slight pinkness to light red
2	Moderate	Definite redness, easily recognized
3	Severe	Marked erythema; fiery red

5.9.3 Telangiectasia Evaluation

The presence or absence of telangiectasia is to be evaluated at Visit 1/Baseline **only prior to first study dose medication application.**

5.10 Application Site Reaction Assessment

At Visit 1/Baseline (Day 1) and each subsequent visit, application site reactions such as dryness, burning/stinging, pruritus and scaling/peeling, and pain are to be recorded on the source document.

[redacted]

At Visit 1/Baseline (Day 1), the investigator should perform the application site reaction assessment before and [redacted] after the subject applies the first dose of the study medication at the site.

The Application Site Reaction Assessment must be conducted by qualified investigators listed on the Form FDA 1572 who have been delegated these tasks by the PI. [redacted].

[redacted]

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

[redacted]

The investigator will assess a subject's application site reaction by rating the following symptoms according to the scales provided below. Pruritus and stinging/burning symptoms will be assessed by discussion with the subject and will be reported as the severity experienced within 24 hours of the study visit.

Dryness: Mild scaling, roughness, feeling of tightness, and possibly itching

SCORE	ASSESSMENT	DESCRIPTION
0	None	[redacted]
1	Mild	[redacted]
2	Moderate	[redacted]
3	Severe	[redacted]

Scaling/Peeling: Skin desquamation; shedding of the outer layers of the skin

SCORE	ASSESSMENT	DESCRIPTION
0	None	[redacted]
1	Mild	[redacted]
2	Moderate	[redacted]
3	Severe	[redacted]

Pruritus: Itching

SCORE	ASSESSMENT	DESCRIPTION
0	None	[redacted]

[redacted]

1	Mild	[redacted]
2	Moderate	
3	Severe	

Stinging/Burning: Stinging/tingling sensation

SCORE	ASSESSMENT	DESCRIPTION
0	None	[redacted]
1	Mild	
2	Moderate	
3	Severe	

Pain: Pain, unpleasant sensation causing discomfort such as tingling, pricking (pins and needles) and/or tenderness

SCORE	ASSESSMENT	DESCRIPTION
0	None	[redacted]
1	Mild	
2	Moderate	
3	Severe	

5.11 Study Medication Use, Subject Instructions and Diary

At the baseline visit, one (1), [redacted] aerosol canister of study medication from the subject kit box will be dispensed, by the third party dispenser (if possible) or designee, to enrolled subjects along with a diary card. Each subject will also receive a copy of written instructions, which detail the proper application method, and general instructions regarding the study ([redacted]). At Visit 1/Baseline/Day 1, the third party dispenser (if possible) or designee should ensure that all subjects met eligibility criteria and all efficacies (IGA, Erythema, Telangiectasia) and safety (application site reactions) assessments are conducted by the investigator before the subjects perform the initial application. The initial application on Day 1 will be performed by the subject and observed by study staff at the study site during the study visit to ensure subjects understand the instructions and are applying the medication appropriately. [redacted] The pump of the aerosol canister should be depressed gently to dispense the smallest amount of the foam necessary to cover each facial area (chin, left cheek, right cheek, nose, and forehead) for each single application. The propellant in the study medication is flammable. Therefore, fire, flame or smoking during and immediately following the application of the study medication should be avoided. [redacted]. Subsequent applications of study medication should be applied as [redacted]

instructed by the subject at home morning and evening ( ). The study staff should instruct the subject to apply all subsequent doses of the study medication twice daily, morning and evening before bedtime. Subjects will apply the second dose of the medication in the evening on Day 1 if first dose was applied in the morning on Day 1 or in the morning of Day 2 if first dose was applied in the afternoon/evening on Day 1. At all subsequent study visits the study medication will be collected to assess compliance and study medication accountability. After the compliance evaluation, empty aerosol canister will be collected and kept by the site. Aerosol canisters with remaining medication will be redispensed to the subject. . The study medication kits must be stored (in an upright position) in a secured area with limited access, at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) until dispensed to the subject. Once dispensed to the subject the study medication will be stored in an upright position at 25°C (77°F).

Subjects will cleanse their face with a mild cleanser using only their hands and pat dry with a soft clean towel. . For a single application, the "smallest" amount of the study medication necessary will be applied to adequately cover each area of the face (chin, left cheek, right cheek, nose, forehead) and avoiding contact with the eyes (upper and lower eyelids), lips, broken skin, inside the nose/nostril and mucous membranes, twice daily in the morning and evening ( ), at approximately the same time for 12 weeks. ( ) Subjects should be instructed to wash hands immediately after applying the study medication. Subjects should continue to use a mild cleanser to wash the face for the duration of the study. Subjects will be instructed to not use any other topical treatments or products (any type of sunscreen is allowed) other than the study medication on their face.

A diary card will be dispensed to each enrolled subject at Visits 1, 2 & 3. The subjects will be instructed to complete the diary card after applying each dose of study medication in the morning and evening daily. At each subsequent visit, study personnel will review and collect the diary card, determine whether the subject requires counseling for dosage compliance, confirm and record use of any prohibited medications, assess AEs, dispense additional study medication and a new diary as required. In addition, each study subject will be reminded to bring with them all previously dispensed aerosol canisters (regardless of content) and the completed diary card at the next visit. Study personnel will schedule the subject's next visit prior to the subject's departure.

5.12 Visit Specific Procedures

The following sections outline the procedures required at each visit.

5.12.1 Baseline Visit 1/ Day 1

Prospective subjects will visit the study center and be examined by the study physician who will perform the procedures below at this visit.

The following procedures: Informed Consent, Inclusion/Exclusion Criteria, Medical History/Demographics, collection and review of Concomitant medications, Physical exam, Vital signs, dermatological assessment (diagnosis), evaluation of the treatment area, IGA, erythema assessment, evaluation telangiectasia and Urine pregnancy test must be completed and documented on the source document before a subject is randomized on the study.

[redacted]

- [redacted]

5.12.2 Telephone Contact/Week 2/Day 14 (± 4 days)

- [redacted]

5.12.3 Visit 2/Week 4/Day 28 (± 4 days)

- [redacted]

[redacted]

- [redacted]

5.12.4 Visit 3/Week 8/Day 56 (± 4 days)

- [redacted]

5.12.5 Visit 4/Week 12/Day 84 (± 4 days) End of Treatment/Early Termination Visit

- [redacted]

5.12.6 Unscheduled Visit

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. 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, an Early Termination Visit conducted, and a standard of care

treatment may be advised at the investigator's discretion. The [redacted]

- [redacted]

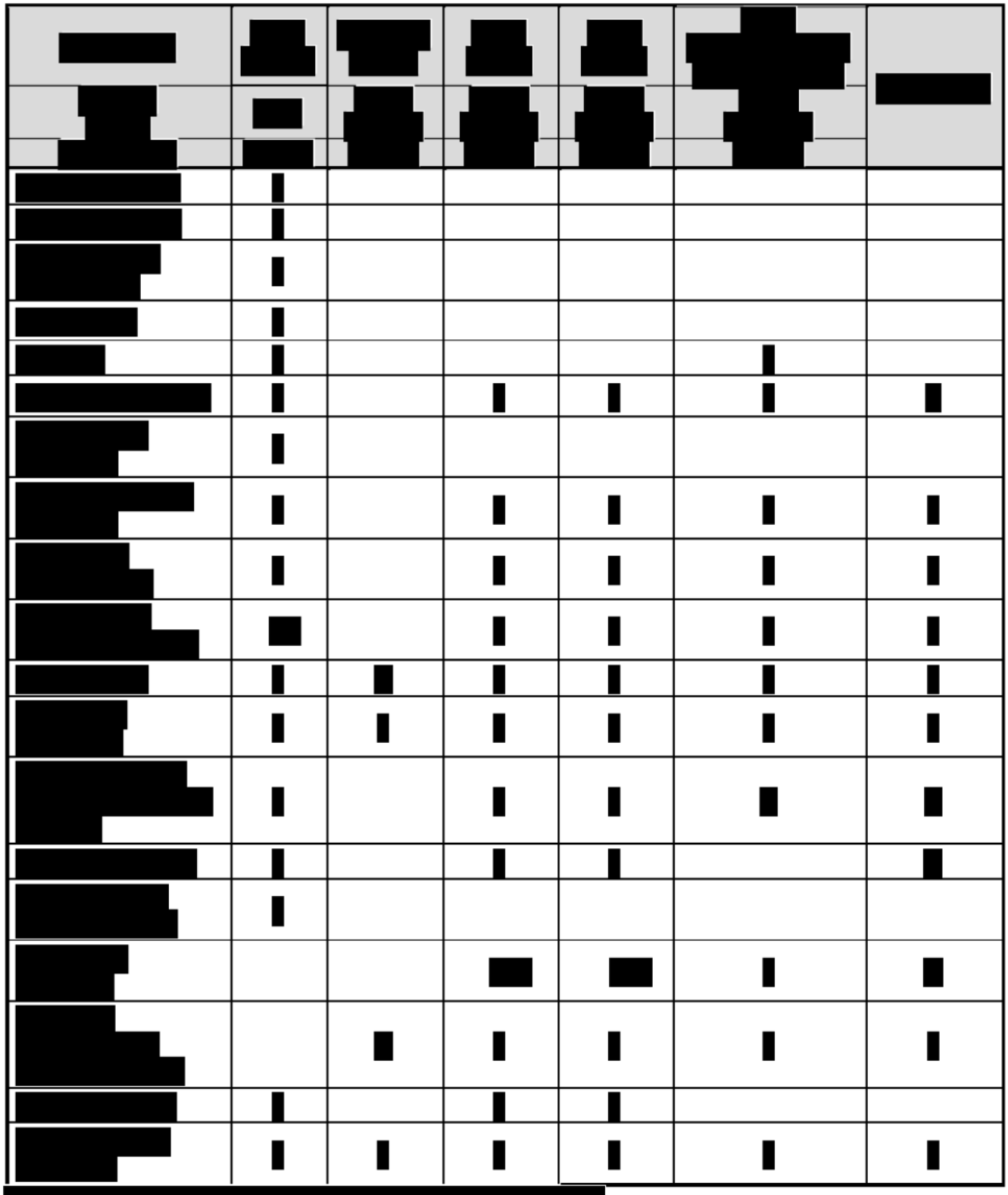
5.13 Summary of Assessments

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

Visit 1/Baseline/Day 1

The following procedures: Informed Consent, Inclusion/Exclusion Criteria, Medical History /Demographics, collection and review of Concomitant medications, Physical exam, Vital signs, dermatological assessment (diagnosis), evaluation of the treatment area, IGA, erythema assessment, evaluation telangiectasia and Urine pregnancy test must be completed and documented on the source document before a subject is randomized on the study.

The safety (application sites reactions) assessments must be completed prior to and [redacted] after the first study medication application.



[e]Study medication to be collected and/ or dispensed, if necessary
[f]UPT to be conducted at Unscheduled Visit, if applicable
** Application sites reactions must be completed prior to and approximately thirty (30) minutes after the first study medication application
*** Once the aerosol canister is opened and used at least once, it expires 8 weeks later

5.14 Screen Failures

Screen failures will not be entered in the database nor included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent, and possibly performing some study related procedures, but was not enrolled, dispensed and applied the investigational product.

5.15 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 Perrigo / [redacted] contacts in Section 15 (Appendix A) at the earliest possible time.

[redacted]

[redacted].

5.16 Subject/Treatment Compliance

Subjects will apply the smallest amount of the study medication on each area of the face (chin, left cheek, right cheek, nose, and forehead) in the morning and evening ([redacted]) twice daily for 12 weeks. On Day 1, subjects will apply their initial dose of study medication at the study site [redacted]. On Week 2/ Day 14 (±4 days), compliance will be assessed via telephone contact. The study coordinator, or designee, will review the Subject Instruction Sheet and Diary with the subject on the phone. The total number of study medication doses applied and/or missed will be determined based upon the first dose applied through and including the last dose applied. The first and last dates

of treatment should be recorded on the CRF. The total number of study medication doses applied and missed should also be recorded. By definition, there are no missed applications before the first date of treatment or after the last date of treatment. [redacted] All used and unused aerosol canisters of study medication will be collected by the study site at appropriate visits or early termination.

5.17 Discontinuation/Withdrawal of Study Subjects

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

- The subject withdraws his or her consent for any reason.
- The subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study or requires an alternative therapy.
- The subject's medication code is unblinded.
- Subject did not meet, or no longer meets, the entry criteria.
- An adverse event, including intercurrent illness, occurs for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued.
- The subject is lost to follow-up. The investigator 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.
- The subject becomes pregnant during the course of the trial.
- Lack of efficacy (treatment failure) after 1 month (30 days) of treatment with a compliance rate of [redacted] (investigator removal from study).
- Investigator discretion (e.g., non-compliant to study protocol requirements).

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

The reason(s) for a subject being discontinued from the study will be documented in the CRF and the enrollment log.

If a subject is discontinued from the study for any reason, the Visit 4 (Day 84)/ 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 Source Document and End of Study CRF.

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.

[redacted]

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo will consist of:

Test Product: Azelaic Acid Foam, 15%,
Perrigo [redacted]

Reference Product: Finacea® (Azelaic acid foam, 15%) Manufactured by Bayer HealthCare Pharmaceuticals Inc.

Vehicle: Vehicle of test product
([redacted].)

6.2 Medication Management

6.2. 1 Labeling, Packaging and Distribution

The study medication assigned to each subject number will be determined by a computer-generated randomization schedule. Study medication is labeled and packaged, according to the randomization code, so that neither the subject nor the investigator can identify the treatment.

[redacted]

The tear-off portion of each kit label contains the identity of the medication in the aerosol canister. The investigator will not remove the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency and preferably with prior authorization from Perrigo or designee, whenever possible. If the occluded portion of the label is removed, each involved subject(s) will be discontinued from the study and the reason will be noted on the source document and CRFs.

[redacted]

The tear-off portion has an adhesive backing to affix to the study medication dispensing log that will be maintained at the investigator site.

[redacted]

The investigator performing the clinical evaluations will not dispense or collect study medication.

6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select one block ([redacted]) of study medication to be maintained as retain 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 (at room temperature, 25°C (77°F); excursions permitted between 15°C to 30°C (59°F and 86°F) even after the study has concluded. 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 or was used." The investigator will store the retained sample study medication until such time of notification is received from Perrigo that the samples are no longer required.

6.2.3 Storage and Test Article Accountability

Study medication used to conduct this study will be maintained under adequate security by the investigator or designee. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The study medication should not be frozen, exposed to heat, or stored at temperatures above 120°F (49°C). The study medication should be stored at room temperature in a secured area with limited access, 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) and aerosol canisters kept in an upright position and tightly closed. The investigator or designee will instruct subjects to store the study medication in a secure area at room temperature at 25°C (77°F), out of reach of children, aerosol canisters are not to be exposed to heat or temperature above 120°F (49°C), punctured or incinerated. The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The clinic personnel at each investigator site will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each aerosol canister of study medication is dispensed and returned. 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 aerosol canisters must be inventoried by the monitor and returned to Perrigo, or designee, for destruction, with the exception of retention samples which shall remain at the Investigator site.

6.2.4 Randomization

Randomization will be performed according to a computer generated randomization scheme where the treatment group designation has been assigned to the subject number. The treatment designation will remain blinded until the final database is locked. An independent third party will hold the randomization code throughout the study. The randomization scheme will be a block randomization, with each block [redacted].

6.2.5 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 for each subject at each investigator site, 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 Azelaic Acid Foam, 15 % are anticipated to be similar to those observed in Finacea® (Azelaic Acid) Foam, 15%.

The following adverse reactions occurred in greater than 0.5% of patients treated with Azelaic Acid Foam, 15%, application site pain (6.2%), described as burning, stinging, “pins and needles”, and/or tenderness , application site erythema (0.7%), application site dryness (0.7%), and application site pruritus (2.5%).

Isolated reports of loss of skin color (hypopigmentation) have been reported following topical use of Finacea®. Finacea® has not been well studied in patients with dark complexion. Therefore, subjects with darker complexion should be monitored closely for early signs of loss of skin color by the investigators and instructed to report immediately any abnormal changes in skin color to the investigators. When significant hypopigmentation are reported by subjects, study medication should be discontinued.

Azelaic acid has been reported to cause irritation of the eyes and mucous membrane irritation. Contact with the study product should be avoided on the eyes, mouth and other mucous membranes and if

there is contact with the eyes, large amounts of water should be used to wash the eyes and subjects should be instructed to consult a physician if eye irritation persists.

Hypersensitivity, rash and worsening of asthma have been reported in post-marketing use of products containing Azelaic acid-containing formulations.

7.1 Departure from the Protocol for Individual Subjects

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or Perrigo by telephone and follow up with a written description as soon as possible. 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 canister therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with 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.

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.

[redacted] [redacted]

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 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. [redacted] 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 [redacted]

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 the source document and recorded in a timely manner on case report forms (CRFs). Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE CRF with the status of the AE noted.

Adverse event reporting begins from the signing of informed consent. 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, the sponsor 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 Perrigo. The adverse event term on the AE CRF 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, event(s) 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 the sponsor 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 the sponsor 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 by telephone 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

[redacted] [redacted]

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 the sponsor 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] Medical Monitor for review. [redacted] will finalize the report and distribute it to the sponsor within 1 (one) day 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 the sponsor 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.

7.4 SAE & AEs Requiring Discontinuation of Study Drug, 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 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 drug will be discontinued from the study.

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

[redacted]

[redacted]

7.4.1 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/or 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 Symbio, 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 the trial is completed before the outcome of the pregnancy is known, [redacted] will assume the responsibility for following up on the pregnancy. [redacted] will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms and fax to [redacted] within 1 day of being notified.

7.5 Post Study Adverse Events

7.5.1 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 CRF with the status of the AE noted.

7.5.2 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 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 associated with the use of the study drug, should be reported to Perrigo.

8. STATISTICAL ANALYSIS

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 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. The SAP will be completed and finalized prior to breaking the blind.

8.1 Statistical Analysis Plan

8.1.1 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject that 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,
  - Who was randomized and received and used study medication,
  - Who met the protocol criteria for compliance [redacted] and
  - Who completed Visit 4/Week 12/Day 84 (End of Treatment/Early Termination Visit) within window OR was discontinued from the study due to treatment failure.
  - Without significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[redacted]

8.1.2 Planned Analysis

All randomized subjects who received/used study medication will be evaluated for safety. The efficacy analysis will be conducted on both the PP and the mITT subject populations. Two-sided hypothesis testing will be conducted. Resulting p-values less than 0.05 will be considered statistically significant. 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 treatment response will be summarized by treatment group for the end-of-treatment evaluation.

The primary efficacy endpoint will be the mean percent change from baseline to Visit 4/Week 12 (Day 84) in the inflammatory (papules and pustules) lesion count.

The secondary endpoint will be the proportion of subjects with clinical success defined as a score of clear or almost clear (score of 0 or 1) on the Investigator Global Assessment (IGA) at Visit 4/Week 12 (Day 84).

[redacted]

8.1.3 Sample Size Considerations

[redacted]

[redacted]

.

8.1.4 Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy measure will be the mean percent change from baseline to Visit 4/Week 12 (Day 84) in the inflammatory (papules and pustules) lesion counts. The secondary efficacy measure will be the proportion of subjects with clinical success defined as a score of clear or almost clear (score of 0 or 1) on the Investigator Global Assessment (IGA) at Visit 4/Week 12 (Day 84).

Equivalent efficacy

For the mean percent change from baseline in the inflammatory lesion count, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the Test-to-Reference ratio of means, calculated by Fieller's Method, falls within the interval 0.80 to 1.25. The treatment means and estimate of residual variance for the confidence interval calculation will come from an Analysis of Variance of the Test and Reference results using a statistical model containing terms for Treatment and Site.

For the proportion of subjects with clinical success, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the difference between Test and the Reference proportions is contained within the interval –20% to +20%. The confidence interval will be constructed using Wald's method with Yates' continuity correction.

Therapeutic equivalence evaluations in the per-protocol (PP) population will be considered definitive and those in the mITT will be considered supportive.

[redacted] [redacted]

Superiority

For the mean percent change from baseline in the inflammatory lesion count, each active treatment will be evaluated to determine if it has superior efficacy to that of the Vehicle at Visit 4/Week 12 (Day 84) via an Analysis of Variance using Proc Mixed of SAS with Treatment and Site as factors.

The proportion of subjects with clinical success for each active treatment will be compared to that of the Vehicle using Z-test with Yate's continuity correction.

Superiority tests will be two-sided at a significance level of $\alpha = 0.05$. Superiority analyses in the mITT population will be considered definitive and those in the PP will be considered supportive

8.1.5 Safety and Adverse Events Analysis

The frequency and percent of subjects with adverse events will be summarized by MedDRA system organ class and preferred term and by severity and relationship to study drug for all three treatment groups. [redacted] 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.

8.2 Comparability of Subjects at Baseline

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group differences will be discussed in the CSR.

9. CONSENT 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. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). 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 form, which shall be approved by the same Institutional Review Board (IRB) responsible for approval of this protocol. Each informed consent 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 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 form shall be signed by the subject (or their parent/legally authorized representative) and the person obtaining consent (investigator or designee). The subject shall be given a copy of the signed informed consent 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 form must be signed.

9.1 Subject Confidentiality

All 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 Perrigo, it is required that the investigator permit the study monitor, any Perrigo 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 Perrigo 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, Perrigo 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.

[redacted] [redacted]

9. 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, within 3.5 months of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

It is agreed that, for reasonable cause, either the investigator or Perrigo 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 Perrigo 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 [redacted] and Perrigo. If agreement is reached regarding the need for an amendment, the amendment will be written by Perrigo. 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. Perrigo will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or Perrigo, 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

CRFs for individual subjects will be provided [redacted]. CRFs must be legible and complete. CRFs for this study will be maintained in a study binder and data recorded on 2-part NCR paper. One copy will be kept by the investigator and the other copy will be submitted to the CRO data management group. All forms should be completed using a black ballpoint pen. Errors should be lined out, but not obliterated, and the correction inserted, initialed, and dated by designated study personnel. Further

data corrections will be performed on data correction forms (DCFs) that will be provided by the CRO to the investigator in case of erroneous or unclear data. The investigator will make the correction on the DCF and sign the DCF. The signed DCF will be submitted to the CRO data management group for processing and a copy retained with the CRFs.

A CRF must be completed and signed by the investigator for each subject enrolled, including those discontinued from the study for any reason. The reason for discontinuation must be noted on a subject's study termination form.

CRFs must be kept current to reflect the subject's status at each phase during the course of the study. Subjects are not to be identified on CRFs by name; appropriately coded identification and the subject's initials must be used. The investigator must keep a separate log of the subject's names and addresses.

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 or Week in the study schedule;
c) General subject status remarks, including any significant medical findings. The severity, frequency, 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 Perrigo, information from the study progress notes and other source documents will be promptly entered into the database. The database also contains a complete audit trail to capture all regulatory components of data correction (e.g., initial entry, new value, initials and date of the change).

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

[redacted] [redacted]

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 21 CFR §312.57 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 Perrigo 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 Perrigo or (2) providing an opportunity for Perrigo 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. Such documentation is subject to inspection by Perrigo 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 CRFs 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 Perrigo 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 Perrigo 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, CRFs), 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 Perrigo 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 Perrigo, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of Perrigo, 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 Perrigo in connection with the development of the drug. The information may be disclosed as deemed necessary by Perrigo to allow the use of the information derived from this clinical study, the investigator is obliged to provide Perrigo with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of Perrigo. [redacted]

[redacted]

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: **PRG-NY-16-009**

[redacted]

PROTOCOL TITLE:

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Azelaic Acid Foam, 15% to Bayer HealthCare Pharmaceuticals Inc., Finacea® (Azelaic acid) Foam, 15%, and Both Active Treatments to a Vehicle Control in the Treatment of Inflammatory Lesions 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: ☐ Visit 2: ☐ Visit 3: ☐ Unscheduled visit: ☐ Date: _____

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

1. [redacted]

[redacted]

3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5. [redacted]

[redacted]

6. [redacted]

[redacted]

9. [redacted]

17. [redacted]

[redacted]

29. [redacted]

[redacted]

Your call is scheduled for: _____ (Week 2)
(Date)

You are scheduled to return at:

_____on _____ (Visit 2, Study Week 4)
(Time) (Date)

_____on _____ (Visit 3, Study Week 8)
(Time) (Date)

_____on _____ (Visit 4, Study Week 12)
(Time) (Date)

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

_____
Name and Telephone Number of Study Coordinator/Study Site

[redacted] [redacted]

15.3 APPENDIX C: [redacted]

[redacted]

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

[redacted]

16. REFERENCES

1. Cohen A.F, Tiemstra J.D: Disease and Treatment of Rosacea. Journal of American Board of Family Practice. May-June 2002 Vol 15. No 3: 214- 217
2. Zuber TJ. Rosacea. Dermatology. Prim Care 2000; 27:309 -18
3. Kligman AM. Ocular Rosacea. Current Concepts and Therapy. Arc Dermatol 1997; 133:89-90.
4. https://www.aad.org/dermatology-a-to-z/diseases-and-treatments
5. Packages insert Finacea® Foam 15% (Azelaic Acid, Foam 15%) dated July 20154.
6. www.finacea.com
7. OGD Draft Guidance on Metronizadole Cream 0.75%; Mar 2010 and Azelaic Acid Gel; May 2010 and Revised Sep 2012
8. Finacea® Foam. https://www.drugs.com/pro/finacea-foam.html.