Clinical Study Protocol with Amendment 01

A Multicenter, Double-blind, Randomized, Parallel-group, Vehicle-Controlled Study to Evaluate the Safety and Clinical Equivalence of a Generic Azelaic Acid Foam, 15% and the Reference Listed Finacea® (Azelaic acid) Foam, 15% in Patients with Moderate Facial Rosacea

Study Number ACTA AZEL 2015

NCT03287791

Protocol with Amendment 01 Approval Date: 28 March 2016

1 TITLE PAGE

Title	A Multicenter, Double-blind, Randomized, Parallel-group, Vehicle-Controlled Study to Evaluate the Safety and Clinical Equivalence of a Generic Azelaic Acid Foam, 15% and the Reference Listed Finacea® (Azelaic acid) Foam, 15% in Patients with Moderate Facial Rosacea
Protocol No.	ACTA/AZEL/2015
Sponsor	Actavis Morris Corporate Center III 400 Interpace Parkway Parsippany, NJ 07054 [redacted]
Protocol Version	Amendment 1
Date of This FINAL Version of the Protocol Amendment 1	03-28-2016

2 AMENDMENTS

Page Number	Current Protocol	Amended Protocol	Reason for Amendment
19	11.3.3 Exclusion Criteria 7d. The use within 1 month prior to baseline of systemic corticosteroids (Note: intranasal and inhalational corticosteroids do not require a washout and maybe used throughout the trial if the patient is on a stable dose).	11.3.3 Exclusion Criteria 7d. The use within 1 month prior to baseline of systemic corticosteroids.	To include a washout period of 1 month for all systemic corticosteroids and to maintain consistency with prohibited medications regarding corticosteroids in section 11.3.1 Prohibited medications/treatment.
20	11.3.4 Patient Discontinuation Criteria (No reference to missed visits)	11.3.4 Patient Discontinuation Criteria 7. If the subject misses more than 1 required visit;	To allow for 1 missed visit (either visit 2 or visit 3) by the subjects.
29	11.7.2 Visit 2/(Day 28 ± 4 days) The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion. A new diary will be issued.	11.7.2 Visit 2/(Day 28 ± 4 days) The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion.	The diaries consist of perforated, tear-off pages for each week. At each post-baseline visit, the completed pages will be teared off and filed with the subjects' charts. The diary with blank pages for the rest of the weeks will be returned to the subject.
29	11.7.2 Visit 3/(Day 56 ± 4 days) 7. The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion. A new diary will be issued.	11.7.2 Visit 3/(Day 56 ± 4 days) The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion.	The diaries consist of perforated, tear-off pages for each week. At each post-baseline visit, the completed pages will be teared off and filed with the subjects' charts. The diary with blank pages for the rest of the weeks will be returned to the subject.

3 CLINICAL STUDY PROTOCOL APPROVAL

PROTOCOL NUMBER: ACTA/AZEL/2015

STUDY TITLE: A Multicenter, Double-blind, Randomized, Parallel-group, Vehicle-Controlled Study to Evaluate the Safety and Clinical Equivalence of a Generic Azelaic Acid Foam, 15% and the Reference Listed Finacea® (azelaic acid) Foam, 15% in Patients with Moderate Facial Rosacea

Sponsor Representative [redacted]	Signature:	Date:
Statistical Consultant [redacted]	Signature:	Date:
CRO Representative [redacted]	Signature:	Date:
Medical Monitor [redacted]	Signature:	Date:

4 CONTACT LIST

Sponsor:
Actavis
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054
[redacted]

Contract Research Organization:
[redacted]

Medical Monitor:
[redacted]

Statistics and Data Management:
[redacted]

5 PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand 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 Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety and welfare, of patients under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide copies of the protocol and all other study-related information supplied by the Sponsor 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 patient information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations.

I will not enroll any patients into this protocol until FDA approval (if required by regulation), IRB approval and Sponsor approval are obtained.

Principal Investigator	**Signature**	**Date**

6 TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	Adverse Event
ANOVA	Analysis of Variance
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGE	Investigator's Global Evaluation
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
IU	International Units
IUD	Intrauterine Device
kg	Kilogram
LOCF	Last-Observation-Carried-Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-the-counter
PP	Per-Protocol
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SPF	Sun Protection Factor

8 SYNOPSIS

Protocol number:	
Title of Study:	A Multicenter, Double-blind, Randomized, Parallel-group, Vehicle-Controlled Study to Evaluate the Safety and Clinical Equivalence of a Generic Azelaic Acid Foam, 15% and the Reference Listed Finacea® (azelaic acid) Foam, 15% in Patients with Moderate Facial Rosacea
Sponsor:	Actavis Laboratories UT
Test Product: **Reference Product:** **Vehicle:**	Azelaic Acid, 15% topical foam (Actavis Laboratories UT) Finacea® (Azelaic acid) Foam, 15% (Bayer HealthCare) Foam Vehicle of the test product (Actavis Laboratories UT)
Objectives:	To compare the safety and efficacy profiles of a generic Azelaic Acid Foam, 15% to the reference listed Finacea® (azelaic acid) Foam, 15% and to demonstrate therapeutic equivalence and safety of the two active foams in the treatment of moderate facial rosacea, and to demonstrate superiority of the reference and test products over the vehicle.
Study Design:	This is a randomized, vehicle-controlled, parallel-group, multicenter, double-blind study of Azelaic Acid Foam, 15% and the reference listed Finacea® (azelaic acid) Foam, 15% in patients with moderate facial rosacea.
Number of Study Centers:	Approximately 26 centers
Duration of Patient Participation:	Each patient will participate in the study for approximately 12 weeks from the time the patient signs the Informed Consent Form (ICF) through date of the final contact with the subject. The study treatment period will last for 84 days (12 weeks).
Key Inclusion Criteria:	Healthy male and non-pregnant female patients aged ≥ 18 years with a diagnosis of moderate facial rosacea will be selected to participate in the study. Moderate facial rosacea is defined as the presence of at least eight and not more than fifty inflammatory facial lesions (i.e. papules/ pustules) and the presence of persistent erythema and telangiectasia.
Dosage and Administration:	Randomized patients will apply the foam to the entire facial area (cheeks, chin, forehead, and nose) twice daily for 12 weeks.
Number of Patients:	Up to 1010 patients will be enrolled in the study to randomize 924 patients to obtain at least 840 mITT patients in a 1:1:1 ratio (280:280:280 patients, respectively) to each treatment group and 672 (224:224:224) evaluable subjects in PP population: • Azelaic Acid, 15% topical foam (Actavis Laboratories UT) • Finacea® (azelaic acid) Foam, 15% (Bayer HealthCare) • Foam Vehicle of the test product (Actavis Laboratories UT)

Clinical Evaluations will be performed at:

Visit 1: Baseline Visit (Day 0);
Visit 2: (Day 28 ± 4 Days);
Visit 3: (Day 56 ± 4 Days);
Visit 4: End of Treatment (Day 84 ± 4 Days).
Early Discontinuation Visit: Same Evaluations as End of Treatment Visit

Criteria for Evaluation:

Primary Endpoint:

Percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts.

Secondary Endpoint:

The Investigator's Global Evaluation outcome at Week 12, expressed as "success" or "failure" A patient is considered to have success if the IGE score is either 0 (clear) or 1 (almost clear), and is considered to have a failure, otherwise.

Measures:

1. Lesion Counts will be performed using the following definitions:

Lesion Name	Lesion Definition
Papule	Inflammatory lesion; small (≤ 5mm in diameter), solid palpable lesion, usually with inflamed elevation of the skin that does not contain pus.
Pustule	Inflammatory lesion; small (≤ 5mm in diameter), inflamed skin swelling that is filled with pus.
Nodule	Large, hard bumps under the skin's surface.

All facial papules, pustules and nodules, located above the jaw line to the hairline, will be counted, including those present on the nose. Counts of nodules will be reported separately and not included in the inflammatory lesion counts.

2. The IGE will be performed and documented using the definitions in table below:

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema.
1	Almost Clear	Very mild erythema present. Very few small papules/pustules.

2	Mild	Mild erythema. Several small papules/pustules.
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules.
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

3. Application site reactions such as erythema, dryness, scaling, pruritus, stinging/burning, and edema, will be recorded at each visit to allow a comparison between treatment groups.

Data Sets to be Analyzed:

Three patient populations are defined as follows:

1. The Safety Population includes any patient who was randomized in the study and had at least one dose of Investigational product.
2. The Modified Intent-to-Treat (mITT) Population includes all randomized patients who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit with lesion count.
3. The Per-Protocol (PP) Population includes all randomized patients who met all inclusion/exclusion criteria, were compliant with the assigned study treatment (who applied 75% to 125% of the scheduled applications), returned to the study site for the primary endpoint visit (12 week evaluation) within +/- 4 days OR discontinued from the study as a treatment failure and did not have any protocol violations.
4. Patients who are discontinued early from the study due to lack of treatment effect after completing at least eight weeks of treatment will be included in the mITT and PP population as treatment failures (i.e., non-responders) and the change in inflammatory lesion count from the baseline visit to the last completed visit prior to discontinuation due to lack of efficacy will be carried forward in the primary endpoint analysis. In addition, patients whose condition worsens after completing at least eight weeks of treatment and require alternate or supplemental therapy for the treatment of facial rosacea during the study will be discontinued, included in the PP population analysis, and provided with effective treatment. A last observation carried forward (LOCF) approach will be used for imputing missing efficacy results in these PP patients and they will be considered as failures in the IGE evaluations.

Patients discontinued prematurely for other reasons will be excluded from the PP population, but included in the mITT population, for which missing efficacy data will be imputed using LOCF.

For the purpose of determining the per-protocol status of the patient, a "protocol violation" is any patient or investigator activity that could have

	possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy. Efficacy analyses will be performed on the mITT and per-protocol populations. All efficacy data will be listed by treatment and patient in data listings.
Statistical Methods:	**<u>Analysis of Primary Endpoint</u>** The percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts is the primary endpoint for the study. A LOCF approach will be used for imputation of missing efficacy results, where appropriate. **Demonstration of Bioequivalence** A two-way ANOVA on the test and reference results for the primary endpoint will be conducted using a statistical model containing terms for treatment and site. Bioequivalence for the primary endpoint will be established if the 90% confidence interval for the test/reference ratio of the mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts is contained within [0.80, 1.25], using the PP population. Non-parametric methods will be used if the skewness factor for the residuals from the ANOVA model are outside the range -2 to +2. **Demonstration of Superiority** To ensure that the study is sensitive enough, the test product and reference listed drug (RLD) will each be compared to the vehicle group to demonstrate their statistical superiority at $p<0.05$ (two sided) for the primary endpoint, using the mITT study population. This evaluation will be performed using separate two-way ANOVA of Test vs. Vehicle and Reference vs. Vehicle, with the statistical model containing terms for treatment and site. Non-parametric methods will be used if the skewness factor for the residuals from the ANOVA model are outside the range -2 to +2. **Analysis of Secondary Endpoint** The dichotomized Investigator's Global Evaluation (IGE) will be treated as a secondary endpoint for supportive evidence. This secondary endpoint will be evaluated as the proportion of patients with a clinical response of "success" at Week 12. Success is defined as an either IGE score 0 (clear) or 1 (almost clear) at the final visit. Any patient who is not considered a success will be considered to be a failure. A LOCF approach will be used for imputation of missing efficacy results, where appropriate. **Demonstration of Bioequivalence** Bioequivalence for the secondary endpoint will be established if the 90% continuity-corrected confidence interval for the difference in clinical

success proportions between the test and reference product is contained within the interval [-0.20, +0.20] for the PP population.

Demonstration of Superiority

Superiority of the efficacy of the test treatment over that of the vehicle will be demonstrated if the test success proportion is greater than, and statistically different from ($p<0.05$) that of the vehicle by two-sided Fisher's exact test. The superiority of the efficacy of the reference treatment over that of the vehicle will be demonstrated in an identical manner.

Analysis of application site reactions

A descriptive analysis comparing the application site reactions for each treatment group will be conducted to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

Safety Analyses

Safety analyses will be conducted on the safety population. Incidence of all adverse events reported during the study will be coded using the MedDRA dictionary and summarized by treatment group, body system, severity, preferred term, and relationship to study drug. In addition, an evaluation will be conducted of the comparability of the test and reference treatments in regard to any treatment emergent adverse events that occur in 5%, or more, of the patients in either test or reference treatment group.

The report of AEs will include date of onset, description of the AE, and date of resolution.

Concomitant medication

The start and stop date of concomitant medication use during the study will be provided in the data listings in addition to the reason for the medication use.

Demographics and Baseline/Randomization Characteristics

Demographic and baseline/randomization characteristics will be compared for the mITT, PP, and Safety populations. Continuous variables will be analyzed with an analysis of variance with factors of treatment and investigational site. Categorical variables such as gender, ethnicity, and race will be analyzed with a Cochran-Mantel-Haenszel test, stratified by investigational site.

Summary of patients who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

9 INTRODUCTION AND BACKGROUND

Rosacea is a chronic disorder characterized by vascular dilation (persistent erythema) of the nose, cheeks and forehead which most commonly occurs in patients between the ages of 30 and 60 years-of-age. The vascular dilation cause is unknown but has been linked with hair follicle mites, Demodex folliculorum and D. brevis, as well as Helicobacter pylori infection. However, after successful treatment (wherein rosacea symptoms were improved) with tetracycline or metronidazole, respectively, actual numbers of the organisms were not found to be reduced. The earliest stage of rosacea is characterized by facial erythema, often primarily on the nose and cheeks, recurrent episodes of flushing, and telangiectasia. The erythema is usually worsened by exposure to sun or heat, or ingestion of trigger foods or beverages. Inflammatory lesions develop in the areas of erythema and appear similar to the inflammatory lesions of acne vulgaris, but present without comedones. The diagnosis of rosacea is based on the presence of one or more of the following: flushing, nontransient erythema, papules/pustules, or telangiectasia.

Topical azelaic acid is used to treat inflammatory papules and pustules of mild to moderate rosacea. Other topical therapies and oral antibiotics are also used to treat rosacea symptoms.

FINACEA® (azelaic acid) FOAM, 15% contains azelaic acid, a naturally occurring saturated dicarboxylic acid that has proven anti-inflammatory effects, as well as anti-keratinizing and antimicrobial action, although its mechanism of action in rosacea is not well understood. This study will be conducted in compliance with the protocol, Good Clinical Practices (GCP) and the applicable regulatory requirement(s). Marketed by Bayer HealthCare, Finacea® (azelaic acid) Foam, 15% is a safe and effective topical therapy used for the treatment of moderate facial rosacea. Actavis Laboratories UT has developed a generic formulation of azelaic acid 15% foam and the current study is designed to evaluate the safety and efficacy of this formulation.

10 STUDY OBJECTIVES

The objectives of this study are to evaluate the therapeutic equivalence and safety of a generic Azelaic Acid Foam, 15% and Finacea® (Azelaic acid) Foam, 15% in the treatment of moderate facial rosacea, and to demonstrate superiority of the efficacy of the two active foams over the vehicle control.

11 INVESTIGATIONAL AND ANALYSIS PLAN

11.1 Overall Study Design

This is a randomized, vehicle-controlled, parallel-group, multicenter, double-blind study of a generic Azelaic Acid Foam, 15% and the reference listed Finacea® (Azelaic acid) Foam, 15% in patients with moderate facial rosacea.

11.2 Study Overview

Up to 1010 patients will be enrolled in the study to randomize 924 patients to obtain at least 840 mITT patients in a 1:1:1 ratio (280:280:280 patients, respectively) to each treatment group and 672 (224:224:224) evaluable subjects in PP population. Patients will be assigned in a 1:1:1 ratio to treatment with the test product, Azelaic Acid Foam, 15% (Actavis Laboratories UT),

the reference product, Finacea® (Azelaic acid) Foam, 15% (Bayer HealthCare) or the vehicle control (Actavis Laboratories UT) in this multicenter, double-blind, randomized, vehicle-controlled, parallel-group study.

The assigned Investigational Product will be self-applied topically to the entire facial area (cheeks, chin, forehead, and nose) twice daily for 84 consecutive days. The Investigational Product should be gently massaged into the affected areas on the face twice daily, in the morning and evening after the patient's face has been washed with a mild cleanser and patted dry with a soft towel. Patients will be required to use diaries to document study treatments, any missed treatments and the occurrence of all adverse events.

The duration of each patient's participation in the study will be 84 days. Scheduled study visits will include: Visit 1 (Baseline Visit, Day 0), Visit 2 (Day 28±4 days), Visit 3 (Day 56±4 days) and Visit 4 (End of Treatment, Day 84±4 days). A window ± 4 days will be considered acceptable for each scheduled visit following the baseline visit.

If the Principal Investigator determines that the patient's condition has worsened to the degree that it is unsafe for the patient to continue in the study, the patient may be discontinued from the study as a treatment failure and the patient may be treated using the standard care.

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a patient is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 4 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the patient will continue to take part in the study), then the activities performed will depend on the reason for the unscheduled visit and will be left to the discretion of the Investigator. The Investigator should perform any activities necessary to appropriately evaluate the patient at this Unscheduled Visit. If the Unscheduled Visit is due to an AE, the Investigator will determine whether additional visits are needed.

At Visit 1, an informed consent will be obtained from the potential study patient before any study procedures take place. After the patient has been consented, the patient's medical history will then be documented, including the patient's concomitant medications. A urine pregnancy test will be performed for all female patients of child-bearing potential. A baseline facial rosacea grade will be assigned to the patient using the Investigator's Global Evaluation (IGE) and a baseline lesion count will be performed. The patient will undergo a physical examination, including the recording of vital signs. The patient will be evaluated for signs and/or symptoms of erythema and telangiectasia. The patient will be reviewed against the inclusion/exclusion criteria. Blinded Investigational Product will be dispensed to patients who meet all of the inclusion and exclusion criteria. Patients will be instructed on the application of Investigational Product and completion of patient diaries.

Patients will return to the study site for Visit 2, Visit 3 and Visit 4. The patient's concomitant medications will be reviewed and documented. A urine pregnancy test will be performed for female patients of child-bearing potential. The patient's facial rosacea will be assessed using the IGE, the patient's lesions will be counted and all results will be documented. The signs and/or symptoms of local irritation will be evaluated for the patient and any other adverse events will be documented. The patient will bring their used Investigational Product and their study diaries to each study visit after the baseline visit. Compliance with drug applications will be assessed at each visit after the baseline visit. New can(s) of Investigational Product

will be dispensed during Visit 2 and Visit 3. In addition, all Investigational Product and diaries will be collected from the patient during each scheduled visit or the Early Discontinuation Visit.

11.3 Study Population

11.3.1 Number of patients

This multicenter study will be comprised of patients presenting with a clinical diagnosis of moderate facial rosacea and who meet all of the inclusion, and none of the exclusion, criteria. Up to 1010 patients will be enrolled in the study to randomize 924 patients to obtain at least 840 mITT patients in a 1:1:1 ratio (280:280:280 patients, respectively) to each treatment group and 672 (224:224:224) evaluable subjects in PP population.

11.3.2 Inclusion Criteria

Each patient **must** meet all of the following criteria:

1. Patient must be willing and able to provide written informed consent for the study.
2. Healthy male or non-pregnant female ≥18 years-of-age with a clinical diagnosis of moderate facial rosacea.
3. Patient must have at least eight and not more than fifty inflammatory facial lesions (i.e., papules/pustules) and ≤2 nodules on the face. For the purposes of study treatment and evaluation, these lesions should be limited to the facial treatment area including those present on the nose. Lesions involving the eyes, and scalp should be excluded from the count.
4. Patients must have persistent erythema on the face with moderate (3) score as per the table below:

Score	Grade	Definition
0	None	No redness present.
1	Very Mild	Slight pinkness.
2	Mild	Pink to light red.
3	Moderate	Definite redness, easily recognized.
4	Severe	Marked erythema; fiery red.

5. Patients must have a mild (1) to moderate (2) score for telangiectasia on the face as per the table below:

Score	Grade	Definition
0	Clear	No telangiectasia.
1	Mild	Only few fine vessels discernible, involves 10% or less of the facial area.
2	Moderate	Multiple fine vessels and/or few large vessels discernible, involves > 10% - 30% of the facial area.
3	Severe	Many fine vessels and/or large vessels discernable, involves > 30% of the facial area.

6. Patients must have a definite clinical diagnosis of moderate facial rosacea (severity score 3) as per the IGE as per table below:

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema.
1	Almost Clear	Very mild erythema present. Very few small papules/pustules.
2	Mild	Mild erythema. Several small papules/pustules.
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules.
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

7. Patient must be willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages) during the course of the study.
8. Patient must be in general good health and free from any clinically significant disease other than rosacea on the face, that might interfere with the study evaluations.
9. Patient must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, return for the required treatment period visits, comply with therapy prohibitions, and be able to complete the study.
10. Male patients and female patients of childbearing potential must use accepted methods of birth control or must agree to practice abstinence, from study start to 30 days after the last administration of study drug. All female patients are considered to be of childbearing potential unless they have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or have been postmenopausal for at least a year. Any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Norplant®), vaginal ring (NuvaRing®), Depo-Provera® (Medroxy progesterone acetate), double barrier methods (e.g., condom and spermicide), Essure or IUD.
11. Female patients of child bearing potential must have a negative urine pregnancy test at baseline.
12. Patients who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to use the same make-up, brand/type, or frequency of use, throughout the study.

11.3.3 Exclusion Criteria

Patients may **not** be enrolled if any of the following criteria exist:

1. Pregnant or lactating or planning to become pregnant during the study period.
2. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.
3. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.

4. History of hypersensitivity or allergy to Azelaic acid, propylene glycol or any other component of the formulation.
5. The use within 6 months prior to baseline of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
6. The use of estrogens or oral contraceptives for less than 3 months prior to baseline.
7. The use within 1 month prior to baseline of:
   a) topical retinoids to the face;
   b) systemic antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim);
   c) systemic corticosteroids
8. Use within 2 weeks prior to baseline of:
   a. topical corticosteroids;
   b. topical antibiotics;
   c. topical medications for rosacea (e.g., metronidazole, azelaic acid).
9. Antipruritics, including antihistamines, within 24 hours of any study visit.
10. Patients with moderate or severe rhinophyma, dense telangiectasia (score 3, severe), or plaque-like facial edema.
11. Patients with a severe irritation grade for erythema, dryness, scaling, pruritus, stinging/burning, and edema.
12. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.
13. A patient who has used a sauna during the 2 weeks prior to study entry and during the study.
14. Patients who have performed wax epilation of the face within 14 days prior to baseline
15. A patient who has a history of being unresponsive to topical Azelaic acid therapy.
16. A patient with bacterial folliculitis.
17. A patient who consumes excessive alcohol, abuses licit or illicit drugs, or has a condition that could compromise the patient's ability to comply with study requirements.
18. Patients who engage in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.
19. A patient who has any clinically significant condition or situation, other than the condition being studied that, in the opinion of the Investigator, would interfere with the study evaluations or optimal participation in the study.
20. A patient who has used any topical Azelaic acid therapy within 30 days of baseline visit.
21. Patients who have participated in an investigational drug study (i.e., patients have been treated with an Investigational Drug) within 30 days prior to baseline will be excluded from study participation. Patients who are participating in non-treatment studies such as

observational studies or registry studies can be considered for inclusion.

22. Patients who have been previously randomized in this study.
23. Patients who have had laser therapy (for telangiectasia or other conditions), electrodessication and phototherapy (e.g., ClearLight®) to the facial area within 180 days prior to study entry.
24. Patients who have had cosmetic procedures (e.g., facials) which may affect the efficacy and safety profile of the Investigational Product within 14 days prior to study entry.
25. Employees or staff of the research site are excluded from participation in the study.
26. No more than one (1) person from the same household can participate in the study.

11.3.4 Patient Discontinuation Criteria

Investigators are urged to enroll only those eligible patients who are likely to complete the entire study and who are willing to comply with the protocol-specified procedures. It is the right and duty of the investigator to interrupt the treatment of any patient whose safety and well-being are determined to be at risk, or who may be experiencing unmanageable factors that may interfere with the study procedures and/or the interpretation of study results. Such patients should be withdrawn from the study rather than continued under a modified regimen.

Discontinuation is permanent; once a patient is discontinued, he/she shall not be allowed to enroll again.

A patient may be discontinued from the study for any of the following reasons:

1. Patient decision/withdrawal of consent;
2. Adverse event, including intercurrent illness, which required study discontinuation;
3. If the patient's condition has worsened to the degree that the Principal Investigator feels it is unsafe for the patient to continue in the study;
4. If the patient's drug code is unblinded;
5. Insufficient therapeutic response (after at least 8 weeks of compliant treatment);
6. If a patient misses more than 6 consecutive doses;
7. If the subject misses more than 1 required visit;
8. Significant protocol violation;
9. If the patient is lost to follow-up;
10. If the patient becomes pregnant;
11. If the patient becomes a prisoner or becomes involuntarily incarcerated;
12. Any other reason that may affect the outcome of the study or the safety of patients; or
13. Termination of the study by the Sponsor.

A patient that discontinues from the study will not be replaced.

A significant protocol violation is defined as any patient or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

The reasons for a patient discontinuation will be documented. If a patient is discontinued from the study for any reason, the procedures scheduled for Visit 4 will be completed and any outstanding data and study drug should be collected, if possible. Information, in addition to the reason for discontinuation and the date of removal, will be documented on the Electronic Case Report Form (eCRF).

Before a patient is considered to be lost to follow-up, the Principal Investigator will attempt to reach the patient twice by telephone and will send a certified follow-up letter and document all these activities. In the event that a patient 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 patient, the Principal Investigator must strive to follow the patient until the adverse event has resolved, becomes clinically insignificant, is stabilized or the patient is lost to follow-up. Should a serious adverse event be noted, procedures stated in Section 10.9.5 must be followed.

11.3.5 Prohibited Medications / Treatments

The following are prohibited during this study. If any of the following prohibited activities occur during the course of the study, the Investigator must consult with the Sponsor and determine if the patient should be disqualified from further study participation.

1. Any other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids); Patients are allowed to use other topical treatments on other areas of the body.
2. Oral retinoids;
3. Systemic (e.g., oral or injectable) antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives);
4. Systemic corticosteroid (including intranasal or inhaled corticosteroids) or immunosuppressive drugs;
5. Antipruritics, including antihistamines, within 24 hours of study visits;
6. The use of any treatment for rosacea, other than the assigned study treatment;
7. The application of new cosmetics or new cleansers to the face is prohibited during this study, other than the cleanser, moisturizer, and sunscreen provided by the Sponsor. Patients who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to not change make-up brand/type or frequency of use throughout the study;
8. The application of alcohol based toners, astringents, medicated topical preparations (prescription and OTC products) or medicated make-up to the face;
9. The use of abrasive cleansers or washes (e.g., exfoliating facial scrubs) on the face;
10. The use of adhesive cleansing strips (e.g., Bioré® Pore Strips) on the face;
11. The use of anti-inflammatory medications (e.g., NSAIDs) and vitamins in quantities above the recommended daily dose (e.g., Vitamin A above about 10,000 IU; NSAID use allowed

on as needed basis for conditions such as headache, menstrual cramps, and minor injuries; Low dose aspirin is also allowed);

12. Patients may use acetaminophen for pain relief, as needed, while taking part in this study;
13. Cosmetic procedures (e.g., facials) which can affect the efficacy and safety profile;
14. Patients are prohibited from use of saunas or PUVA therapy while participating in the study;
15. Use of tanning booths, sunbathing, or excessive exposure to the sun;
16. Wax epilation should not be performed on skin treated with the Investigational Product.

11.3.6 Precautions

The following precautions are to be taken during this study:

1. Patients should avoid any foods or beverages that provoke erythema, flushing/blushing (e.g., spicy foods, alcoholic beverages, and thermally hot drinks, including hot coffee and tea);
2. Patients should avoid contact of the study medication with the mouth, eyes, and other mucous membranes; The hands should be washed following application;
3. Patients should limit all sun exposure to the extent possible; Patients should use sunscreen when outdoors and avoid tanning beds;
4. To minimize exposure to sunlight, a wide-brimmed hat or other protective clothing should be worn;
5. The non-comedogenic sunscreen with a SPF 15 rating or higher provided by the Sponsor may be used;
6. Patients should avoid exposure to weather extremes including strong wind or cold;
7. Patients should not apply any moisturizers (other than the provided moisturizer), new brands of make-up, creams, lotions, powders or any topical product other than the study medication to the treatment area;
8. Cosmetics should be applied only after the application of IP has dried;
9. Occlusive dressings or wrappings should be avoided in treatment areas;
10. Patients must not wear make-up to any study visits to avoid interference with the evaluations;
11. The Investigational Product should not be applied to cuts, abrasions or eczematous skin;
12. Patients should report abnormal changes in skin color to the Principal Investigator.

If a reaction suggesting sensitivity or chemical irritation occurs, the Principal Investigator should assess the patient's condition as soon as possible (i.e., during an Unscheduled Visit) and determine whether treatment should be discontinued. If the patient is discontinued from the study during an Unscheduled Visit, procedures from Visit 4 should be followed and the visit will be referred to as an Early Discontinuation Visit.

There have been isolated reports of hypopigmentation after use of Azelaic acid. Since Azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

11.4 Study Schedule

This study will require 4 "scheduled" patient visits:

Visit 1: Baseline Visit (Day 0);
Visit 2: Day 28 ± 4 Days;
Visit 3: Day 56 ± 4 Days;
Visit 4: End of Treatment (Day 84 ± 4 Days).

11.5 Assessment of Safety and Tolerability

11.5.1 Physical Examination

A physical examination including heart, lung and abdomen evaluation as well as height, weight, and vital signs will be performed.

Vital signs are to include sitting blood pressure, oral temperature, heart rate and respiratory rate. Vital signs will be measured after the patient has rested in a seated position for at least 5 minutes.

11.5.2 Urine Pregnancy Test

All female patients of child-bearing potential will undergo a urine pregnancy test during Visit 1 and at each subsequent study visit.

All female patients of childbearing potential must use accepted methods of birth control or must agree to practice abstinence, from study start to 30 days after the last administration of study drug. All female patients are considered to be of childbearing potential unless they have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or have been postmenopausal for at least a year. Any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Norplant®), vaginal ring (NuvaRing®), Depo-Provera® (Medroxy progesterone acetate), double barrier methods (e.g., condom and spermicide), Essure or IUD.

11.5.3 Medical History

A complete medical history will be obtained for the patient's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity, heart attack, stroke, congestive heart failure, kidney disease, auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

11.5.4 Record Concomitant Medications

Concomitant medications, including the use of sunscreen and the moisturizer, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A record of concomitant medications taken by the patient is to be obtained using 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 a regular basis, including aspirin and acetaminophen, should be recorded.

11.5.5 Telangiectasia Assessment

The severity of telangiectasia is to be rated at baseline as follows. Patients must have a mild (1) to moderate (2) score for telangiectasia on the face at the baseline visit to be enrolled in the study. Patients with severe (3) score for telangiectasia will not be enrolled in the study.

Talangiectasia:

Score	Grade	Description
0	None	No telangiectasia
1	Mild	Only few fine vessels discernible, involves 10% or less of the facial area.
2	Moderate	Multiple fine vessels and/or few large vessels discernible, involves > 10% - 30% of the facial area.
3	Severe	Many fine vessels and/or large vessels discernable, involves > 30% of the facial area.

11.5.6 Irritation/Application Site Reactions

The severity of Irritation/Application site reactions such as erythema, dryness, scaling, pruritus, stinging/burning, and edema will be rated at each visit to allow a comparison between treatment groups. These are some of the expected application site reactions.
Patients with a severe irritation grade at baseline will not be enrolled in the study.
After baseline, increase in irritation will be reported as an adverse event.

Erythema:

Score	Grade	Definition
0	None	No redness present.
1	Very Mild	Slight pinkness.
2	Mild	Pink to light red.
3	Moderate	Definite redness, easily recognized.
4	Severe	Marked erythema; fiery red.

Dryness:

Score	Grade	Definition
0	None	No dryness.
1	Mild	Slight but definite dryness.
2	Moderate	Moderate dryness.
3	Severe	Marked dryness.

Scaling:

Score	Grade	Definition
0	None	No scaling.
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing.
2	Moderate	Obvious but not profuse scaling.
3	Severe	Heavy scale production.

Pruritus:

Score	Grade	Definition
0	None	No itching.
1	Mild	Slight itching but not bothersome.
2	Moderate	Definite itching, somewhat bothersome without loss of sleep.
3	Severe	Intense itching that has caused pronounced discomfort; interrupted sleep and excoriation of the skin may be present.

Stinging/Burning:

Score	Grade	Definition
0	None	No stinging/burning.
1	Mild	Slight warm stinging/burning sensation but not bothersome.
2	Moderate	Definite warm stinging/burning sensation somewhat bothersome.
3	Severe	Hot stinging/burning sensation that has caused definite discomfort.

Edema:

Score	Grade	Definition
0	None	No swelling.
1	Mild	Slightly or barely perceptible swelling.
2	Moderate	Distinct presence of swelling.
3	Severe	Marked or intense swelling.

Local irritation reactions in the treatment area are common and the Investigator may instruct patients to stop the application of treatment ("rest period") to reduce patient discomfort and to allow local skin reactions to subside based upon the Investigator's clinical assessment. Treatment should resume as soon as the reaction subsides sufficiently to allow reapplication. If significant discomfort continues, or if the patient cannot return to daily applications after missing more than six consecutive doses the patient should be discontinued from the study. Multiple rest periods during the study are allowed, but they should only be used when absolutely necessary based upon the patient's tolerability needs as determined by the Investigator. The patient should not modify or resume the treatment regimen without consultation with the Investigator. The Investigator may make this decision based upon a

documented phone consultation or at an unscheduled visit. All dose modifications will be captured in the source documents.

The treatment period should not be extended beyond 12 weeks due to missed doses or rest periods. Patients whose condition worsens or lesions that do not respond to treatment should be re-evaluated by the Investigator and treatment management reconsidered.

11.5.7 Adverse Events

An adverse event is defined as any untoward medical occurrence (sign, symptom or laboratory finding) regardless of severity and whether or not attributed to the Investigational Product. All adverse events, whether observed by an Investigator or Study Coordinator or reported by the patient, whether related to study drug or not related to study drug, shall be documented in the eCRF and patient records. Details such as date of onset, the duration and intensity of each episode, the action taken, the relationship to the Investigational Product, and the degree of severity, the seriousness, and the outcome should be recorded.

11.6 Clinical Assessments

An examination of the patient's face

will be performed at baseline and at each subsequent visit. During the dermatologic examination, evaluations to determine efficacy of treatment will be conducted, including lesion counts and grading of the patient's facial rosacea using the criteria outlined in the IGE.

Whenever possible, a single Investigator (i.e., Principal Investigator or Sub-Investigator) will perform evaluations of efficacy (i.e., lesion counts and IGE) for each patient at each visit from the beginning to the end of the patient's participation to maintain consistency. However, up to two Investigators may perform evaluations of efficacy for a single patient if necessary. All Investigators who will perform evaluations of efficacy must attend study-specific training for the conduct of these evaluations (i.e., lesion counts and IGE).

11.6.1 Inflammatory Lesion Count

All facial papules, pustules and nodules, located above the jaw line and extending to the hairline, are to be counted at Visit 1/Baseline and at each subsequent visit. When counting facial lesions, it is important that all lesions be counted, including those present on the nose. The total count for each lesion type is to be recorded and the total number of inflammatory lesions (papules and pustules) will be calculated. A papule with a pustule on its apex will be counted as a pustule.

A patient must have at least eight and not more than fifty inflammatory facial lesions (i.e., papules/pustules) and $\leq$2 nodules on the face to be eligible for the study. Counts of nodules and cysts will be reported separately and not included in the inflammatory counts.

Inflammatory lesion types:

Lesion Name	Lesion Definition
Papule	Inflammatory lesion; small (≤ 5mm in diameter), solid palpable lesion, usually with inflamed elevation of the skin that does not contain pus.
Pustule	Inflammatory lesion; small (≤ 5mm in diameter), inflamed skin swelling that is filled with pus.
Nodule	Large (>5 mm in diameter), hard bumps under the skin's surface.

For optimal visualization, the Investigator, or other qualified lesion counter, should use the same light source, either fluorescent or natural light, in approximately the same position during each count. To avoid counting sub-clinical lesions, the skin should not be stretched and magnification should not be used during this assessment.

11.6.2 Investigator's Global Evaluation (IGE)

For each patient at each visit, the Investigator will make an independent clinical evaluation of the patient's rosacea severity. For study enrollment, the patient must have an IGE rosacea severity score of 3 at Visit 1/Baseline.

IGE:

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema.
1	Almost Clear	Very mild erythema present. Very few small papules/pustules.
2	Mild	Mild erythema. Several small papules/pustules.
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules.
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

11.7 Study Procedures

A study flow chart can be found in Appendix I, outlining visit procedures.

11.7.1 Visit 1/Baseline/Day 0

The prospective patients will visit the study center and be examined by the study physician. If the patient is screened and not randomized to study drug on the same day (e.g. due to the required washout of a prohibited medication), the Visit 1/Day 0 procedures should be re-confirmed on the day the patient returns prior to being randomized to study medication. The following procedures will be performed at the Baseline Visit:

1. The study personnel will review the ICF with each patient and give the patient an opportunity to have all questions answered before proceeding. A copy of the signed consent will be given to every patient and the original will be maintained with the patient's records.

2. A medical history and demographic information will be obtained by the Investigator or qualified designee prior to starting study medication. The medical history will include a complete review of all past and current diseases and their respective durations and treatments. It will also include the date of original onset of rosacea
3. A record of prior medications taken by the patient within at least the last 6 months of signing the Informed Consent is to be obtained using 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 a regular basis, including aspirin and acetaminophen, should be recorded.
4. A physical examination including heart, lung and abdomen evaluation as well as height, weight, and vital signs will be performed. Vital signs are to include sitting blood pressure, oral temperature, heart rate and respiratory rate.
5. A urine pregnancy test will be conducted for all females of child-bearing potential.
6. All facial papules, pustules and nodules, located above the jaw line and extending to the hairline, will be counted (see Section 10.6.1).
7. The overall status of the patient's facial rosacea will be assessed using the IGE (see Section 10.6.2).
8. Telangiectasia assessment will be performed (see Section 10.5.5).
9. Patients will be evaluated for any signs and/or symptoms of facial irritation (see Section 10.5.6).
10. When the patient has completed all screening procedures, compliance with the inclusion and exclusion criteria will be reviewed. After the inclusion and exclusion criteria have been confirmed, the patient will be randomized to a treatment group. The patient will be assigned a randomization number (see Section 10.8.3).
11. The following will be dispensed during Visit 1:

    - One can of the Investigational Product
    - A diary card to record product use from Visit 1 to Visit 2
    - One bottle of cleanser
    - One bottle of sunscreen
    - One bottle of moisturizing lotion
    - One pack of towels

    Depending upon the severity of facial irritation and to prevent the side effects, the Investigator may instruct the patient to use a non-medicated moisturizer.
12. Randomized patients will be instructed on the correct method for the application of the Investigational Product. Investigational Product will not be applied during the patient's clinic visit and must be applied at home. The Investigational Product can be applied the night of Visit 1 or the day following Visit 1. The Investigational product must not be opened at the clinic. The day the patient begins dosing will be captured as Day 1.
13. The study restrictions will be reviewed with the patient.

14. Randomized patients will be provided with a diary and instructed on how and when to complete the diary. They will be told that they are to document all treatments administered, and all treatments missed. In addition, patients will be instructed to document all AEs. Patients will also be instructed to call the study site if they experience any severe intolerability (i.e., local skin reactions) to Investigational Product.
15. Visit 2 (Day 28 ± 4 days) will be scheduled and the patient will be instructed to bring all Investigational Product (used, unused and partially used) and the patient diary with him or her to this visit.

11.7.2 Visit 2/ (Day 28±4 days)

The following procedures will be performed at Visit 2:

1. A urine pregnancy test will be conducted for all females of child-bearing potential.
2. All facial papules, pustules and nodules, located above the jaw line and extending to the hairline will be counted (see Section 10.6.1).
3. The overall status of the patient's facial rosacea will be assessed using the IGE (see Section 10.6.2).
4. Patients will be evaluated for any signs and/or symptoms of facial irritation (see Section 10.5.6).
5. The occurrence of all AEs will be assessed and documented following procedures in Section 10.9.
6. The use of concomitant medications since the previous study visit will be documented for each patient. The use of moisturizer, including the type and how often it has been used, will also be documented. (see Section 10.5.4).
7. The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion.
8. Study drug compliance will be performed and the patient's used Investigational Product will be returned to the site.
9. The following will be dispensed during Visit 2:
    - One can of the Investigational Product
    - Diary will be returned to patient

    Depending upon the severity of the side effects, the Investigator may instruct the patient to use a non-medicated moisturizer. Additional supplies will be dispensed if required.
10. Study instructions will be reviewed with the patient, including the procedure for application of the Investigational Product.
11. Visit 3 (Day 56 ± 4 days) will be scheduled and the patient will be instructed to bring all Investigational Product (used, unused and partially used) and the patient diary with him or her to this visit.

11.7.3 Visit 3/ (Day 56±4 days)

The following procedures will be performed at Visit 3:

1. A urine pregnancy test will be conducted for all females of child-bearing potential.
2. All facial papules, pustules and nodules, located above the jaw line and extending to the hairline will be counted (see Section 10.6.1).
3. The overall status of the patient's facial rosacea will be assessed using the IGE (see Section 10.6.2).
4. Patients will be evaluated for any signs and/or symptoms of facial irritation (see Section 10.5.6)
5. The occurrence of all AEs will be assessed and documented following procedures in Section 10.9.
6. The use of concomitant medications since the previous study visit will be documented for each patient. The use of moisturizer, including the type and how often it was used, will also be documented. (See Section 10.5.4).
7. The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion.
8. Study drug compliance will be performed and the patient's used Investigational Product will be returned to the site.
9. The following will be dispensed during Visit 3:

    - One can of the Investigational Product
    - Diary will be returned to patient

    Depending upon the severity of the side effects, the Investigator may instruct the patient to use a non-medicated moisturizer. Additional supplies will be dispensed, if required.
10. Study instructions will be reviewed with the patient, including the procedure for application of the Investigational Product.
11. Visit 4 (Day 84 ± 4) will be scheduled and the patient will be instructed to bring all Investigational Product (used, unused and partially used) and the patient diary with him or her to this visit.

11.7.4 Visit 4/ (Day 84±4 days) /End of Treatment/ Early Discontinuation

The following procedures will be performed at Visit 4:

1. A urine pregnancy test will be conducted for all females of child-bearing potential.
2. All facial papules, pustules and nodules, located above the jaw line and extending to the hairline, will be counted (see Section 10.6.1).
3. The overall status of the patient's facial rosacea will be assessed using the IGE (see Section 10.6.2).

4. Patients will be evaluated for any signs and/or symptoms of facial irritation (see Section 10.5.6).
5. The occurrence of all AEs will be assessed and documented following procedures in Section 10.9.
6. The use of concomitant medications since the previous study visit will be documented for each patient. The use of moisturizer, including the type and how often it was used, will also be documented. (see Section 10.5.4).
7. The patient's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The patient's diary will be collected and reviewed for completion.
8. Study drug compliance will be performed and the patient's used Investigational Product will be returned to the site.

11.7.5 Unscheduled Visit

An Unscheduled Visit is allowed at any time, for any reason, if, in the Principal Investigator's opinion, it is warranted.

If a patient is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 4 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the patient will continue to take part in the study), then the activities performed will depend on the reason for the unscheduled visit and will be left to the discretion of the Investigator.

The Investigator should perform any activities necessary to appropriately evaluate the patient. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed.

If the patient's condition has worsened to the degree that it is unsafe for the patient to continue in the study, the patient may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Principal Investigator's discretion.

11.8 Investigational Product

The Investigator will take responsibility for, and will take all steps, to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of study materials in accordance with the protocol and any applicable laws and regulations. IMP will be handled by an independent dispenser at the site who will be unblinded with regard to treatment the subject is receiving.

11.8.1 Dosage and Formulations

Test Product:	Azelaic Acid, 15% topical foam (Actavis Laboratories UT)
Reference Product:	Finacea® (azelaic acid) Foam, 15% (Bayer HealthCare)
Vehicle:	Foam Vehicle of the test product (Actavis Laboratories UT)

11.8.2 Dispensing and Application

All study medication will be stored at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C), in a climate-controlled, limited access area.

The Investigator agrees to store and dispense the study medication only at the site(s) listed on the Form FDA 1572 (or Investigator Agreement/Statement). The Investigator agrees that the study medication will be dispensed by the Investigator or Sub-Investigator(s) named on the Form FDA 1572 (or Investigator Agreement/Statement), or their qualified designees. The Investigator, Sub-Investigator(s), or qualified designees also agree that the study medication will be dispensed only to patients who have provided written informed consent, and have met all entry criteria. Clinical supplies may not be used for any purpose other than as stated in the protocol.

At baseline, and as needed during the study, Investigational Product will be dispensed to randomized patients along with a diary, which includes study instructions. Dispensing will be done by an independent dispenser who is unblinded to the treatment the subject is receiving. The containers should not be opened by the patient at the study center. Each patient will receive training, which details the proper application method of the Investigational Product and general study instructions.

Areas to be treated should be washed with a mild cleanser before application and patted dry with the provided towel. A thin layer of study treatment should be gently massaged into the entire facial area (cheeks, chin, forehead, and nose) twice daily, once in the morning after waking up and once in the evening before going to bed, for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands must be washed following application of study treatment.

Patients will be instructed not to bathe, shower, wash or swim for at least 4 hours after the application of the Investigational Product.

At each visit during the study, the Investigator or designee should review proper application of the Investigational Product.

The Investigational Product is to be applied at home. The Investigational product should not be opened at the clinic.

11.8.3 Method of Treatment Assignment and Randomization

After satisfying all of the inclusion/exclusion criteria, patient will be eligible to enter the study and be randomly allocated in a 1:1:1 ratio to Test, Reference or Vehicle treatment groups respectively. Randomization will be performed according to a computer-generated, block randomization code, with 3 sequential patient numbers assigned to each block. The randomization code will be generated by an independent third party. A sealed copy of the randomization scheme will be provided to each study site and will be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each patient.

Only one patient number will be assigned to each patient. The patient will maintain the same patient number and treatment assignment throughout the study.

11.8.4 Blinding Study Medication

A double-blind technique will be used. The test, the reference product, and the vehicle will be identical in appearance and will be packaged identically so that treatment blind is maintained. Neither the patient nor the investigational staff (Sponsor, Investigator, and evaluators) will know which treatment the patient is receiving.

The Investigator must not break the blind unless absolutely necessary, in order to provide medical treatment to a patient in an emergency, and only with prior authorization from the Sponsor or designee. If the blind is broken for a patient, the patient will be discontinued from the study and the reason recorded.

11.8.5 Unblinding Study Medication

In the event of an emergency, the patient-specific treatment may be identified, however, every effort should be made to maintain the blind. Each patient kit will be labeled with a 2-part label. In the blinded part of the label, included information will contain the compound name, strength and lot number. To unblind, scratch-off the black portion of the label to reveal the treatment received.

11.8.6 Method of Packaging, Labeling and Storage

Study medications will be supplied in cans by the Sponsor. Cans will be labeled and packaged so that neither the patient nor the Investigator can identify the treatment.

The medication will be supplied to the sites in blocks. Each block will contain 3 patient kits (in a 1:1:1 randomization). Each patient kit includes a can; each patient kit will also have a 2-part label on the outside. Each 2-part label will clearly disclose the protocol number, patient number, content statement, storage statement, caution statement, and sponsor's name and address. The label will also contain the compound name, strength and lot number in the blinded panel. The tear-off kit label will be attached to the source document.

The Sponsor’s independent packaging and labeling facility will be responsible for labeling and assembly of investigational product, as well as, for shipment of clinical supplies to investigational sites.

All study medication will be stored at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C), in a climate-controlled, limited access area.

11.8.7 Replacement Cans

In the event of loss/spillage, extra cans of medication may need to be dispensed. See IMP manual for details.

Before dispensing the replacement can, the information will be recorded on the Study Medication Accountability Log.

11.8.8 Study Medication Accountability

Patients will be instructed to return all used, partially used and unused test articles at all protocol-specified visits for study medication inventory and assessment of patient compliance.

The dispensing and return of all study medication will be recorded on the Study Medication Accountability Log. The patient number/initials, and the initials and date of the person dispensing and receiving the returned medication will be documented on this form.

Each can will be weighed before dispensing to a subject and after collecting from the subject at each visit and the weights recorded in the source documents.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time.

11.8.9 Assessment of Compliance

At all protocol-specified visits, the Investigator or qualified designee is to record whether treatment was applied according to protocol instructions in the preceding interval.

Patients will apply the medication twice daily for 12 weeks. Compliance will be determined from the diary cards, in which the patient will be instructed to record all applications. The number of applications will be totaled by the study personnel and recorded on the eCRF. Patients who miss more than six (6) consecutive doses of medication during the treatment period will be considered non-compliant and will be excluded from PP population and discontinued from the study. The used cans of study medication will be collected by the study site at appropriate visits or early termination. Patients will be considered compliant if they apply at least 75% and not more than 125% of doses for the entire duration of the study.

11.8.10Retention of Study Medication Samples

Samples of study drug will be randomly selected for retention at the investigational site prior to dispensing to patients, in accordance with 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the Investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should not be returned to sponsor at any time.

The retention samples will be shipped to a third party storage facility as instructed in the Investigational Product Manual.

The samples can be retrieved from the storage facility at any time upon FDA notification of the visit or during a preapproval inspection conducted by authorized FDA personnel. The samples can be returned to the investigational site or submitted to the place identified in the agency's request.

The request has to be sent directly to the BioRepository Resources by email or fax. The Sponsor (Actavis) and CRO ([redacted]) must be notified and copies of documentation should be sent to the individuals listed below:

Retention Samples Storage Facility:	**Sponsor:**	**CRO:**
[redacted] or faxing a copy at [redacted]	[redacted] Actavis Morris Corporate Center III 400 Interpace Parkway Parsippany, NJ 07054 [redacted]	[redacted]

11.8.11Return of Clinical Supplies

With the exception of the retention samples, at the completion of the study all used and unused cans of Investigational Product will be returned to Actavis's Drug Labeling, Packaging and Shipping Facility. Instructions for returning IP will be provided in the IP Manual.

11.8.12Additional Supplies Provided by the Sponsor

Patients will be provided with a non-medicated cleanser to cleanse the face, paper towels to pat the face dry before applying the study medication, and sun screen for use after product application. A non-medicated moisturizer will also be provided. Depending upon the severity of the side effects, the Investigator may instruct the patient to use the non-medicated moisturizer; instructions for use will be provided.

For the purpose of this study, the following will be provided by the Sponsor:

- Cleanser
- Sunscreen
- Towels
- Moisturizing Lotion

11.9 ADVERSE EVENTS

11.9.1 Reporting of Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical-trial patient 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, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any adverse event associated with the use of a drug in humans, whether or not considered product-related, includes the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Reporting an adverse event does not necessarily reflect a conclusion that the product caused or contributed to the adverse event.

All adverse events, whether observed by an Investigator, Study Coordinator or reported by the patient, whether related to study drug or not related to study drug, shall be documented in the eCRF and patient records, together with details of the duration and intensity of each episode, the action taken, the relationship to the Investigational Product and the degree of severity, the seriousness and the outcome.

The potential adverse reactions of Actavis Laboratories UT azelaic acid, 15% topical foam are anticipated to be similar to those observed with the use of Bayer HealthCare's Finacea® (azelaic acid) Foam, 15%. The following adverse experiences have been reported with the use of Finacea® (azelaic acid) Foam, 15%: erythema, dryness, pain and pruritus.

The Principal Investigator must strive to follow the patient until the adverse event has resolved, becomes clinically insignificant, is stabilized or the patient is lost to follow-up. The Principal Investigator must immediately report all patients who discontinue use of study drug due to adverse events to the Contract Research Organization by telephone and follow-up in writing.

11.9.2 Assessment of Severity

The intensity or severity of an adverse event (AE) is characterized as:

- Mild: an AE that is easily tolerated
- Moderate: an AE sufficiently discomforting to interfere with daily activity
- Severe: an AE that prevents normal daily activities

11.9.3 Relationship to Study Medication

The relationship is characterized as:

- Not Related: This applies to any AE that is clearly not related to use of the study drug.
- Possible: This means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out.
- Probable: There is a reasonable temporal relationship between the use of the study drug and the AE. Based upon the Principal Investigator's clinical experience, the association of the event with the study drug seems likely.
- Definite: The AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. It disappears or decreases upon discontinuation of the study drug and reappears on a re-challenge of the Investigational Product.

11.9.4 Action taken regarding the IMP

- None: There was no action taken. The subject receives IMP in accordance with the protocol.
- Dose reduced: The dosage of IMP was reduced.
- Interrupted: Discontinued temporarily. The treatment is expected to be re-

introduced.

- Discontinued: Discontinued permanently. Subject is taken off the trial therapy.
- Not applicable: The adverse event occurred during the Screening Period

11.9.5 Assessment of Subject outcome

- Subject remains in the trial
- Withdrawn from the trial
- Lost to follow-up
- Death

11.9.6 Definition of AE outcome

- Recovered without sequelae: Subject has recovered fully from the AE without any remaining effects or impairment.
- Recovered with sequelae: Subject has recovered but with remaining effects or impairment present at the time of the report.
- Not yet recovered: The outcome is not yet known or the AE is still ongoing
- Died
- Unknown

11.9.7 Treatment Required

- Yes (if yes specify on concomitant therapy page of the CRF)
- No

11.9.8 Pregnancy

All female patients of childbearing potential must use accepted methods of birth control or must agree to practice abstinence, from study start to 30 days after the last administration of study drug. All female patients are considered to be of childbearing potential unless they have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or have been postmenopausal for at least a year. Any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Norplant®), vaginal ring (NuvaRing®), Depo-Provera® (Medroxy progesterone acetate), double barrier methods (e.g., condom and spermicide), Essure or IUD.

A negative result of a urine pregnancy test having a minimum sensitivity of at least 50mIU/ml for hCG should be obtained, prior to study participation, at Visit 1. Pregnancy testing will also be performed at every study visit and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of Investigational Product exposure, the subject will be permanently discontinued. The Principal Investigator must immediately notify the Medical Monitor of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient. Other appropriate pregnancy follow-up procedures should be considered if

indicated. In addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

Pregnancy occurring during a patient's participation in a clinical trial must be notified to the sponsor within 24 hours after Study Coordinator becomes aware of its occurrence. Outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

Timeline for follow up:

- Site should follow the patient until termination of the pregnancy or until at least 30 days after the birth.
- Infant(s) should be followed for a minimum of eight weeks after birth.

Timeline for reports:

- Pregnancy notification: within 24 hours after Study Coordinator becomes aware of its occurrence;
- Pregnancy initial report: expected within 1to 3 days of notification;
- Pregnancy follow up report: at least every 3 months;
- Pregnancy final report: upon termination of the pregnancy or until at least 30 days after the birth;
- Infant follow up report: 30 days after the birth;
- Infant final report: eight weeks after birth.

Cases of pregnancy must be reported on a Pregnancy Report and sent to the Sponsor Study Manager.

An SAE needs to be reported for pregnancy with abnormal outcome before or after the end of study.

11.9.9 Serious Adverse Events

An **Adverse Event or Suspected Adverse Reaction** is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life threatening adverse event; (Note: the term "life-threatening" as used here refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- In-patient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- A congenital anomaly/birth defect;
- Any "other" important medical event.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered Serious Adverse Events when, based on appropriate

medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Regardless of the above, any additional adverse events which the Principal Investigator considers significant should be immediately reported to the Contract Research Organization ([redacted].

Any Serious Adverse Event, whether deemed drug-related or not, must be reported by the Investigator to the Contract Research Organization ([redacted]) Project Manager by telephone **within 24 hours** after the Principal Investigator or Study Coordinator becomes aware of its occurrence. The Principal Investigator or the Principal Investigator's Designee must complete a Serious Adverse Event (SAE) Form and fax it to the Contract Research Organization ([redacted], along with the patient's Adverse Events Log and Concomitant Medications Log **within 24 hours** of notification of the event. The CRO [redacted] must notify the Medical Monitor, Actavis Study Manager and Actavis's Drug Safety Department **within 24 hours** of the initial notification of the event. When appropriate, the Actavis's Drug Safety Department will notify the U.S. Food and Drug Administration (FDA) of drug related Serious Adverse Events.

Documentation should be sent to the CRO Study Manager and Actavis's Drug Safety Department listed below:

CRO Study Manager	Medical Monitor	Sponsor Study Manager	Drug Safety Department
[redacted]	[redacted]	[redacted] Actavis. Morris Corporate Center III 400 Interpace Parkway Parsippany, NJ 07054 [redacted]	Actavis Pharmacovigilance [redacted]

The Principal Investigator or the Principal Investigator's Designee must be prepared to supply the Medical Monitor with the following information:

a. Principal Investigator name and Site Number
b. Patient I.D. Number
c. Patient initials and date of birth
d. Patient demographics
e. Clinical event
    1) Description
    2) Date of onset
    3) Severity
    4) Treatment (including hospitalization)
    5) Relationship to study drug
    6) Action taken regarding study drug
f. If the AE was fatal or life-threatening
    1) Cause of death (whether or not the death was related to study drug)

2) Autopsy findings (if available)
3) Death Certificate

The Sponsor must notify FDA as soon as possible, but no later than 7 calendar days for a fatal or life threatening adverse event. The Sponsor must notify FDA and all participating investigators within 15 calendar days for any drug-related serious adverse events observed during the conduct of the study.

The Principal Investigator must provide a follow-up written report within 5 calendar days of reporting the event to the CRO. The written report must contain a full description of the event and any sequelae. Patients who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized. The Investigator must also report follow-up information if it becomes known to the Investigator. Actavis Study Manager and Actavis Drug Safety Department must receive any follow-up **within 24 hours** of receipt by Medical Monitor.

Reports of all SAEs must be communicated as soon as possible to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or reported in accordance with local laws and regulations.

12 STATISTICAL METHODS

12.1 Sample Size Rationale

The sample size for this protocol is based on published data (Finacea® Summary Basis of Approval); Finacea® produced a percent reduction for inflammatory lesions of approximately 55% and the vehicle had a percent reduction of 40% after 12 weeks of treatment.

The anticipated standard deviation for inflammatory lesions is < 47%. A sample size of $n_1 = 280$, $n_2 = 280$ and $n_3 = 280$ evaluable mITT patients (1:1:1 ratio) to provide at least 224 PP patients in each of the Test and Reference treatment groups should provide at least an [redacted] probability of showing that, the 90% confidence interval on the Test/Reference ratio of percent reduction from baseline is contained within the interval 0.800 to 1.250 in the PP population and at the same time demonstrating that the Test and Reference products are superior to the vehicle in the mITT population.

In this study, enrolled patients will be randomized in the ratio of 1:1:1 to test, reference and vehicle treatments. It is anticipated that 75% of the mITT patients will qualify for the PP population. Accordingly, approximately 924 patients will be randomized in the study to obtain at least 840 mITT patients in a 1:1:1 ratio (280:280:280 patients, respectively) to each treatment group.

12.2 Randomization and Unblinding Procedures

Patients will be randomly assigned in a 1:1:1 ratio to receive the test product, the reference product, or the vehicle control, respectively. The randomization assignment will be a block randomization, with 3 sequential patient numbers in each block.

An independent third party will generate the randomization code using SAS and hold it throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme will be retained at each study site.

The treatment assignments will remain blinded until the final database is locked. The contents of the cans of IP may not be viewed by the PI, any Sub-investigator, evaluator or any other (blinded) member of the site staff.

In the event of an emergency, the patient-specific treatment may be identified; however, every effort should be made to maintain the blind.

In the event of unblinding, the patient should be excluded from the PP population. The Sponsor or designee must be notified in the event the blind is broken.

12.3 Significance Level

All statistical tests will be carried out at a significance level of $\alpha = 0.05$ (two sided), unless otherwise indicated. No adjustment will be made for multiplicity.

12.4 Efficacy Assessment

12.4.1 Primary Endpoint

The primary endpoint is the percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts.

12.4.2 Secondary Endpoint

The secondary endpoint is the clinical response of "success" or "failure" at Week 12 on the IGE. Success is defined as an IGE score of 0 (clear) or 1 (almost clear). Any patient who is not considered to be a success will be considered to be a failure.

12.4.3 Measures

Lesion Counts will be performed using the following definitions:

Lesion Name	Lesion Definition
Papule	Inflammatory lesion; small (≤ 5mm in diameter), solid palpable lesion, usually with inflamed elevation of the skin that does not contain pus.
Pustule	Inflammatory lesion; small (≤ 5mm in diameter), inflamed skin swelling that is filled with pus.
Nodule	Large (> 5 mm in diameter), hard bumps under the skin's surface.

When counting facial lesions, all lesions will be counted, including those present on the nose. Counts of nodules will be reported separately and not included in the inflammatory lesion counts.

The IGE will be performed and documented using the definitions in table below:

IGE:

Score	Grade	Definition
0	Clear	No inflammatory lesions present; at most, mild erythema.
1	Almost Clear	Very mild erythema present. Very few small papules/pustules.
2	Mild	Mild erythema. Several small papules/pustules.

3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules.
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

Application site reactions such as erythema, dryness, scaling, pruritus, stinging/burning, and edema, will be recorded at each visit to allow a comparison between treatment groups. A detailed scale is presented in Section 10.5.6.

12.4.4 Datasets to be Analyzed

Three analysis populations will be used in the analysis of the clinical data and they are defined as follows:

1. The Safety population includes any individual who was randomized into the study and used at least one dose of Investigational Product.
2. The mITT population includes all randomized patients who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit with lesion count.
3. The PP population includes all randomized patients who met all inclusion/exclusion criteria, were compliant with the assigned study treatment (who applied 75% to 125% of the scheduled applications), returned to the study site for the primary endpoint visit (12 week evaluation) within +/- 4 days OR discontinued from the study as a treatment failure (after completing at least 8 weeks of compliant study medication use), and did not have any protocol violations. The compliance will be verified by the use of patient diaries. Patients who are discontinued early from the study due to lack of treatment effect, or who require alternate or supplemental therapy to treat their rosacea, after completing at least eight weeks of treatment will be included in the mITT and PP population as treatment failures on the IGE and their change in inflammatory lesion count from baseline to the last completed visit prior to discontinuation will be carried forward (LOCF).

Patients discontinued prematurely for other reasons will be excluded from the PP population, but included in the mITT population, with missing efficacy data imputed using LOCF.

For the purpose of determining the per-protocol status of the patient, a “protocol violation” is any patient or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

Efficacy analyses will be performed on the mITT and Per-protocol populations.

12.5 Statistical Analysis

12.5.1 Analysis of Primary Endpoint

Demonstration of Bioequivalence

The 90% confidence interval on the test-to-reference ratio for the mean change from baseline in inflammatory lesions will be constructed using Fieller’s method. The analysis will use the common error term from the Analysis of Variance (ANOVA) of the test and reference results with a statistical model containing terms for treatment and site.

Bioequivalence will be established if the 90% confidence interval on the test-to-reference ratio is contained within the interval [0.80, 1.25] in the PP population.

An identical analysis will be performed on the results from the mITT population to test for robustness of the findings in the PP population. A LOCF approach will be used for missing efficacy results in the mITT analysis.

Demonstration of Superiority

To ensure that the study has adequate sensitivity to a difference between products, should such a difference exist, the primary efficacy results for the test and reference treatments will each be compared to those of the vehicle treatment.

The evaluation of the superiority of the test treatment over the vehicle treatment will be conducted using ANOVA with a statistical model containing terms for treatment and center. If the mean percent change from baseline for inflammatory lesions for the test treatment is greater than, and statistically different from ($p<0.05$) that of the vehicle in the mITT population, then the test product will be considered superior to the vehicle. The results for the reference treatment will be compared to those for the vehicle in an identical manner. The same analyses will be conducted for the results from the PP population to test for robustness of the findings in the mITT population. A LOCF approach will be used for missing efficacy results in the mITT analysis.

For both the Bioequivalence and Superiority evaluations, a non-parametric rank based ANOVA will be considered when the data is highly skewed. The evaluation of skewness, (SAS® PROC UNIVARIATE) will be performed using the residuals from each ANOVA and if the skewness statistic is less than -2 or greater than +2, the analysis will be performed on the ranks of the percent change in inflammatory lesion count values.

12.5.2 Analysis of Secondary Endpoint

Demonstration of Bioequivalence

Bioequivalence for the secondary endpoint, will be established if the 90% confidence interval, Wald's method with Yate's continuity correction, for the test-to-reference difference in IGE success proportions is contained within the interval [-0.20, +0.20] in the PP population. An identical analysis will be conducted on the mITT population to test for the robustness of the findings for the PP population. A LOCF approach will be used for missing efficacy results in the mITT analysis.

Demonstration of Superiority

The evaluation of the superiority of the test treatment over the vehicle treatment for the proportion of patients with success on the IGE at Week 12 will be conducted using Fisher's exact test. If the success proportion for the test treatment is greater than, and statistically different from ($p<0.05$) that of the vehicle in the mITT population, then the test product will be considered superior to the vehicle. The results for the reference treatment will be compared to those for the vehicle in an identical manner. The same analyses will be conducted for the results from the PP population to test for robustness of the findings in the mITT population. A LOCF approach will be used for missing efficacy results in the mITT analysis.

12.5.3 Analysis of application site reactions

A descriptive analysis comparing the application site reactions for each treatment group will be conducted to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

12.5.4 Safety Analyses

Safety analyses will be conducted on the safety population. Incidence of all adverse events reported during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by treatment group, body system, severity, preferred term, and relationship to study drug. In addition, an evaluation will be conducted of the comparability of the test and reference treatments in regard to any treatment emergent AEs that occur in 5%, or more of the patients in either test or reference treatment group.

The report of AEs will include date of onset, description of the AE, and date of resolution.

12.5.5 Concomitant Medication

The start and stop dates of concomitant medication used during the study will be provided in the data listings in addition to the reason for the medication use.

12.5.6 Demographics and Baseline/Randomization Characteristics

Demographic and baseline/randomization characteristics will be compared for the mITT, PP, and Safety populations. Continuous variables will be analyzed with an analysis of variance with factors of treatment and investigational site. Categorical variables including gender, ethnicity, race, and some baseline/randomization characteristics will be analyzed with a Cochran-Mantel-Haenszel test, stratified by investigational site.

12.5.7 Summary of patients who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

13 ETHICS

13.1 Informed Consent

The principles of Informed Consent, according to FDA Regulations and ICH guidelines on GCPs, will be followed. A copy of the proposed consent form must be submitted to the IRB, together with the protocol, for approval.

Patients must provide written informed consent prior to any study procedures being completed. The Investigator is responsible for obtaining informed consent, signed by each patient prior to entry into the study. Each patient's signed informed consent must be kept on file by the Investigator for Regulatory Authorities' inspection at any time. A copy of the signed consent form will be given to the patient. A notation will be made in the patient's medical record indicating the date and time informed consent was obtained.

A volunteer who signs the ICF but is not eligible at Visit 1 will be listed on the Screening Log as a screen failure and may rescreen at a later date. The signed consent document will be in effect for 28 days from the date of signature.

13.2 Institutional Review Board or Independent Ethics Committee

The study and the patient informed consent form must be approved in writing by an appropriate IRB or Independent Ethics Committee (IEC) as defined by FDA regulations prior to enrollment of any study patients.

Any changes to the protocol as well as a change of Investigator, which is approved by the Sponsor, must also be approved by the site's IRB/IEC and documentation of this approval provided to the Sponsor or designee. Records of the IRB/IEC review and approval of all documents pertaining to this study must be kept on file by the Investigator and are patient to inspection by FDA or other Regulatory Authorities during or after completion of the study. SAEs must also be reported to the IRB/IEC.

Periodic status reports must be submitted to the IRB/IEC at least annually, as well as notification of completion of the study and a final report within approximately 1 month of study completion or termination. A copy of all reports submitted to the IRB/IEC must be sent to the Sponsor or designee.

The Investigator will ensure that an IRB/IEC that complies with the requirements set forth in Part 56 (Title 21 Code of Federal Regulations) will be responsible for the initial and continuing review and approval of the proposed clinical study.

13.3 Patient Confidentiality

All patient data will be identified only by a patient identification number and patient initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the Sponsor, it is required that the Investigator permit the study monitor, Sponsor representative or auditor, and/or FDA representative to review that portion of the patient's medical record that is directly related to the study. This shall include all study relevant documentation including patient medical histories to verify eligibility, admission/ discharge summaries for hospital stays occurring while the patient is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the patients must be informed that his/her medical chart may be reviewed by the Sponsor, the Sponsor's authorized representatives, or 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 patient in writing before the patient is enrolled into the study.

14 DATA HANDLING AND RECORD KEEPING

14.1 Site Regulatory Documents Required for Initiation

The Sponsor, or designee, will receive the following documents prior to the initiation of the study:

1. Completed, signed Form FDA 1572.
2. Current curricula vitae, signed and dated, for the Principal Investigator and sub-investigators named on the Form FDA 1572.
3. Current license(s) of the Principal Investigator and sub-Investigators named on Form FDA 1572.
4. Documentation of IRB approval of this study protocol, Investigator, and informed consent.

5. Current IRB membership list.
6. A copy of the protocol agreement page signed by the Principal Investigator.
7. Financial Disclosure Statement for all individuals captured on the Form FDA 1572.
8. Debarment Certification for the Principal Investigator and sub-investigators named in Form FDA 1572.

14.2 Maintenance and Retention of Records

The study will be conducted according to Good Clinical Practices as outlined in ICH step 5 guidelines by the Food and Drug Administration. It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by the Sponsor, as well as the regulations, in a secure and safe facility with limited access. Regulations require retention for a period of at least two (2) years after marketing approval and notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities.

Archiving of data - Copies of all pertinent records will be retained by the Investigator for at least two (2) years following final approval of the drug and notification from the Sponsor. These records include documents pertaining to the receipt and return of drug supplies, IRB, Informed Consent, source documents, as well as final signed case report forms. No documents shall be transferred from the site or destroyed without first notifying the Sponsor.

A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each patient.

14.3 Data Collection and Reporting

Data for individual patients will be collected on source documents designed by the Contract Research Organization and then entered into a data management system, which for this study will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including patient identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

Source documents such as the clinic chart are to be maintained in order to allow data verification. Because of the potential for errors, inaccuracies and illegibility in transcribing data into eCRFs, originals of laboratory and other test results must be kept on file. Source documents and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

1. Patient Screening Log – reflecting the reason any patient screened for the study was found to be ineligible
2. Delegation of Authority/Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/Designee

will be documented
4. Enrollment Log – documenting patient initials and start and end dates for all patients enrolled
5. Drug Accountability Log – reflecting the total amount of Investigational Product dispensed to and returned by each patient
6. Informed Consent Form – which must be available for each patient and be verified for proper documentation

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the CRO's data management personnel will be answered by site personnel and verified by the monitor.

14.4 Primary Source Documents

The investigator must maintain primary source documents supporting significant data for each patient's medical notes. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the patient is being studied
- General information supporting the patient's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the Investigator(s), occurrence (or lack) of adverse events, and changes in medication usage, including the date the study drug commenced and completed
- Any additional visits during the study
- Any relevant telephone conversations with the patient regarding the study or possible adverse events
- An original, signed informed consent form for study participation
- Patient Diary

The Investigator must also retain all patient-specific printouts/reports of tests and procedures performed as a requirement of the study. During monitoring visits the monitor will need to verify data on the eCRFs against these sources of data.

14.5 Study Monitoring

The study will be monitored by a representative of the CRO to assess compliance with ICH-GCP and applicable regulations. The Principal Investigator will be visited by a study monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol. The study monitor will review the informed consent forms and verify CRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The study monitor will review the maintenance of regulatory documentation and drug accountability (to the can level). The study monitor will review on a regular basis the progress of the study with the Investigator and other site personnel. Electronic case report forms may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring

visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The study coordinator and/or Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Investigator and study staff.

14.6 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be audited by authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with recognized GCP/ICH guidelines and laws.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the course of the study and/or after it has been completed.

THE INVESTIGATOR MUST NOTIFY THE CONTRACT RESEARCH ORGANIZATION [redacted] and SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each patient.

14.7 Modifications to the Protocol

The procedures defined in the protocol and in the eCRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no deviations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB prior to implementation. All amendments to the protocol, which involve substantial changes in study design, procedure or analyses, will be submitted to the IRB for prior approval. The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a patient or patients. However, the Investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

14.8 Termination of the Study

The Sponsor reserves the right to terminate the clinical study at any time upon written notice. The termination of the study for any reason will be communicated to the IRB.

14.9 Completion of the Study

The Investigator is required to submit all close-out documents and any other required records to the Contract Research organization [redacted]

The Investigator must submit a final report to the IRB and the Sponsor within one (1) month of study completion or discontinuation of study.

14.10 Publications

Direct publications arising from this study may only be published with the consent of the sponsor while maintaining the patient's confidentiality.

15 REFERENCES

- Package insert - FINACEA® (azelaic acid) Foam, 15%
- U.S. Food and Drug Administration: Individual Product Bioequivalence Recommendations for Azelaic Acid (http://www.fda.gov).
- http://www.finacea-us.com/

APPENDIX I: STUDY FLOW CHART

Visit Title	Baseline	Interim	Interim	End of Treatment/ Early Discontinuation
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Scheduled Day	**Day 0**	**Day 28±4**	**Day 56±4**	**Day 84±4**
Informed Consent	X			
Demographics	X			
Medical History	X			
Inclusion/Exclusion Criteria	X			
Physical Exam including vital signs	X			
Pregnancy Test*	X	X	X	X
Concomitant Medications	X	X	X	X
Adverse Events		X	X	X
Inflammatory Lesion Count	X	X	X	X
Investigator's Global Evaluation (IGE)	X	X	X	X
Telangiectasia Assessment	X			
Irritation Assessment	X	X	X	X
Patient Instruction/Compliance Review	X	X	X	X
Dispense Study Medication and Diary**	X	X	X	
Collect Study Medication and Diary (Accountability)		X	X	X

* Urine pregnancy test for all females of child-bearing potential enrolled in study.

**Day 1 will occur the date patient begins dosing. This may be the evening of Visit 1 or the following day.

APPENDIX II: FINACEA ® PACKAGE INSERT