CLINICAL STUDY PROTOCOL

A Vehicle-Controlled, Double-Blind, Randomized Phase II Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Subjects with Mild to Moderate Rosacea.

Protocol Number: **RB244-001**

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Sponsor:

AOBiome, LLC

125 Cambridgepark Drive

Cambridge, MA 02140

AOBiome

SIGNATURE PAGE

PROTOCOL NUMBER: **RB244-001**
STUDY TITLE: **A Vehicle-Controlled, Double-Blind, Randomized Phase II Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Subjects with Mild to Moderate Rosacea.**

The signatures below constitute the approval of this protocol and any attachments and provide the necessary assurances that this trial will be conducted according to this protocol, local legal and regulatory requirements, applicable United States federal regulations, and ICH E6R2 guidelines.

S. Jamas — 16 JAN 2019

Spiros Jamas
Head of Therapeutics
AOBiome, LLC
Date

16 JAN 2019

Masha Gaber
Clinical Operations
AOBiome, LLC
Date

17 JAN 2019

Sumit Bajracharya
Project Manager
Biorasi, LLC
Date

17 Jan 2019

Mark Vieder
VP, Drug Safety & Pharmacovigilance
Biorasi, LLC
Date

INVESTIGATOR SIGNATURE PAGE

The signature below constitutes approval of this protocol and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements of confidentiality and in accordance with ICH GCP and local regulatory requirements.

Print Name	
Title	
Address of Institution / Site:	_____ _____ _____ _____
Telephone Number:	

Investigator Signature: _____ Date: _____

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES

Section	Description of Changes
Synopsis	Added Exploratory Endpoints: IGA treatment success and CEA treatment success defined as "clear" or "almost clear" with a 2-grade improvement in score from baseline to the end of treatment.
Section 3 Study Endpoints	Added Section 3.3 Exploratory Endpoints: IGA treatment success and CEA treatment success, defined as "clear" or "almost clear" with a 2-grade improvement in score from baseline to the end of treatment.
Section 14 Statistical Analysis	Added 14.3.3.1 Exploratory Endpoints: IGA treatment success and CEA treatment success defined as "clear" or "almost clear" with a 2-grade improvement in score from baseline to the end of treatment.

Administrative changes: Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment.

Additional formatting and stylistic adjustments have been made to facilitate the reading process.

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GLOSSARY OF ABBREVIATIONS

ABBREVIATION	MEANING
AE	Adverse Event
AOB	Ammonia-Oxidizing Bacteria
BID	Bis in Die (twice a day)
BP	Blood Pressure
CEA	Clinician Erythema Assessment
CRA	Clinical Research Associate
CI	Confidence Interval
CRF	Case Report Form
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
ETR	Erythematotelangiectatic rosacea
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference On Harmonization
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IGE	Investigator's Global Evaluation
IP	Investigational Product
IPL	Intense Pulsed Light
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine system
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward

mITT	Modified Intent-To-Treat
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over the Counter
PP	Per-Protocol
PRN	Pro Re Nada (as needed)
PSA	Patient Self-Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Simple Imputation
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal Range
UPT	Urine Pregnancy Test
UV	Ultraviolet
WBC	White Blood Cell Count
WOCBP	Women of Child Bearing Potential

PROTOCOL SYNOPSIS

TITLE:	A Vehicle-Controlled, Double-Blind, Randomized Phase II Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Subjects with Mild to Moderate Rosacea.
INVESTIGATIONAL PRODUCT	B244 Topical application
STUDY ARMS	1. B244 2. Vehicle
PURPOSE:	The aim of the study is to assess the safety and efficacy of B244 in the treatment of mild to moderate rosacea.
STUDY OBJECTIVES:	**Primary Objective:** • To assess the safety and tolerability of B244 applied twice daily (BID) to the face for 8 weeks in subjects with mild to moderate rosacea. **Exploratory Objectives:** To assess the efficacy of B244 in subjects with mild to moderate rosacea. • Proportion of subjects with IGA improvement at Week 8 relative to baseline • Proportion of subjects with CEA improvement at Week 8 relative to baseline • Change in IGA from Week 8 to Baseline • Change in CEA from Week 8 to Baseline • Proportion of Subjects with improvement in IGA or CEA at Week 1, Week 4, and Week 12. • Change in Skindex 16 patient reported outcome from Baseline to Week 1, Week 4, Week 8, and Week 12. • Proportion of subjects with change in PSA at Week 1, Week 4, Week 8 and Week 12 from Baseline. • Evaluation of Telangiectasia Score at Baseline/Day1 and Week 8

STUDY DESIGN:	This is a Prospective, Vehicle Controlled, Double Blind, Multicenter, Randomized Phase II trial, comparing the effect of twice daily B244 application for 8 weeks vs. vehicle application on treatment of mild to moderate rosacea. At Screening and Baseline: • All subjects must have diagnosis of mild to moderate Rosacea. • Subjects must have IGA score of 2-3 and CEA score of 2-3 in order to qualify for the study. • After screening and recruitment, participants will be randomized to active or vehicle application for 8 weeks. • Subjects will apply a total of 4 pumps of IP per application to the face twice-a-day • Randomization will be 1:1 B244 to Vehicle. • Subjects will be provided with cleanser and moisturizer to use for the duration of the study • All B244 randomized subjects will be treated at the dose of $4x10^9$ cells/ml via spray application • Screening period will occur at Days -21 to -1 • Washout will occur after Screening visit (Days -14 to -1) • Randomization will occur during the baseline visit for the study • Efficacy will be assessed using Investigator Global Assessment (IGA) score, Clinician's Erythema Assessment (CEA) score, Patient Self-Assessment (PSA) score and patient reported Skindex 16. • Clinical assessments of response to treatment will be made at Week 1(Day 7), Week 4 (Day 28), and Week 8 (Day 56) • At Baseline visit, subjects will receive a kit containing the drug product. Each bottle will be used for 2 weeks. At Week 4, subjects will return the used bottles from the kit and will be issued a new kit of drug product to be used from Week 4 through Week 8. • Subjects will stop applying investigational product at Week 8 and will return investigational product at that visit. • Subjects will come back for a 4-week post-treatment follow up visit at Week 12 (Day 84).

	• Participant's safety will be monitored throughout the study. Safety will be assessed by monitoring reported adverse events, vital signs, clinical chemistry and hematology and overall tolerability of the investigational product. • Subjects would be required to discontinue the investigational product under the following circumstances: o Development of an intercurrent illness that would jeopardize the safety, or significantly affect assessments of clinical status of a subject o Either at the discretion of the Investigator or at the participant's request o Development of any investigational product-related SAE o Suspected or laboratory-confirmed pregnancy
STUDY POPULATION:	**Inclusion Criteria** In order to be eligible for the study, subjects must have fulfilled all of the following criteria. 1. Male and female subjects ≥18. 2. A clinical diagnosis of mild to moderate facial rosacea. 3. In good general health as determined by a thorough medical history, physical examination, clinical chemistry and hematology. 4. Presence of 3 to 20 inflammatory lesions on the face (i.e. papules/pustules). 5. A Clinician Erythema Assessment (CEA) score of 2-3 at Screening and at Baseline Visits (prior to the investigational product application). 6. Mild to Moderate IGA score of 2-3 at Screening and at Baseline Visits (prior to the investigational product application). 7. Willing to refrain from using any topical or systemic treatments for the treatment of rosacea, other than the investigational product. 8. Females of childbearing potential with a negative urine pregnancy test (UPT) at Screening and

	Baseline/Day 1 (prior to the investigational product application). 9. Ability to comprehend and comply with study procedures. 10. Agree to commit to participate in the current protocol. 11. Provide written informed consent prior to any study procedure being performed.
STUDY POPULATION:	**Exclusion Criteria** Any subject who meets one or more of the following criteria is excluded from this study: 1. Female subjects who are pregnant, lactating or who are trying to conceive will be excluded from participation in this study. 2. Any uncontrolled chronic or serious disease or medical condition that would normally prevent participation in a clinical trial, or, in the judgment of the Investigator, would put the subject at undue risk, or might confound the study assessments (e.g., other dermatological diseases), or might interfere with the subject's participation in the study, (e.g., planned hospitalization during the study). 3. Particular forms of rosacea (e.g., rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin, Ocular rosacea Phymatous rosacea, Steroid-induced rosacea, severe rosacea including pyoderma faciale) or other concomitant facial dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia. 4. Presence of more than two (2) nodulocystic lesions on the face. 5. Presence of less than 3 and more than 20 inflammatory lesions on the face (i.e. papules/pustules). 6. Severe papulopustular rosacea requiring systemic treatment. 7. Participation at the time of eligibility assessment (Screening) in any other investigational drug or device study or may have participated within 30 days prior to Screening.

	8. Commencement of new hormonal therapy or dose change to hormonal therapy within 30 days prior to baseline. Dose and frequency of use of any hormonal therapy started more than 30 days prior to baseline must remain unchanged throughout the study. Hormonal therapies include, but are not limited to, oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (e.g. vaginal ring or transdermal hormone contraception) 9. Presence of beard or excessive facial hair at Screening which would interfere with the study treatments or study assessments and refusal to remove for duration of study. 10. Carcinoid, Pheochromocytoma or other systemic causes of flushing. 11. Known sensitivity to B244 or its components. 12. Refusal to submit to blood and urine sampling for laboratory analysis. 13. Treatment with the following:

Prohibited Topical Treatments:

Topical Treatment	Prohibited Time Frame prior to Baseline
Astringents or abrasives	2 days
RHOFADE™ (oxymetazoline HCl) Cream, 1%	1 week
Bleach baths	1 week
Mirvaso (brimonidine) topical cream	1 week
Vinegar	1 week
Topical Prescription/OTC medications for treatment of acne	2 weeks
Soolantra (Ivermectin 1%) topical cream	1 week
Topical Antibiotic	2 weeks
Use of over the counter antimicrobial	2 weeks
Benzoyl Peroxide	2 weeks
Immunomodulators	4 weeks
Oracea (doxycycline) topical cream	2 weeks
Corticosteroids	4 weeks
Electrocoagulation, Dermabrasion; Facial peels	4 weeks
Dermatologic/surgical procedure on the face	4 weeks

Topical Prescription medications for the treatment of rosacea (e.g. azelaic acid, metronidazole, etc.)	4 weeks
Laser, Phototherapy, Photodynamic Therapy or IPL (intense pulsed light) treatment	4 weeks
Over the counter topical retinoid use on the face	4 weeks

Prohibited Systemic Treatments:

Systemic Treatment	Prohibited Time Frame prior to Baseline
Exposed to excessive ultraviolet (UV) radiation and/or subject was unwilling to refrain from excessive exposure to UV radiation during the course of the study	1 week
Prescription anti inflammatory	2 weeks
Prescription/OTC anti-inflammatory medications (excludes low dose aspirin)	2 weeks
Systemic Antibiotics	4 weeks
Systemic medications for the treatment of rosacea (e.g. doxycycline, tetracycline, macrolides)	4 weeks
Prescription medications for treatment of acne	4 weeks
Corticosteroids (oral or injectable)	4 weeks
Immunomodulators	12 weeks
Oral retinoid use (e.g., isotretinoin), vitamin A supplements greater than 10,000 units/day	6 months

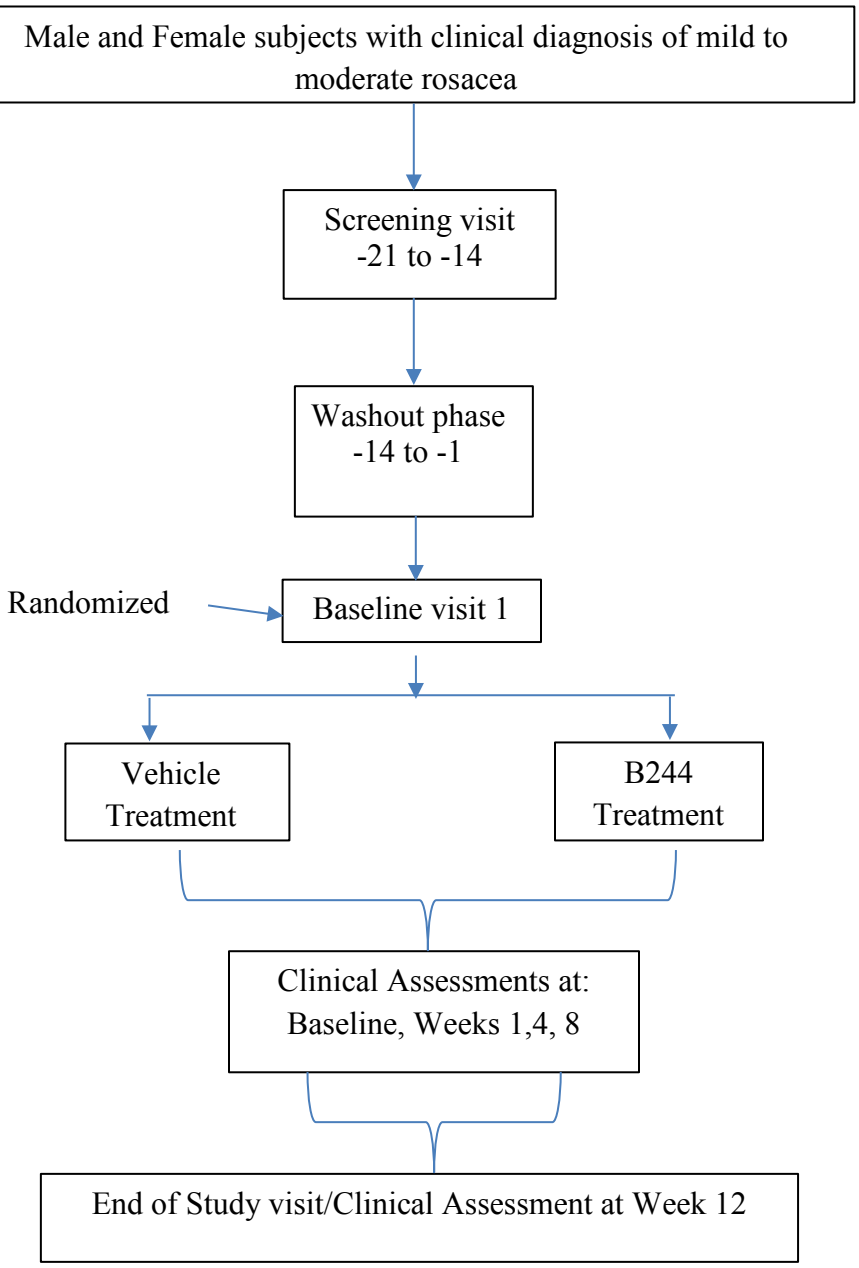
STATISTICAL ANALYSIS:	**Analysis Populations:** • **Safety Population:** The safety population includes all randomized subjects who received investigational product. • **Modified Intent-to-Treat (mITT) Population:** A modified intent-to-treat population includes all subjects who are randomized, applied at least one dose of assigned product, and returned for at least one post-baseline evaluation visit. • **Per Protocol (PP) Population:** The PP population includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, returned to the study site for the primary endpoint visit within the specified window (±2 days) OR discontinued from the study as

	a treatment failure, and did not have any major protocol violations. Subjects who administered at least 50 % of IP, have at least one baseline and post baseline in clinic visit and did not have any major protocol violations. **Efficacy Analysis:** • IGA score at Baseline to Week 1, Week 4, Week 8 and Week 12 • CEA score at Baseline to Week 1, Week 4, Week 8 and Week 12. • Skindex 16 patient reported outcome from Baseline to Week 1, Week 4, Week 8 and Week 12 • PSA score at Baseline to Week 1, Week 4, Week 8 and Week 12. **Safety & Tolerability Analysis:** Safety and tolerability endpoints will consist of all adverse events reported during the study duration. **Exploratory Endpoints:** IGA treatment success, defined as "clear" or "almost clear" with a 2-grade improvement in IGA score from baseline to the end of treatment. CEA treatment success, defined as "clear" or "almost clear" with a 2-grade improvement in CEA score from baseline to the end of treatment.

STUDY FLOWCHART

Figure 1. Study Flowchart

STUDY SCHEMA



SCHEDULE OF ACTIVITIES

Table 1: Schedule of Study Activities

Visit Name	**Screening**	**Baseline/ DAY 1**	**Week 1**	**Week 4**	**Week 8**	**Week 12/ End of Study Visit**	**Early Termination Visit**
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	
Visit window in days	**-21 to -1**	**1**	**7+/-2**	**28 +/- 2**	**56 +/- 2**	**84 +/- 2**	
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Demographics	X						
Medical History	X	X					
Concomitant Medications	X	X	X	X	X	X	X
Physical Exam	X	X				X	X
BP & Pulse[2]	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP[1]	X	X	X	X	X	X	X
Clinical chemistry and hematology and urinalysis[3]	X	X		X	X		X
Biomarkers[4]		X			X		X
CEA	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X
Skindex 16	X	X	X	X	X	X	X
PSA score	X	X	X	X	X	X	X
Telangiectasia Evaluation		X			X		X
Fitzpatrick skin type	X						
IWRS		X		X			
Dispense Investigational product to Subject [5/6]		X		X			
Collect Investigational product from Subject[5]				X	X		X

Visit Name	Screening	Baseline	Week 1	Week 4	Week 8	Week 12/End of Study Visit	Early Termination Visit
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	
Visit window in days	**-21 to -1**	**1**	**7+/-2**	**28 +/- 2**	**56 +/- 2**	**84 +/- 2**	
Investigational product Compliance[5]		X		X	X		X
Study Cleanser and moisturizer dispensation[9]		X		X			
Study Cleanser and moisturizer collection					X		X
Study Diary[8]		X	X	X	X		X
Study Counseling[7]		X	X	X	X		
AE Collection and Assessment	X	X	X	X	X	X	X

1. Urine pregnancy test for WOCBP will be done at every visit.
2. Blood pressure readings will be obtained at every visit. Subject should be allowed to rest for more than 5 minutes sitting, then BP measurements and pulse (x3) will be performed, using the non-dominant arm with a calibrated electronic sphygmomanometer. The average of the second and third readings will be documented.
3. Subjects should fast for at least 8 hours before the test. Laboratory work includes: hematology and Lipid Panel, Albumin, Alkaline Phos, ALT, AST, Total Bilirubin, BUN, BUN: Creatinine ratio, Calcium, Chloride, Creatinine, eGFR, Glucose, Potassium, Sodium, Uric Acid, and urinalysis. HIV Ab, HCV Ab, HBsAg. will only be done at screening.
4. Subjects should fast for at least 8 hours before the test.
5. Weight of the investigational product kit will be obtained at the Baseline visit. Study staff will be asked to weigh all dispensed bottles without the carton box PRE- FIRST DOSE. Weight will be recorded in grams.
6. Subjects will be asked to bring all dispensed bottles back for the Week 4 and Week 8 visits. Upon return for the study visit, all bottles will be weighed again without the carton box. Subjects will be asked to apply the investigational product twice daily. First investigational product application will happen at the site under medical supervision.
7. Subjects will be counseled on the use of study medication and answer any questions subject may have.
8. Subjects will be asked to fill out study diary for the duration of the study.
9. Cleanser and moisturizer will be dispensed at the Baseline visit. Subjects will be asked to refrain, if possible, from using any other cleanser and/or moisturizer on their face and apply the provided product while they are participating in the trial. Any left over moisturizer /cleanser will be collected at Week 8 visit, at which point subjects will be asked to go back to their regular routine.

PRINCIPAL CONTACTS

Clinical Protocol and Conduct Inquiries	AOBiome Masha Gaber Clinical Operations mgaber@aobiome.com
Sponsor's Medical Expert for the Trial	Name: Larry Weiss, MD Title: Chief Medical Officer Email: lweiss@aobiome.com
Reporting of Serious Adverse Events (SAEs)	Biorasi Safety and Pharmacovigilance 19495 Biscayne Blvd., Suite #900 Aventura, FL 33180 Fax: +1 (786) 221-3531 RB244-001-safety@biorasi.com

1 BACKGROUND AND RATIONALE

1.1 Background

Rosacea is a chronic dermatologic disorder that primarily affects convexities of the central face with skin lesions located on the cheeks, chin, nose, and central forehead. An estimated 14 million Americans have rosacea.[1] Rosacea prevalence is highest (between 2.7 and 10%) in patients with northern European or Celtic heritage.[2] Rosacea is more common among female patients, and incidence peaks between the ages of 30 and 50 years. In 2002, National Rosacea Society Expert Committee established a standard classification system of rosacea subtypes based on the clinical characteristics. The four basic stages of the disease are erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea, ocular rosacea and one variant rosacea, granulomatous rosacea (GR) [3].

Diagnostic criteria of rosacea include primary features such as flushing, persistent central facial erythema, pustules, papules in the central facial distribution, thickened skin with irregular contours overlying the ears, cheeks, chin (gnathophyma), forehead (metophyma), and nose (rhinophyma), watery, burning, dry, itchy, and light sensitive ocular sensation with a bloodshot appearance.[3]

Men are more prone to the phymatous skin changes associated with rosacea. Rosacea patients experience periods of relapses and remissions. There are trigger factors that can lead to a relapse such as: sun exposure, stress, hot weather, alcohol, spicy foods, exercise, wind, hot baths, cold weather, hot drinks and certain skin care products and medications.[4]

Pathogenic mechanisms that lead to the development of the skin lesions have not yet been fully elucidated. However, the pathology of rosacea may be multifactorial: abnormal vascular and immune system responses; hair follicle mite Demodex folliculorum and Demodex brevis; bacteria such as *H. pylori and Bacillus oleronius*; prolonged steroid use and other aggravating trigger factors like sun and stress.[5,6] Gallo and colleagues found an abnormally high level of the naturally occurring antimicrobial peptide cathelicidins upon histopathological staining in the skin of patients with rosacea.[7] Over the years, there have been numerous attempts to connect etiopathogenesis of rosacea with the presence of some microorganisms, specifically Demodex mite and bacteria. It has been well documented, that people with rosacea have higher density of Demodex mites on their skin compared to controls[8,9].

In addition, presence of Demodex mite on facial skin has also been associated with itching, with or without erythema[10].

Bacillus bacteria found in the *Demodex* mite stimulate immune response and produce an antigen that could be responsible for the tissue inflammation[11].

Epidermal cells and sebum components are the main food sources for the Demodex mites, therefore these ecto-parasites are found in the areas rich in sebaceous glands, such as the face, including cheeks, nose, chin and forehead[12].

It is thought that Demodex mites may carry the bacteria into areas of the face most susceptible to rosacea changes, which in turn may produce higher density of bacteria and thus create an inflammatory response[11].

In the process of destroying epithelial cells, Demodex penetrates the dermis, stimulating Toll Like receptors (TLR) leading to increased skin inflammation and hyperreactivity to environmental stimuli.

1.2 Rationale of the Study

The proposed study is aimed to evaluate the safety and efficacy of B244 topical spray. A Vehicle-Controlled, Double-Blind, Multicenter, Randomized Study Design has been Selected in Order to Evaluate the Safety and Efficacy of the B244 Investigational product in the Treatment of Mild-to-Moderate Rosacea.

There is no cure for rosacea and treatment is aimed at alleviating the symptoms. Topical or oral medications are generally prescribed for mild to moderate papulopustular rosacea. These topical medications include: metronidazole, azelaic acid, sodium sulfacetamide and sulfur, erythromycin, and tretinoin[8]. Currently these approved topical medications may cause local irritation to the skin. The oral medications prescribed for severe disease include tetracycline, doxycycline, minocycline, erythromycin and metronidazole. The systemic therapies may result in systemic adverse events such as gastrointestinal upset and photosensitivity.

It is believed, that topical application of Ammonia-Oxidizing Bacteria (AOB) will reduce survival of pathogenic bacteria present on the skin and thus improve rosacea symptoms in those affected by it.

AOBs are essential for the initial step in environmental nitrification processes, specifically the oxidation of ammonia (NH_3) to nitrite (NO_2-). *Nitrosomonas* are Gram-negative chemolithoautotrophic betaproteobacteria that obtain energy solely from NH_3 oxidation, while fixing CO_2 for their carbon needs[13]. Oxidation of NH_3 proceeds in two steps (Figure 2) leading to sequential generation of hydroxylamine (NH_2OH) and NO_2- that require two enzyme complexes: the membrane-bound ammonia monooxygenase (AMO) comprised of subunits AmoA, AmoB and AmoC; and the periplasmic NH_2OH oxidoreductase (HAO). In addition to high NO_2- levels, NH_3 oxidation leads to nitric oxide (NO) and N_2O production through two independent pathways downstream of NH_2OH production: nitrifier denitrification and NH_2OH oxidation[14].

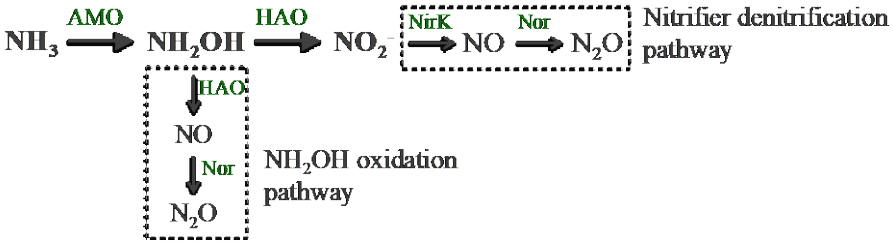


Figure 2 Nitrifier Denitrification Pathway

B244 is a purified strain of *Nitrosomonas eutropha*, designated D23, originally isolated from soil samples. Sequencing of the B244 genome revealed a distinct genetic profile from that of other published *Nitrosomonas* strains and AOB genomes. Based on *in vitro* co-culture studies, B244 was able to reduce survival of pathogenic bacteria. Nitrite generation from ammonia concurrently with medium acidification by B244 led to strong antibacterial effects and a marked reduction (~100-fold) in viable counts of methicillin-resistant *Staphylcoccus aureus* and *Pseudomonas aeruginosa*, two pathogens frequently isolated from infected skin and wound sites. In contrast, control cultures with B244 in the absence of ammonium or with heat-killed B244 supplemented with ammonium, had no antibacterial effects. The unique metabolic and antimicrobial activity of *Nitrosomonas*, in combination with their lack of virulence render these bacteria as attractive candidates for topical delivery of nitrite and nitric oxide on human skin with potential to improve health in both normal and abnormal skin conditions or wound sites. NO-releasing drugs or NO donors have also shown activity against *Propionibacterium acnes* and other pathogenic bacteria, anti-inflammatory activity, and inhibition of lipogenesis by insulin-stimulated immortal sebocytes[15, 16].

1.2.1 Clinical Experience

B244 is being developed as a 'live topical' to provide a natural source of AOB and NO/NO_2 to the human skin. A phase 1b/2a clinical trial entitled A Double Blind, Vehicle-Controlled, Single Center, Randomized, Sequential, Ascending 14-Day Multiple Dose Study in Subjects with Acne Vulgaris to Evaluate the Safety, Tolerability and Preliminary Efficacy of B244 Delivered as a Topical Spray was completed in 2016 where 36 participants with clinical diagnosis of facial acne vulgaris were randomized to receive ascending doses of investigational product (IP) over 14 days. Safety analyses have been completed and there have been no attributable drug related SAEs reported. In addition, a Phase 2b/3 clinical trial entitled A Randomized, Double Blinded, Phase IIb/III, Decentralized Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Participants with Mild to Moderate Acne Vulgaris in 372 patients with clinical diagnosis of facial acne has been completed. B244 was safe and well tolerated with no attributable drug related SAEs. Efficacy was supported by statistically significant 2-point reduction in IGA with B244 and a trend in the reduction of the number of inflammatory lesions compared to vehicle.

Additionally, other topical development programs with B244 include hypertension and atopic dermatitis. A study titled, "A Prospective, Controlled, Double Blinded, Multicenter, Randomized, Vehicle controlled, Phase II Study of B244 delivered as a topical spray to Determine Safety and Efficacy in Subjects with elevated blood pressure" has been completed. Safety data indicated that B244 was safe and well tolerated. Overall, 16% subjects experienced at least 1 TEAE during the study with comparable incidence in the B244 and Vehicle groups. The most commonly reported types of events in the study were nervous system disorders (5% incidence) and investigations (4% incidence). No TEAE was reported in more than 1 subject in the B244 group. There was no apparent increase in the incidence of TEAEs with increasing dose in either treatment group. All TEAEs were Grade 1 or Grade 2 in severity. There were no deaths in the study. Overall, there were no unexpected safety signals observed following treatment with B244.

A study titled, "A Prospective, Vehicle Controlled, Double Blind, Multicenter, Randomized, Phase II Study of B244 Delivered as a Topical Spray to Determine Safety and Efficacy in Subjects with Mild to Moderate Atopic Dermatitis" is currently enrolling subjects.

Furthermore, a nasal spray of B244 is being developed for treatment of allergic rhinitis and migraines. A rat toxicology study performed by intranasal administration of B244 twice daily for 28 days found that B244 was safe and well tolerated in rats at levels of up to the maximum dose 8x109 cell/mL. A study titled, "A Prospective, Controlled, Double Blinded, Single Center, Randomized, 3 arm, Phase 1b/2a Study to Assess the Safety, Tolerability, and Preliminary Efficacy of B244 Delivered as an Intranasal Spray in Healthy Volunteers and Subjects with Seasonal Allergic Rhinitis" has been initiated. In addition, a study titled "A Prospective, Randomized, Vehicle-Controlled, Double-Blind, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of B244 Delivered as an Intranasal Spray for Preventive Treatment in Subjects with Episodic Migraine" is being initiated.

1.2.2 Safety Profile

To date, there have been no reported infections or health risks associated with topical application or ingestion of *Nitrosomonas* species. The absence of any illnesses attributed to these bacteria despite our widespread exposure indicates that they pose a minimal health risk, if any at all. Infection or tissue damage by *Nitrosomonas* is unlikely, because the sequenced genomes of several *Nitrosomonas* and other AOB lack genes encoding cytotoxins, or other known bacterial virulence factors. Further, AOB are slow growing, as compared to most heterotrophic bacteria, with optimum doubling times of 8 hours or higher. In particular, *Nitrosomonas* growth is rate limited by the availability of ammonia requiring the oxidation of 27 moles NH_3/mole CO_2 fixed. Due to their dependence on ammonia for their growth, the numbers of *Nitrosomonas* on the skin will be necessarily limited and naturally regulated by the amount of ammonia produced in sweat. This would ensure that the amount of nitrite and NO generated would be relatively low, without any adverse effects.

2 STUDY OBJECTIVES

2.1 Study Objectives

2.1.1 Primary Objective

- To assess the safety and tolerability of B244 applied twice daily (BID) to the face for 8 weeks in subjects with mild to moderate rosacea.

2.1.2 Exploratory Objectives

- To assess the efficacy of B244 in subjects with mild to moderate rosacea.
    - Proportion of subjects with IGA improvement at Week 8 relative to baseline.
    - Proportion of subjects with CEA improvement at Week 8 relative to baseline.
    - Change in IGA from Week 8 to Baseline.
    - Change in CEA from Week 8 to Baseline.
    - Proportion of Subjects with improvement in IGA or CEA at Week 1, Week 4, and Week 12.
    - Change in Skindex 16 patient reported outcome from Baseline to Week 1, Week 4, Week 8, and Week 12.
    - Proportion of subjects with change in PSA at Week 1, Week 4, Week 8 and Week 12 from Baseline.
    - Evaluation of Telangiectasia Score at Baseline/Day 1 and Week 8

3 STUDY ENDPOINTS

3.1 Safety & tolerability

- Safety and tolerability endpoints will consist of all adverse events reported during the study duration.

3.2 Efficacy

- IGA score at Baseline to Week 1, Week 4, Week 8 and Week 12.
- CEA score at Baseline to Week 1, Week 4, Week 8 and Week 12.
- Skindex 16 patient reported outcome from Baseline to Week 1, Week 4, Week 8 and Week 12.
- PSA score at Baseline to Week 1, Week 4, Week 8 and Week 12.

3.3 Exploratory

- IGA treatment success, defined as "clear" or "almost clear" with a 2-grade improvement in IGA score from baseline to the end of treatment.
- CEA treatment success defined as "clear" or "almost clear" with a 2-grade improvement in CEA score from baseline to the end of treatment.

4 INVESTIGATIONAL PLAN

4.1 Study Design

- This is a Prospective, Vehicle Controlled, Double Blind, Multicenter, Randomized Phase II trial, Comparing the effect of twice daily B244 application for 8 weeks vs. vehicle application on treatment of mild to moderate rosacea.
- We will enroll approximately 130 subjects and complete 104 subjects.
- At Screening and Baseline:
  - All subjects must have clinical diagnosis of mild to moderate rosacea.
  - Subjects must have IGA score of 2-3 and CEA score of 2-3 in order to qualify for the study.
- After screening and recruitment, participants will be randomized to active or vehicle application for 8 weeks.
- Subjects will apply a total of 4 pumps of IP per application to the face twice-a-day.
- Randomization will be 1:1 B244 to Vehicle.
- Subjects will be provided with cleanser and moisturizer to use for the duration of the study.
- All B244 randomized subjects will be treated at the dose of $4x10^9$ cells/ml via spray application.
- Screening will occur at Days -21 to -1.
- Washout will occur after Screening visit (Days -14 to -1).
- Randomization will occur during the baseline visit for the study (Day 1).
- Efficacy will be assessed using Investigator Global Assessment (IGA) score, Clinician's Erythema Assessment (CEA) score, Patient Self-Assessment (PSA) score and patient reported Skindex 16.
- Clinical assessments of response to treatment will be made at Week 1(Day 7), Week 4 (Day 28), and Week 8 (Day 56).
- At Baseline visit, subjects will receive a kit containing the drug product. Each bottle will be used for 2 weeks. At Week 4, subjects will return the used bottles from the kit and will be issued a new kit of drug product to be used from Week 4 through Week 8.
- Subjects will stop applying investigational product at Week 8 and will return investigational product at that visit.

- Subjects will come back for a 4-week post-treatment follow up visit at Week 12 (Day 84).
- Participant's safety will be monitored throughout the study. Safety will be assessed by monitoring reported adverse events, vital signs, clinical chemistry and hematology and overall tolerability of the investigational product.
- Subjects would be required to discontinue the investigational product under the following circumstances:
    - Development of an intercurrent illness that would jeopardize the safety, or significantly affect assessments of clinical status of a subject
    - Either at the discretion of the Investigator or at the participant's request
    - Development of any investigational product-related SAE
    - Suspected or laboratory-confirmed pregnancy

4.2 Number of Subjects and Sites

Approximately 130 subjects are planned to be enrolled, and assuming a 20% drop out rate, the planned overall sample size for this clinical trial is approximately 104 adult male and female subjects, 18 years of age and older with mild to moderate rosacea. Subjects will be randomized at a 1:1 ratio (B244: Vehicle) at about 8 clinical research centers in the United States.

5 SELECTION AND WITHDRAWAL OF STUDY POPULATION

5.1 Eligibility Criteria

Subjects who satisfy ALL of the following **inclusion** and have NONE of the following **exclusion** criteria may be enrolled in the study:

5.1.1 Inclusion Criteria

1. Male and female subjects ≥18.
2. A clinical diagnosis of mild to moderate facial rosacea.
3. In good general health as determined by a thorough medical history, physical examination, clinical chemistry and hematology.
4. Presence of 3 to 20 inflammatory lesions on the face (i.e. papules/pustules).
5. A Clinician Erythema Assessment (CEA) score of 2-3 at Screening and at Baseline Visits (prior to the investigational product application).
6. Mild to Moderate IGA score of 2-3 at Screening and at Baseline Visits (prior to the investigational product application).
7. Willing to refrain from using any topical or systemic treatments for the treatment of rosacea, other than the investigational product.
8. Females of childbearing potential with a negative urine pregnancy test (UPT) at Screening and Baseline/Day 1 (prior to the investigational product application).

9. Ability to comprehend and comply with study procedures.
10. Agree to commit to participate in the current protocol.
11. Provide written informed consent prior to any study procedure being performed.

5.1.2 Exclusion Criteria

Any subject who meet one or more of the following criteria are excluded from this study.

1. Female subjects who are pregnant, lactating or who are trying to conceive will be excluded from participation in this study.
2. Any uncontrolled chronic or serious disease or medical condition that would normally prevent participation in a clinical trial, or, in the judgment of the Investigator, would put the subject at undue risk, or might confound the study assessments (e.g., other dermatological diseases), or might interfere with the subject's participation in the study, (e.g., planned hospitalization during the study).
3. Particular forms of rosacea (e.g., rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin, Ocular rosacea Phymatous rosacea, Steroid-induced rosacea, severe rosacea including pyoderma faciale) or other concomitant facial dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia.
4. Presence of more than two (2) nodulocystic lesions on the face.
5. Presence of less than 3 and more than 20 inflammatory lesions on the face (i.e. papules/pustules).
6. Severe papulopustular rosacea requiring systemic treatment.
7. Participation at the time of eligibility assessment (Screening) in any other investigational drug or device study or may have participated within 30 days prior to Screening.
8. Commencement of new hormonal therapy or dose change to hormonal therapy within 30 days prior to baseline. Dose and frequency of use of any hormonal therapy started more than 30 days prior to baseline must remain unchanged throughout the study. Hormonal therapies include, but are not limited to, oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (e.g. vaginal ring or transdermal hormone contraception)
9. Presence of beard or excessive facial hair at Screening which would interfere with the study treatments or study assessments and refusal to remove for duration of study.
10. Carcinoid, Pheochromocytoma or other systemic causes of flushing.
11. Known sensitivity to B244 or its components.
12. Refusal to submit to blood and urine sampling for laboratory analysis.
13. Treatment with the following:

Prohibited Topical Treatments:

Topical Treatment	Prohibited Time Frame prior to Baseline
Astringents or abrasives	2 days
RHOFADE™ (oxymetazoline HCl) Cream, 1%	1 week
Bleach baths	1 week
Mirvaso (brimonidine) topical cream	1 week
Vinegar	1 week
Topical Prescription/OTC medications for treatment of acne	2 weeks
Soolantra (Ivermectin 1%) topical cream	1 week
Topical Antibiotic	2 weeks
Use of over the counter antimicrobial	2 weeks
Benzoyl Peroxide	2 weeks
Immunomodulators	4 weeks
Oracea (doxycycline) topical cream	2 weeks
Corticosteroids	4 weeks
Electrocoagulation, Dermabrasion; Facial peels	4 weeks
Dermatologic/surgical procedure on the face	4 weeks
Topical Prescription medications for the treatment of rosacea (e.g. azelaic acid, metronidazole, etc.)	4 weeks
Laser, Phototherapy, Photodynamic Therapy or IPL (intense pulsed light) treatment	4 weeks
Over the counter topical retinoid use on the face	4 weeks

Prohibited Systemic Treatments:

Systemic Treatment	Prohibited Time Frame prior to Baseline
Exposed to excessive ultraviolet (UV) radiation and/or subject was unwilling to refrain from excessive exposure to UV radiation during the course of the study	1 week
Prescription anti inflammatory	2 weeks
Prescription/OTC anti-inflammatory medications (excludes low dose aspirin)	2 weeks
Systemic Antibiotics	4 weeks
Systemic medications for the treatment of rosacea (e.g. doxycycline, tetracycline, macrolides)	4 weeks
Prescription medications for treatment of acne	4 weeks

Corticosteroids (oral or injectable)	4 weeks
Immunomodulators	12 weeks
Oral retinoid use (e.g., isotretinoin), vitamin A supplements greater than 10,000 units/day	6 months

5.2 Study Withdrawal

A subject may voluntarily withdraw from the study at any time and for any reason without prejudice to his or her future medical care. The Investigator, Sponsor, or Medical Monitor may also withdraw a subject at any time if it is medically necessary or in the interest of subject's safety. Additional reasons for premature discontinuation of investigational product may include adverse events and major non-compliance with study procedures, as described below. The withdrawal of a subject from investigational product by the Investigator will be discussed with the Medical Monitor before the subject stops investigational product, whenever possible.

A subject will be discontinued from this study if any of the following criteria are met:

- Withdrawal of consent by the subject is received.
- In the opinion of the Investigator, Medical Monitor or Sponsor, it is not in the subject's best interests to continue in the study.
- Significant non-compliance with study procedures that would interfere with the study results or increase the subject's risks in the study, as determined by the Investigator.
- Development of an intercurrent illness that would jeopardize the safety, or significantly affect assessments of clinical status of a subject.
- Development of any investigational product-related SAE.
- Suspected or laboratory-confirmed pregnancy.

Subjects who discontinued early from the study due to lack of treatment effect after completing at least four weeks of treatment (Day 28) will be included in the mITT and PP population as treatment failures and the change in IGA and CEA 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. Subjects discontinued early for other reasons will be excluded from the PP population.

5.3 Early Discontinuation

If a subject discontinues prematurely, the Investigator will perform Early Termination (ET) visit, capturing the reason for discontinuation.

If a subject does not return for a scheduled visit, every effort will be made to contact the subject and document the End of Study visit assessments. The Investigator must document the primary reason for discontinuation of a study subject in the source document and on the appropriate electronic case report form (eCRF).

Randomized subjects who discontinue due to an adverse event will have all events documented and followed to satisfactory resolution, as detailed in Section 12.

6 INVESTIGATIONAL PRODUCT TREATMENT AND ADMINISTRATION

6.1 Identity of Investigational product(s)

The term *investigational product* is used to refer to the B244 and vehicle drug products. Please see the study ***Pharmacy Manual*** for full details.

6.2 Investigational Product

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from the Sponsor upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the Investigator and authorized site staff. Investigational product must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance. The Investigator or designated site personnel must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to the Sponsor and the amount administered to participants. The required accountability unit for this study will be the bottle. Discrepancies are to be reconciled or resolved.

Product name:	B244, 30ml/bottle	Vehicle, 30ml/bottle
Dosage form:	B244 suspension	Vehicle solution
Unit dose strength:	$4x10^9$ cfu/ml	50nM Na_2HPO_4-2mM $MgCl_2$ (pH 7.6)
Route/administration/duration:	Topical application BID for 8 weeks	Topical application BID for 8 weeks
Dosing instruction:	4 pumps of spray to saturate the entire face applied BID. Applications should occur in the morning and at night for 8 weeks.	4 pumps of spray to saturate the entire face applied BID. Applications should occur in the morning and at night for 8 weeks.
Physical description:	Odorless, cloudy, light pink suspension	Odorless, clear, and colorless solution

Manufacturer/source of procurement:	AOBiome, LLC	AOBiome, LLC

6.3 Packaging and Labeling

The investigational product bottles to be dispensed to the subject will be packaged and labeled in accordance with Good Manufacturing Practice. Each individual bottle of the investigational product will be provided in a subject's kit. The contents of the label will be in accordance with all applicable regulatory requirements. B244 and matching vehicle will be packaged in identical 30 ml white bottles.

6.4 Storage of the Investigational product at Site

All investigational drug supplies in the study will be stored in a secure, refrigerated (2-8ºC) safe place, under the responsibility of the Investigator or other authorized individual.

The Investigator will maintain temperature monitoring of the investigational product with daily temperature readings. All temperature excursions must be reported to the Sponsor using the Temperature Excursion log. If the investigational product was exposed to the temperature excursion outside the range of 2-8ºC, but for the period greater than 24 hours, the investigational product must be quarantined until the Sponsor's approval on future use. Please refer to the ***Pharmacy Manual*** for additional detail on the Temperature Excursions and temperature monitoring during the shipment and storage at the site pharmacy.

6.5 Treatment Assignment (Randomization)

Randomization will be performed using an Interactive Web Response System (IWRS) at the time the subject has met all eligibility criteria and is ready for enrollment. Subjects will be randomized in a 1:1 ratio to receive either B244 or vehicle and will be stratified by site.

Interactive Web Response System (IWRS) will assign subjects to the treatment arm and specify the kit number to be dispensed.

The randomization scheme will be generated and held by the independent third party throughout the conduct of the study and will not be available to the Sponsor, Investigator, or study staff, or to clinical staff who could have an impact on the outcome of the study.

6.6 Blinding/Unblinding Procedures

This is a double-blind study, thus Sponsor, CRO, site staff, study monitors, and subjects will be blinded to the randomization scheme. The packaging of the investigational product products will be identical in appearance to make difference in treatment less obvious to the subjects.

The blinding scheme for each set of the investigational product will be available to the FDA or other regulatory agency investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

The blinding code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Investigator to complete a serious adverse event report. In such situations, the Investigator will use the IWRS system in order to unblind the treatment for the individual subject. Unblinded information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded and reported appropriately to the IRB.

As the study is blinded, the Investigator should promptly document and explain to the Sponsor and Medical Monitor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

The Investigator may unblind a participant's treatment assignment only in the case of emergency or in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant, as determined by the Investigator. It is preferred (but not required) that the Investigator first contacts the Medical Monitor to discuss options before unblinding the participant's treatment assignment. The Investigator must notify the Sponsor as soon as possible when a participant's treatment assignment is unblinded without revealing the treatment assignment of the unblinded participant unless that information is deemed important for the safety of participants currently in the study. The date and reason for the unblinding must be documented in the participant's study record.

The Investigator may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to clinical Investigators in accordance with local regulations and/or Sponsor policy.

6.7 Investigational product Dispensation, Application, and Home Storage

At Baseline visit, Subjects will receive a kit containing two 30 ml white bottles. Each bottle will be used for 2 weeks. At Week 4, subjects will return the used bottles from the kit and will be issued a new kit of two 30mL white bottles to be used from Week 4 through Week 8. Subjects will store the unused bottle in the refrigerator until utilized. The bottle which is being used for treatment at a given week may be kept at ambient temperature to be used during the treatment period.

Subjects will be asked not to expose the treatment kit to conditions which are unnatural or harmful to the product, such as excessive heat (temperatures over 77°F (25°C) and freezing temperatures (at 0ºC). Subjects may travel with their study medication but should not leave it in the hot car, outside in the cold temperatures etc. Subjects will also be asked not to tamper or cause damage to investigational product bottle.

Each subject will be instructed by the Investigator on proper application technique. The following application instructions will be provided to the subject:

- Subjects will apply 4 pumps of investigational product to saturate their face in the

morning and 4 pumps of investigational product at night.

- Subject should saturate the application area well.
- Subjects will be asked to let the product air dry.
- Subjects may not wash their face for 2 hours post morning application of the investigational product.
- Participants may not bathe, shower or wash their face until morning post evening application of IP.
- While in use, one spray bottle may be stored at ambient temperature. The bottle that is not in current use by the subject, must be stored in the refrigerator.
- DO NOT FREEZE.

6.8 Accountability, Destruction and Return of Study Supplies

In accordance with federal and local regulatory requirements, the Investigator and designated site personnel must document the amount of investigational product dispensed to study Subjects, the amount returned by study Subjects, and amount received and returned to the Sponsor, when applicable. Product accountability records must be maintained throughout the course of the trial. Any quality issue noticed with the receipt or use of an investigational product (deficient investigational product in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

All investigational product must be stored in a secure locked room with access limited to the Investigator and designated site personnel. Study product is to be stored in a refrigerator between 2-8º C. Maintenance of a temperature log is required.

Under no circumstances will the Investigator allow investigational product to be used other than as directed by this Clinical Trial Protocol, or dispose of investigational product without Sponsor direction.

The Sponsor will supply sufficient quantities of the investigational product for the completion of this study.

The study pharmacist or designated study personnel will maintain an Investigational Materials Accountability Record and a Subject Investigational Product Accountability Log itemizing all investigational product received, dispensed to and returned from each subject during the study. All dispensed bottles must be accounted for, and any discrepancies explained. Study site should contact site Clinical Research Associate (CRA) or designee in case of any dispensing errors or if discrepancies are discovered.

Prior to site closure and at appropriate intervals during the study, site CRA will perform investigational product accountability and reconciliation. At the end of the study, the Investigator will retain all the original documentation regarding investigational product accountability, return, and copies will be sent to the Sponsor.

All unused and used investigational product tubes will be returned to the Sponsor or its designee for destruction at the end of the study.

6.9 Treatment of Investigational Product Overdose

The Sponsor does not recommend specific treatment for an overdose. Washing with conventional cleanser and water will remove the product. The Investigator will use clinical judgment to treat any overdose.

6.10 Dose Changes

No dose changes are anticipated.

7 CONTRACEPTION REQUIREMENTS

7.1 Contraception and Pregnancy Avoidance Measures

Effective contraception is required for all women of childbearing potential (WOCBP) during study participation.

Female subjects must be post-menopausal OR surgically sterile or using highly effective birth control methods (note below) with a negative urine pregnancy test at the Baseline Visit. Male subjects must be willing to not attempt to conceive a child during the participation in the study.

Acceptable forms of contraception include:

Total abstinence; oral (birth control pills), intravaginal (e.g. NuvaRing®), implantable (e.g. Norplant®), injectable (e.g. Depo-Provera®) or transdermal (e.g. Ortho Evra®) contraception, intrauterine device (IUD), double-barrier (diaphragm or condom with spermicidal gel or foam) for one month prior to study enrollment or a vasectomized partner (6 months status post vasectomy).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 30 days before the baseline visit.

If a subject, or female partner of male subject becomes pregnant during the participation in the study, the Investigator will immediately discontinue the Subject from the study and contact the Medical Monitor and the Sponsor. Diligent efforts will be made to determine the outcome for all pregnancy exposures in the clinical trial. Information on the status of the mother and the child will be forwarded to the Sponsor's Safety Team using the Pregnancy Data Collection Form. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Detailed guidance on the reporting of Pregnancies will be provided in **SAE and Pregnancy Reporting Guidance**.

Payment for all aspects of obstetrical care, child-or related care will be the study participant's responsibility.

8 CONCOMITANT MEDICATIONS

8.1 Prior, Concomitant and Prohibited Therapy

Current medications and any medications taken within the 30 days prior to the start of the study will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication, start and stop dates. The medications to be recorded include prescription, all over-the-counter (OTC) medications and all dietary supplements. All medications taken on a regular basis should be recorded prior to commencing the use of the investigational product. Any medications started during the study (including "as needed" medications) will be recorded in the concomitant medication list as soon as the Investigational Site will become aware of the medication being added.

Prohibited Therapies are those medicinal products and treatment methods that are not allowed during the study period and within the timeframes specified in Table 2.

Table 2. List of Prohibited Medication and Treatment Methods

Prohibited Topical Treatments:

Topical Treatment	Prohibited Time Frame prior to Baseline
Astringents or abrasives	2 days
RHOFADE™ (oxymetazoline HCl) Cream, 1%	1 week
Bleach baths	1 week
Mirvaso (brimonidine) topical cream	1 week
Vinegar	1 week
Topical Prescription/OTC medications for treatment of acne	2 weeks
Soolantra (Ivermectin 1%) topical cream	1 week
Topical Antibiotic	2 weeks
Use of over the counter antimicrobial	2 weeks
Benzoyl Peroxide	2 weeks
Immunomodulators	4 weeks
Oracea (doxycycline) topical cream	2 weeks
Corticosteroids	4 weeks
Electrocoagulation, Dermabrasion; Facial peels	4 weeks
Dermatologic/surgical procedure on the face	4 weeks
Topical Prescription medications for the treatment of rosacea (e.g. azelaic acid, metronidazole, etc.)	4 weeks

Laser, Phototherapy, Photodynamic Therapy or IPL (intense pulsed light) treatment	4 weeks
Over the counter topical retinoid use on the face	4 weeks

Prohibited Systemic Treatments:

Systemic Treatment	Prohibited Time Frame prior to Baseline
Exposed to excessive ultraviolet (UV) radiation and/or subject was unwilling to refrain from excessive exposure to UV radiation during the course of the study	1 week
Prescription anti inflammatory	2 weeks
Prescription/OTC anti-inflammatory medications (excludes low dose aspirin)	2 weeks
Systemic Antibiotics	4 weeks
Systemic medications for the treatment of rosacea (e.g. doxycycline, tetracycline, macrolides)	4 weeks
Prescription medications for treatment of acne	4 weeks
Corticosteroids (oral or injectable)	4 weeks
Immunomodulators	12 weeks
Oral retinoid use (e.g., isotretinoin), vitamin A supplements greater than 10,000 units/day	6 months

8.2 Prohibited procedures

Participants will be asked refrain from cosmetic facial procedures for the possible treatment of rosacea or acne, such as chemical peels, micro or dermabrasion, comedone extraction, electrocautery, Phototherapy, Photodynamic Therapy or IPL (intense pulsed light) treatment laser peels or laser light therapy (including ThermaClear ^{TM}, blue light, tanning devices or photodynamic therapy), steroid injections throughout the study until the final follow-up visit.

If the Investigator becomes aware of a subject having taken a prohibited medication or performed prohibited procedure, they will report the incident to the Medical Monitor within 24 hours, and the Medical Monitor and/or Sponsor will provide written approval of the subject's continuation or discontinuation from the study.

9 LIFESTYLE RESTRICTIONS

9.1 Use of cleanser and moisturizer during the trial

At the beginning of the trial, subjects will be provided with cleanser and moisturizer to use for the duration of the trial as needed. The subject may choose not to use a moisturizer, as it is not required. If moisturizer is used, subject should be advised to apply it 10 minutes after the application of the IP.

Subjects may use other cleansers to wash other parts of their body not treated during the study.

At Week 8 (End of Investigational product application) subjects will be asked to return cleanser and moisturizer that was provided to them by the Sponsor and will be asked to go back to their regular regimen and use their preferred cleanser and moisturizer.

9.2 Use of makeup, moisturizers and sun screen

- Use of anti-aging, anti-acne or rosacea treatment products or procedures on the face will be prohibited during the study.
- Subjects will be encouraged not to use other topical products on the face, such as emollients, sunscreen, moisturizers, etc. These should be used minimally or used sparingly while in the active phase (Baseline-Week 8) of the trial.
- Participants will be advised to use minimally or use sparingly liquid or powder makeup during the active phase (Baseline-Week 8) of the study.

10 STUDY PROCEDURES AND SCHEDULE OF STUDY ACTIVITIES

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same Investigator or site personnel whenever possible.

10.1 Administrative Procedures

10.1.1 Subject Informed Consent

A signed and dated, study-specific, approved by Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and applicable regulatory authorities Informed Consent Form must be obtained from each subject prior to performing any study related procedures. No study related procedures or activities may be performed until each subject is fully informed and the consent form is signed and dated.

10.1.2 Documentation of Screen Failures

Investigators must account for all subjects who sign informed consent and will maintain an Subject Screening and Enrollment Log capturing subjects screened and indicating who was

enrolled or excluded and the reason why. If the subject is found not to be eligible prior to enrollment, the reason(s) for ineligibility must be documented by the Investigator. Subject Numbers assigned to subjects who fail screening will not be re-used.

10.2 Study Procedures

10.2.1 Visit 1- Screening Visit (Day -21 to -1)

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Medical History
- Concomitant and Prohibited Therapies review and documentation
- Physical examination
- Collection of Vital Signs
- Urine pregnancy test for WOCBP
- Venipuncture for Laboratory Assessment & Urinalysis
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex-16
- Patient Self-Assessment (PSA)
- Fitzpatrick skin type
- Start AE collection and assessment

10.2.2 Washout Phase (-14 to -1)

Washout phase may be initiated after Screening procedures have been completed.

10.2.3 Visit 2- Baseline visit (Day 1):

Baseline visit will include the following procedures and assessments:

- Review of inclusion/exclusion criteria
- Review of Medical History
- Concomitant and Prohibited Therapies review and documentation
- Physical examination
- Collection of Vital Signs
- Urine pregnancy test for WOCBP
- Venipuncture for Laboratory Assessment & Urinalysis
- Blood for biomarkers
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex 16
- Patient Self-Assessment (PSA)

- Telangiectasia Evaluation
- Randomization
- IP dispensation
- IP compliance
- IP application under medical supervision
- Study cleanser and moisturizer dispensation
- Study counseling
- Study Diary
- Adverse Events collection and assessment

10.2.4 Visit 3- Week 1 (Day 7) ±2 days

The following procedures will be performed:

- Concomitant and Prohibited Therapies review
- Collection of Vital Signs
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex 16
- Patient Self-Assessment (PSA)
- Study Counseling
- Study Diary
- Urine pregnancy test for WOCBP
- Adverse Event collection and assessment

10.2.5 Visit 4- Week 4 (Day 28) ±2 days

The following procedures will be performed:

- Concomitant and Prohibited Therapies review
- Collection of Vital Signs
- Venipuncture for Laboratory Assessment & Urinalysis
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex 16
- Patient Self-Assessment (PSA)
- Urine pregnancy test for WOCBP
- Study cleanser and moisturizer dispensation
- IP compliance
- IP collection
- IP dispensation
- Study Counseling
- Study Diary

- Adverse event collection and assessment

10.2.6 Visit 5- Week 8 (Day 56) ±2 days

The following procedures will be performed:

- Concomitant and Prohibited Therapies review
- Collection of Vital Signs
- Venipuncture for Laboratory Assessment & Urinalysis
- Blood for biomarkers
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex 16
- Patient Self-Assessment (PSA)
- Telangiectasia Evaluation
- Urine pregnancy test for WOCBP
- IP collection
- IP compliance
- Study cleanser and moisturizer collection
- Study Counseling
- Study Diary
- Adverse event collection and assessment

10.2.7 Visit 6- End of Study Visit-Week 12 (Day 84) ±2 days

The following procedures will be performed:

- Concomitant and Prohibited Therapies review
- Physical Exam
- Collection of Vital Signs
- Urine Pregnancy Test for WOCBP
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex 16
- Patient Self-Assessment (PSA)
- Adverse event collection and assessment

10.2.8 Unscheduled Visit

If an event arises that requires subject to come in to the research center, subjects should be scheduled for the Unscheduled visit and assessments are performed based on investigator discretion.

Subjects will be encouraged to report any complications or adverse effects during their participation. Investigator may evaluate the subject at an unscheduled visit, if subject's condition will be considered as worsening.

10.2.9 Early Termination Visit

Every attempt should be made to complete all visits during the defined window periods. Subjects who do not complete all required study visits and withdraw from the study before Week 12 final visit, will be asked to complete the Early Termination Visit.

During the visit, the following will be obtained:

- Concomitant and Prohibited Therapies review
- Physical Exam
- Collection of Vital Signs
- Urine Pregnancy Test for WOCBP
- Venipuncture for Laboratory Assessment & Urinalysis
- Blood for biomarkers
- Investigator's Global Assessment [IGA]
- Clinician's Erythema Assessment [CEA]
- Skindex 16
- Patient Self-Assessment (PSA)
- Telangiectasia Evaluation
- IP collection
- IP compliance
- Study cleanser and moisturizer collection
- Study diary
- Adverse event collection and assessment

11 METHODS OF ASSESSMENT

11.1 Clinical Evaluations

Study activities will take place according to the Schedule of Study Activities table. The following clinical evaluations will be conducted during the course of the study.

11.1.1 Subject Demographics

Basic demographic information, including date of birth, Fitzpatrick skin type (classification of skin type (or phototype) depending on the amount of melanin pigment in the skin), gender, ethnicity, and race will be recorded at the Screening Visit.

11.1.2 Medical history

Medical history will be collected at the Screening Visit. Relevant medical history, including past history of rosacea will be documented.

11.1.3 Concomitant Medication Recording

All medications (both prescription and nonprescription, and including vitamins, herbals, topicals, inhaled, and intranasal) taken within 30 days prior to the start of the investigational product and through the final study visit will be recorded on the appropriate eCRF (using their generic and brand name, if known) with the corresponding indication, start and stop dates. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (as needed) medication use.

Previous treatment of rosacea must be recorded irrespectively of the term it was given. Corresponding condition shall be captured in the subject's Medical History.

11.1.4 Vital Signs

Vital signs will be collected at each visit. Blood pressure readings will be obtained at every visit as described in the Schedule of Study Activities. Subject should be asked to remove all clothing that covers the location of cuff placement. The individual should be comfortably seated in the chair, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). Neither the subject nor the observer should talk during the measurement. After 5 minutes sitting, serial clinic BP measurements and heart (x3) rate will be performed, using the non-dominant arm with a calibrated electronic sphygmomanometer. The average of the second and third readings will be documented.

Any abnormal characteristics will be evaluated by the Investigator based on their significance. Abnormal vital signs will be considered AEs if they require therapeutic medical intervention, and/or if the Investigator considers them to be AEs based on his/her clinical judgement.

11.1.5 Physical examination

Physical examination, including height, weight, and evaluation of organs and systems (General Appearance, Heart/Cardiovascular, Lungs, Gastrointestinal, Ears / Nose / Throat, Extremities, and Skin) will be assessed at the Screening, Baseline and EOS/ET visits.
Clinically significant abnormalities other than presence of rosacea lesions will disqualify subject from participation.

11.1.6 Investigator's Global Assessment (IGA)

An Investigator's Global Assessment (IGA) will be evaluated at each study visit (Table 3). This scale should not be a reflection of treatment response, but should describe the condition

at each visit. Therefore, no reference should be made to baseline in the evaluation. The Investigator will grade the severity of facial erythema, lesions, papules, pustules, and nodules from 0 to 4. 0=none, 1=almost clear, 2=mild, 3=moderate, 4=severe.

Table 3. Investigator's Global Assessment (IGA) scale

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

Questionnaire can be found in Appendix 1.

11.1.7 Clinician's Erythema Assessment (CEA)

Clinician's Erythema Assessment (CEA) will be will be evaluated at each study visit. The Investigator will assess the extent of rosacea based on the 5-point severity scale summarized below.
The Investigator will perform a static ("snap-shot") evaluation of erythema severity using the CEA, and report the one integer that best describes the overall severity beginning from the Baseline Visit (Table 4). Although inflammation (papules, pustules, plaques) or dry appearance may obscure the level of erythema, underlying redness should be evaluated disregarding this effect. Inflammation or dry appearance may be noted, but perilesional erythema should not be included in this assessment. Transient erythema (flushing) will also not be included.

Table 4. Clinician Erythema Assessment

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

Questionnaire can be found in Appendix 2.

11.1.8 Skindex 16

Skindex-16 instrument will be evaluated at each study visit. The participant will answer a questionnaire examining the relationship between the patient's skin health and quality of life. Skindex16 questionnaire can be found in Appendix 4.

11.1.9 Patient Self-Assessment (PSA)

Subjects will be asked to perform static ("snap-shot") evaluations of their rosacea-associated facial erythema severity using the Patient Self Assessment scale (PSA) at each study visit, and report the one integer that best describes the overall severity of their facial redness as seen in a mirror at the time of the evaluation.

Table 5: Patient Self-Assessment

Circle the number that best describes your rosacea-related facial redness RIGHT NOW.		
Score	**Severity**	**Description**
0	No redness	Clear of unwanted redness
1	Very mild redness	Nearly clear of unwanted redness
2	Mild redness	Somewhat more redness than I prefer
3	Moderate redness	More redness than I prefer
4	Severe redness	Completely unacceptable redness

Questionnaire can be found in Appendix 3.

11.1.10 Telangiectasia Evaluation

Telangiectasia evaluation will be performed at Baseline and Week 8 visit as indicated in the Schedule of Study Activities. The Investigator will assess the extent of telangiectasia based on the 4-point severity scale summarized below.
The Investigator will perform a static ("snap-shot") evaluation of telangiectasia severity using the below scoring system.

Table 6: Telangiectasia Evaluation

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

Questionnaire can be found in Appendix 6.

11.2 Safety Assessments

11.2.1 Assessment of Adverse Events

Beginning with the screening visit and through the EOS/ET visit, the Investigator and study personnel will review each subject's clinical evaluation findings and query the subject directly regarding AEs (see Section 12, Safety Data Collection, Recording and Reporting). Subjects must be followed for AEs until 30 days post study conclusion or until the PI determines AEs are stable, whichever is later.

11.2.2 Pregnancy Test

A urine pregnancy test will be performed at all visits for females of childbearing potential. The baseline result must be available and must be negative before the subject apply the first application of investigational product. Positive pregnancy test will disqualify the subject from the participation.

11.2.3 Laboratory Assessments

Blood samples will be taken at the times indicated in the Schedule of Study Activities.
Blood samples should be taken using standard venipuncture techniques. Blood sampling will be performed according to the site SOPs.
The following routine clinical chemistry, hematology and Lipid Panel will be performed according to the Schedule of Study Activities. Albumin, Alkaline Phos, ALT, AST, Total Bilirubin, BUN, BUN:Creatinine ratio, Calcium, Chloride, Creatinine, eGFR, Glucose, Potassium, Sodium, Uric Acid.
Lipid Panel: HDL Cholesterol, LDL cholesterol, Total Cholesterol, Triglycerides, VLDL Cholesterol, LDL/HDL Cholesterol Ratio, Non HDL Cholesterol.
Hematology: WBC, RBC, Hemoglobin, Hematocrit, Platelets, WBC Differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), HbA1C.
Serology will only be done at Screening: HIV Ab, HCV Ab, HBsAg.
Urinalysis will be performed according to the Schedule of Study Activities.

Patients will be asked to fast for at least 8 hours before all blood tests are done.

The total blood volume collected for clinical labs for Screening visit will be approximately 20 ml of whole blood. Volume collected for subsequent visits would be approximately 10 ml of whole blood.
Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance. If the result of the clinical chemistry test from the samples taken during the screening phase is indicated as clinically significant, the study subject will NOT be allowed into the study.

11.2.4 Biomarkers

In addition to the blood drawn for the safety laboratory assessments, additional blood will be collected for the biomarker analysis at the times indicated in the Schedule of Activities.
Samples will be processed on site and aliquots stored in the -80° C freezer.
Approximately 20 ml of whole blood will be drawn for biomarkers at each visit. Subjects will be asked to fast for at least 8 hrs. before blood for biomarkers is drawn.
Biomarkers will be evaluated for cytokines, chemokines, inflammatory markers and immune response.

11.2.5 Samples Shipment

All clinical chemistry samples are to be shipped to the central laboratory where samples will be analyzed.
Biomarker samples are to be shipped frozen monthly on dry ice to the central laboratory.
Shipments should be made only on Mondays and Tuesdays to ensure receipt of the specimens by Friday.

11.2.6 Treatment Adherence Evaluations

11.2.6.1 Study Diary Compliance Review

The subject will be given a Study Diary at each study visit of the treatment period to record date and time of applications, any adverse events, quality of life assessments, of the investigational product. Subjects will record every application during the treatment period and will bring the Subject Diary to each of the post-baseline study visits for compliance review. The Investigator will verify that the subject complied with the application requirements and will file the completed Subject Diary in the study files at each study visit until the EOT/ET visit. Any missed application notations will be clarified with the subject and documented in the subject's CRF.

11.2.6.2 Treatment Compliance

Each site participating in the trial will be instructed to assess subject's compliance by weighing the investigational product and obtaining the weight of the bottles in grams pre- and post-application. Study personnel will be asked to take out the bottles from the carton, weigh both bottles and record the weight pre-first application. At the Day 28 and Day 56 visit, study personnel will need to weigh both bottles without the carton and record the weight. This procedure should be followed every time study medication is dispensed and returned. Sites will be provided scales, which will be calibrated prior to each use. Study personnel will be instructed to record measurements into the eCRF.

12 SAFETY DATA COLLECTION, RECORDING AND REPORTING

The Investigator will monitor each subject for clinical evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any Adverse Event (AE) in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to investigational product, an alternate etiology for events not considered "related" or "probably related" to investigational product, final diagnosis, if known, and any action(s) taken. For AEs to be considered intermittent, the events must be of similar nature and severity and each intermittent AE will be reported separately. AEs and SAEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded, monitored and followed-up until the resolution (or until the Investigator deems the event to be stable/chronic).

12.1 Definitions

12.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a Subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the investigational product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. If a new rosacea signs or symptom or worsening of a rosacea sign or symptom was believed by the investigator to be related to the investigational product and not the disease, then it will be recorded as an AE. Clinically significant abnormalities are to be followed to resolution (i.e., become stable, return to normal, return to baseline, or become explainable). Laboratory abnormalities and changes in vital signs are considered to be AEs only if they necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

12.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to the Sponsor's Safety department and Pharmacovigilance as a Serious Adverse Event (SAE) using SAE report form within 24 hours of occurrence or notification to the study site:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been

	taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an out-patient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly/birth defect	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Other Important Medical Event	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life- threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

12.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE and SAE:

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

12.3 Causality of Adverse Events

The Investigator will use the following definitions to assess the relationship of the AE/SAE to the use of investigational product:

Related	The event occurred within a reasonable time after drug administration or drug concentration and body fluids demonstrated that the investigational product was present: the event could not be reasonably explained by known characteristics including concomitant therapies; the adverse event abated after discontinuing the investigational product.
Probably Related	The event has a strong temporal relationship to investigational product or recurs on re-challenge and another etiology is unlikely or significantly less likely.
Possibly Related	The event has a strong temporal relationship to the investigational product and an alternative etiology is equally or less likely compared to the potential relationship to investigational product.
Probably Not Related	The event has little or no temporal relationship to the investigational product and/or a more likely alternative etiology exists.
Not Related	The event is due to an underlying or concurrent illness or effect of another drug and is not related to the investigational product (e.g., has no temporal relationship to investigational product or has a much more likely alternative etiology).

If an Investigator's opinion of possibly, probably not, or not related to investigational product is given, an alternate etiology must be provided by the Investigator for the AE.

12.4 Adverse Event Collection Period

Adverse Event Collection Period starts with the Screening visit once the ICF has been signed through the follow-up visit (week 12). Any AE/SAE prior to the Screening visit will be considered past medical history (PMH).

SAE(s) that are observed or spontaneously reported during the subject's participation in the trial will be captured and monitored until the Investigator deems the event to be chronic or not clinically significant or the subject to be stable.

12.5 Adverse Event Reporting

In the event of a SAE, whether related to investigational product or not, the Investigator or representative must make an accurate and adequate report consisting of at least the minimum criteria (Site and Subject ID, Date site became aware of the event, SAE Term, Seriousness criteria, investigational product, Investigator/Reporter and site address) within 24 hours by email, fax, or telephone to the Sponsor's Safety and Pharmacovigilance team. Sponsor's Safety

and Pharmacovigilance team will complete the SAE report for further evaluation and review by the Medical Monitor and Sponsor designee.

Copies of each report with the associated documentation received (i.e., queries, medical records, lab records, IRB/IEC communications and all source documents) will be kept in the site's study file.

Primary Contact for AE/SAE Reports and Queries
Email: RB244-01-safety@biorasi.com **Medical Monitor: Dr. Jeffrey Sugarman** **Email:** pediderm@yahoo.com **Phone: 707-280-0283**

13 MEDICAL MONITOR

13.1 Unblinding due to SAE

Subjects, Investigators, site staff, AOBiome, and the Medical Monitor will be blinded to treatment assignment.

Reasons to unblind Subject should be clearly documented in subject notes, and the monitoring site visit report. In the event of an emergency necessitating unblinding the PI/site staff will make every effort to contact and discuss the event with the Medical Monitor prior to unblinding.

Treatment assignment for an individual subject should be unblinded only in an emergency by the Investigator, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Treatment should be provided in accordance with the medical condition and with regard to the information provided in the Investigator's Brochure.

According to the FDA guidance *Safety Assessment for IND Safety Reporting* IND safety reports submitted should be unblinded. If the blind is broken and a subject with an adverse event that would meet the criteria for reporting as a single event was receiving vehicle, the event will not be reported in an IND safety report because there is a reasonable possibility that the drug did not cause the adverse event but in the event of an SAE determined to be as a result of drug exposure reporting to the FDA will take place.

The Investigator must document the breaking of the code, and the reasons for doing so on the eCRF, in the site file, and in the medical notes.

The Investigator must notify the IRB and the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break, all other members of the research team should remain blinded.

14 DATA ANALYSIS

The data analysis will be conducted on all participant data when the trial ends. Data will be presented by treatment group and overall.

Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, etc.).

Adverse events will be summarized by treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment-emergent AEs (TEAEs), treatment-related AEs (those considered by the Investigator as at least possibly drug related), SAEs, discontinuations due to AEs, and AEs ≥Grade 3 severity. By-subject listings will be provided for any deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics for each treatment group will be provided for clinical laboratory values (e.g., hematology, serum chemistry, and urinalysis) and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation. Abnormal clinical laboratory values will be listed.

All data will be provided in by-subject listings.

14.1 Subject Population/Data Sets to Be Evaluated

The subject populations are defined as follows:

- **Safety Population:** The safety population includes all randomized subjects who received investigational product.
- **Modified Intent-to-Treat (mITT) Population:** A modified intent-to-treat population includes all subjects who are randomized, applied at least one dose of assigned product, and returned for at least one post-baseline evaluation visit.
- **Per Protocol (PP) Population:** The PP population includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, returned to the study site for the primary endpoint visit within the specified window (±2 days) OR discontinued from the study as a treatment failure, and did not have any major protocol violations. Subjects who administered at least 50 % of IP, have at least one baseline and post baseline in clinic visit and did not have any major protocol violations.

Subjects who discontinued early from the study due to lack of treatment effect after completing at least eight weeks of treatment should be included in the mITT and PP population as treatment

failures and the change in IGA and CEA from the baseline visit to the last completed visit prior to discontinuation due to lack of efficacy should be carried forward in the primary endpoint analysis. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population.

The results in the mITT population will be considered definitive for superiority of each active treatment to vehicle with those in the PP population considered supportive. Safety analyses will be performed using the Safety population.

14.2 Sample Size Determination

Sample size of 104 randomized 1:1 Active to Vehicle based on 80% power to detect 33% IGA response in Active group versus 10% in the Vehicle group, with two-sided test and alpha =0.05.

14.3 Statistical Analyses

14.3.1 Subject Disposition and Demography

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number randomized, the number treated, and the reasons for study discontinuation. Summaries of the number in each analysis set will be presented. Entry criteria violations and protocol deviations will be listed.

Demographic and baseline characteristic data summarization will be performed in order to descriptively assess the comparability of treatment groups. Data to be tabulated will include age, race, ethnicity, height, weight, and BMI, as well as baseline characteristics related to medical history.

14.3.2 Assessment of Safety

The reporting of safety data is descriptive, and will include all subjects who receive at least one dose of investigational product. The variables for safety endpoints are AEs, Local Application Site Reactions, vital signs measurements, clinical chemistry and hematology. AEs will be summarized based on the frequency of AEs and their severity for all treated subjects. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Data will be summarized using preferred term and primary system organ class.

If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to investigational product will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to investigational product.

Summaries of AEs will include any AEs reported beginning with the first dose of investigational product on Day 1. The occurrence of adverse events will be summarized by

treatment group using preferred terms, system organ classifications, and severity. Separate summaries of serious adverse events, adverse events related to investigational product, and events leading to the discontinuation of investigational product will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary. This data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

14.3.3 Hypothesis Testing/ Assessment of Efficacy

Further details of the planned statistical methods presented below will be provided in the study Statistical Analysis Plan (SAP). The purpose of the SAP is to further elaborate the statistical methods described in the protocol and describe analysis conventions to guide the statistical programming work. Any changes to the final SAP will be documented. Unless otherwise specified, the hypothesis testing will be conducted by the difference of means for a two-sample two-sided test with a significance level of 0.050.

The Evaluable Period for the outcome variables will be weeks 1, 4, 8 and 12. During each Evaluable Period an ordinal value based on IGA, CEA, PSA scores will be collected. The probability of improving will be the criteria to assess the superiority of the drug over the vehicle. The null and alternative statistical hypotheses for the primary effectiveness endpoints are given by:

(*Ho*) : The null hypothesis is that the probability of inproving (across the scale) with drug T (*PrT*)is less than or equal to the probability of inproving with vehicle (*PrV*)

$$Ho: PrT \leq PrV;\ PrT - PrV \leq 0$$

(*Ha*): The alternative hypothesis is that the probability of inproving with drug T (*PrT*) is greater than to the probability of inproving with vehicle (*PrV*).

$$Ha: PrT > PrV;\ PrT - PrV > 0$$

The change from baseline score of Skindex-16 will be compared among treatment at weeks 1, 4, 8 and 12 by a repeated measure analysis.

14.3.3.1 Exploratory Endpoints

IGA treatment success, defined as “clear” or “almost clear” with a 2-grade improvement in IGA score from baseline to the end of treatment.

CEA treatment success defines as “clear” or “almost clear” with a 2-grade improvement in CEA score from baseline to the end of treatment.

14.3.4 Handling of Missing Values & Sensitivity Analysis

For the primary and secondary analysis no missing values will be imputed. A sensitivity analysis will be performed by Multiple Imputation Regression Analysis using the following factors: treatment, age, gender, baseline IGA, baseline CEA, baseline PSA and the results of the same variable from previous visits.

14.3.5 Handling of Multiplicity

No correction for multiplicity will be made.

14.3.6 Primary Objective

Assess the safety and tolerability of B244 applied twice daily to the face for 8 weeks in subjects with mild to moderate rosacea.

14.3.7 Exploratory Objectives

To assess the efficacy of B244 in subjects with mild to moderate rosacea.

- Proportion of subjects with IGA improvement at Week 8 relative to baseline.
- Proportion of subjects with CEA improvement at Week 8 relative to baseline.
- Change in IGA from Week 8 to Baseline.
- Change in CEA from Week 8 to Baseline.
- Proportion of Subjects with improvement in IGA or CEA at week 1, week 4, and week 12.
- Change in Skindex 16 patient reported outcome from Baseline to week 1, week 4, week 8, and week 12.
- Proportion of subjects with change in PSA at Week 1, Week 4, Week 8 and Week 12 from Baseline.
- Evaluation of Telangiectasia score at Baseline/Day1 and week 8.

14.3.7 Clinical Trial Protocol deviations

At minimum, the following deviations will be summarized on the ITT population:

- Inclusion or exclusion criteria not satisfied.
- Deviations related to the investigational product administration
- Not permitted concomitant medications.

15 STUDY CONDUCT

15.1 Ethical Conduct of the Study

The study will be conducted according to the protocol, GCP, as outlined in the ICH Guidelines and Code of Federal Regulations. Written informed consent for the study must be obtained from all subjects before protocol specific procedures are performed. Subjects must be informed of their right to withdraw from the study at any time and for any reason.

15.2 Other Required Approvals

In addition to IRB/IEC approval, all other required approvals (e.g. approval from local Research and Development Board or Scientific Committee) required by the individual site for participating in this study will be obtained by the Investigator prior to recruitment of subjects into the study and shipment of the investigational product(s). It is the responsibility of the Investigator to notify the Sponsor and the CRO of the requirement of such approvals prior to participating in the study.

15.3 Informed Consent

It is the responsibility of the Investigator to give each subject (or the subject's acceptable representative), prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial at any time.

Furthermore, it is the responsibility of the Investigator, or a person designated by the Investigator, to obtain signed informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the trial. The Investigator will retain the original of each subject's signed consent form.

The informed consent form will be in compliance with ICH GCP, local regulatory, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use.

15.4 Subject Confidentiality

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as gender,

age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's CRF).

15.5 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (e.g., recruitment advertisements, subject's diaries, if applicable) from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the Sponsor or its designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In case of such an event, the Investigator must notify the IRB/IEC and the Sponsor in writing immediately after the implementation.

15.6 Publication

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

16 ADMINISTRATIVE OBLIGATIONS

16.1 Curriculum Vitae

An updated, signed, and dated copy of the curriculum vitae with the experience, qualification and training for each Investigator and/or Sub-Investigator(s) will be provided to the Sponsor prior to the beginning of the Clinical Trial.

16.2 Source Documentation Forms

The Investigator/institution will permit study-related monitoring, audits/inspections, IRB/IEC review and regulatory inspection providing direct access to source documents, including all medical records or pertinent data relevant to the audit/inspection. Source documents will represent a record of the raw data. Source document templates may be provided by either the clinical site or the Sponsor. The source documents will become part of the subject's permanent medical record maintained by the clinical site. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidances (ex. 21 CFR Part 11 and 312).

eCRFs will be used in this study. eCRFs are required and should be completed for each subject participating in the study. eCRFs will contain data captured from subject source documents and results of laboratory tests. In most cases, the source documents are contained in the subject's chart at the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts. Data must be transcribed from the source documents (e.g. physical exam report, associated medical records, date and version of informed consent form) onto the CRF by clinical site personnel prior to data monitoring.

Any corrections to entries made in the source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms.

Investigator will sign eCRFs electronically after completion of data entry, to attest that the data contained on the CRFs is complete and accurate. Completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

16.3 Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).

The records will be retained by the Investigator according to the International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor will be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

17 PUBLICATIONS

All data generated from this study are the property of AOBiome LLC and shall be held in strict confidence along with all information furnished by AOBiome. Independent analyses and/or publication of these data by the Investigator or any member of his/her staff is not permitted without prior written consent of AOBiome.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Sponsor personnel. Authorship will be determined by mutual agreement. Written permission to the Investigator will be contingent on the review by the Sponsor of the methodology and statistical analysis and any publication or presentation will provide for nondisclosure of AOBiome confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties at least 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

18 PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

19 CLINICAL TRIAL PROTOCOL AMENDMENTS

Any protocol amendments will be added as stand-alone documents. In addition, any and all revisions dictated by the amendments will be made in the protocol. Each time a protocol is amended, a new amended version date will be added to the cover page.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment. The Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 12 must be followed by the Study Lead.

20 PROPERTY RIGHTS

All information, documents and investigational product provided by the Sponsor or its designee are and remain the sole property of the Sponsor. The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights. All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The complete verified database will be shared with the Operations Committee, which shall have full access to all data. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial. As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

21 DATA PROTECTION

The subject’s personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

22 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

22.1 Quality Control (QC) and Quality Assurance (QA)

22.1.1 Study Site Monitoring Visits

During study conduct, the Sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The Investigator/institution will allow the Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to quality assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the IRB/IEC, and/or to inspection by appropriate regulatory authorities

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

22.1.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site will notify the Sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments. Deviations from the inclusion/exclusion criteria will not be permitted unless written approval by the Sponsor has been obtained. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator will contact the Sponsor or designee at the below mentioned address to determine the appropriate course of action.

Site will be responsible for proper maintaining and filing of all PD related documentation in the site files.

22.2 Trial Discontinuation/Investigative Site Termination

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects.

After such a decision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the trial.

22.2.1 Criteria for Premature Termination or Suspension of the Study

The following criteria may result in either temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the investigational product that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The Sponsor reserves the right to discontinue the trial for other valid administrative reasons.

22.2.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

22.2.3 Procedures for Premature Termination or Suspension of the Study or Investigational Site(s)

In the event that the Sponsor and or a regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

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24 APPENDICES

Appendix 1: Investigator Global Assessment (IGA)

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

Appendix 2: Clinician Erythema Assessment (CEA)

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

Appendix 3: Patient Self-Assessment (PSA)

Circle the number that best describes your rosacea-related facial redness RIGHT NOW.

Score	Severity	Description
0	Absent redness	Clear of unwanted redness
1	Very mild redness	Nearly clear of unwanted redness
2	Mild redness	Somewhat more redness than I prefer
3	Moderate redness	More redness than I prefer
4	Severe redness	Completely unacceptable redness

Appendix 4: Skindex 16

Skindex16
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THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓						Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

Skindex16 - United States/English - Mapi.
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Skindex16
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ESTAS PREGUNTAS SE RELACIONAN CON LA AFECCIÓN EN LA PIEL QUE MÁS LE HA MOLESTADO DURANTE LOS ÚLTIMOS 7 DÍAS

Durante los últimos 7 días, ¿con qué frecuencia le ha molestado...?	Nunca me molestó ↓						Siempre me molestó ↓
1. La **picazón** en la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. El **ardor o escozor** en la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. El **dolor** en la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. La **irritación** en la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. La **persistencia / recurrencia** de la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. La **preocupación** por la afección en la piel (Por ejemplo: de que se extenderá, empeorará, dejará cicatriz, sea impredecible, etc.)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. El **aspecto** de la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. La **frustración** por la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. La **vergüenza** por la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Sentirse fastidiado** por la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Sentirse deprimido** por la afección en la piel	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. Los efectos de la afección en la piel en sus **relaciones con los demás** (Por ejemplo: relaciones con su familia, amigos, relaciones cercanas, etc.)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. Los efectos de la afección en la piel en su **deseo de estar con otras personas**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Que la afección en la piel le dificulte **demostrar afecto**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. Los efectos de la afección en la piel en sus **actividades diarias**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Que la afección en la piel le dificulte **trabajar o hacer lo que disfruta**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

¿Ha respondido cada pregunta? Sí ☐ No ☐

Skindex16 - United States/Spanish - Version of 27 Jun 12 - Mapi
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Appendix 5: Fitzpatrick Skin Assessment

Score		0	1	2	3	4
	What is the natural color of your hair?	Sandy red	Blond	Chestnut, dark blond	Dark brown	Black
	What is the eye color?	Light blue, Gray, Green	Blue, Gray, Green	Blue	Dark Brown	Brownish Black
	What is the color of sun unexposed skin areas?	Reddish	Very pale	Pale with beige tint	Light brown	Dark brown
	How many freckles on unexposed skin areas?	Many	Several	Few	Incidental	None
	What happens when you are in the sun TOO long without sunblock?	Painful redness, blistering, peeling	Blistering followed by peeling	Burns, sometimes followed by peeling	Rarely burns	Never had a problem
	How well do you turn brown?	Hardly or not at all	Light color tan	Reasonable tan	Tan very easily	Turn dark very quickly
	Do you turn brown within one day of sun exposure?	Never	Seldom	Sometimes	Often	Always
	How does your face respond to the sun?	Very sensitive	Sensitive	Normal	Very resistant	Never had a problem
	When did you last expose yourself to the sun or artificial sun treatments?	More than 3 months ago	2-3 month ago	1-2 months ago	Less than 1 month ago	Less than 2 weeks ago
	Do you expose the area to be treated to the sun?	Never	Hardly ever	Sometimes	Often	Always

- 00-07 points = Skin type I
- 08-16 points = Skin type II
- 17-25 points = Skin type III
- 25-30 points = Skin type IV
- 30-40 points = Skin type V & VI

Appendix 6: Telangiectasia Assessment

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