TITLE PAGE

Study Title: A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical End-points Comparing Test Product "Oxymetazoline hydrochloride Cream, 1%" to Reference Product "RHOFADE™ Cream, 1%" in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea.

Short Title: A Clinical Endpoint Bioequivalence study of "Oxymetazoline hydrochloride Cream"

Test Drug:	Oxymetazoline hydrochloride Cream, 1%
Clinical Study Phase:	Clinical Endpoint Bioequivalence study
Protocol No.:	OXY2018-01
Protocol Version:	3.0;
Protocol Effective Date:	29 JAN 2020
Supersedes Protocol Version:	2.0; Amendment 2
Sponsor:	TEVA Pharmaceuticals USA, Inc. [redacted]

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Protocol No.:	OXY2018-01
Protocol Version:	3.0;
Protocol Effective Date:	
Study Title:	A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical End-points Comparing Test Product "Oxymetazoline hydrochloride Cream, 1%" to Reference Product "RHOFADE™ Cream, 1%" in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea.

Signatures of the noted individuals ensure that all designated persons have agreed this version is final:

Date: 1/31/2020

Date: 1/30/2020

CRO SIGNATURE PAGE

Protocol No.:	OXY2018-01
Protocol Version:	3.0;
Protocol Effective Date:	
Study Title:	A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical End-points Comparing Test Product "Oxymetazoline hydrochloride Cream, 1%" to Reference Product "RHOFADE™ Cream, 1%" in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea.

Signatures of the noted individuals ensure that all designated persons have agreed this version is final:

Date: 1/30/2020

STUDY ACKNOWLEDGMENT / DISCLOSURE

Protocol No.:	OXY2018-01
Protocol Version:	3.0;
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Study Title:	A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical End-points Comparing Test Product "Oxymetazoline hydrochloride Cream, 1%" to Reference Product "RHOFADE™ Cream, 1%" in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea.

I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the Health Insurance Portability and Accountability Act (HIPAA), if applicable, the World Medical Association Declaration of Helsinki and local regulatory guidelines. I will attempt to complete the study within the time designated.

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

I will provide access to the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me & who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all study subject information (Case Report Forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations. I agree to retain and maintain strict accountability of the Investigational Products supplied to the study site.

I will not enroll any subjects into this study until applicable Regulatory approval & IRB approval are obtained.

_____ Date: _____

Principal Investigator's Signature

Address:

……

……

CONTACT DETAILS

CRO
[redacted]
BIOSTATISTICS, DATA MANAGEMENT and CLINICAL STUDY REPORT PREPARATION
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PROTOCOL SYNOPSIS

Title	A Randomized, Double-blind, Parallel-group, Three-arm, Placebo-controlled, Multi-Site Therapeutic Equivalence Study with Clinical Endpoints, Comparing Test Product "Oxymetazoline hydrochloride Cream, 1%" to Reference Product "RHOFADE™ Cream, 1%" in the Treatment of Moderate to Severe Persistent Facial Erythema of Rosacea.
Short title	A Clinical Endpoint Bioequivalence study of "Oxymetazoline hydrochloride Cream"
Clinical phase	Clinical Endpoint Bioequivalence study
Study Site(s)	[redacted]
Objectives	**Primary Objectives:** To establish the **therapeutic equivalence** between Test Product (Oxymetazoline hydrochloride Cream, 1%, manufactured by Actavis Laboratories, Salt Lake City, UT) and Reference Product (RHOFADE™ Cream, 1%, Allergan) using the primary endpoint (proportion of subjects with treatment success at all time-points 3, 6, 9, and 12 hours post application on Day 29) , in subjects with moderate to severe persistent facial erythema of rosacea. To evaluate study sensitivity, the Test and Reference products will be statistically evaluated with regard to their superiority ($P < 0.05$) over placebo for the primary endpoint. **Safety Objectives:** (1) To monitor adverse events (AEs) and assess the safety and tolerability of Test Product and Reference Product in subjects with moderate to severe persistent facial erythema of rosacea.
Study Treatment Duration	The total treatment duration for each subject will be of approximately 29 days. The 4 study visits will include: - Visit 1: Screening visit [redacted] - Visit 2: Baseline visit (Day 1[redacted]) - Visit 3: Telephone Follow-up visit (Day 14[redacted]) - Visit 4: EoT visit (Day 29[redacted])

Investigational products	**Test drug:** Oxymetazoline hydrochloride Cream, 1% **Name of active ingredient(s):** Oxymetazoline hydrochloride **Manufactured by:** Actavis Laboratories, Salt Lake City, UT (a subsidiary of Teva Pharmaceuticals USA, Inc.) **Strength:** 1% (each gram of cream contains 10 mg [1%] oxymetazoline hydrochloride, equivalent to 8.8 mg [0.88%] of oxymetazoline free base)
	Reference drug: RHOFADE™ Cream, 1% **Name of active ingredient(s):** Oxymetazoline hydrochloride **Marketed by:** Allergan, Inc. **Strength:** 1% (each gram of cream contains 10 mg [1%] oxymetazoline hydrochloride, equivalent to 8.8 mg [0.88%] of oxymetazoline free base)
	Placebo: Vehicle Cream **Name of active ingredient(s):** Not applicable **Manufactured by:** Actavis Laboratories, Salt Lake City, UT (a subsidiary of Teva Pharmaceuticals USA, Inc.) **Strength:** Not applicable
Indication	Treatment of moderate to severe persistent facial erythema of rosacea
Route of Administration	Topical
Dosage Regimen	Subjects will be instructed to apply a pea-sized amount, as a thin layer, once daily at approximately the same time of day for 29 [redacted] days. Subjects will apply the first dose of study product at Visit 2 under supervision of the independent dispenser. The last dose should be administered at the clinic during the last visit (Visit 4).
Study Design	A randomized, double-blind, parallel-group, three-arm, placebo-controlled, multi-site therapeutic equivalence study with clinical endpoints.
Study Population	Approximately [redacted] males and non-pregnant females, 18 years of age and older, with a clinical diagnosis of persistent (non-transient) facial erythema associated with rosacea.
[redacted]	[redacted]
Diagnosis and Key	**Inclusion criteria:**

Inclusion/Exclusion Criteria

(1) Study subjects must have provided IRB approved written informed consent using the latest version of the IRB informed consent form, (or assent in applicable states/countries). In addition, study subjects must sign a HIPAA authorization, if applicable.

(2) Healthy male or non-pregnant females, ≥18 years-of-age with a clinical diagnosis of rosacea with persistent (non-transient) facial erythema.

(3) Ability to follow study instructions and complete subject diary without assistance.

(4) Females of child bearing potential must not be pregnant or lactating at screening visit and at baseline visit, as documented by a negative urine pregnancy test.

(5) Female subjects of childbearing potential must be willing to use an acceptable form of birth control from the day of the first dose administration to 30 days after the last administration of Investigational Product (IP). A sterile sexual partner is NOT considered an adequate form of birth control.

(6) Moderate to severe persistent facial erythema associated with rosacea, defined as a grade of ≥3 on the CEA scale as assessed by the Investigator at Screening and on Baseline (Day 1) visit prior to study drug application.

(7) Moderate to severe persistent facial erythema associated with rosacea, defined as a grade of ≥3 on the SSA scale as assessed by the subject at Screening and on Baseline (Day 1) visit prior to study drug application.

(8) Stable erythema (for at least 3 months prior to screening) associated with rosacea, with minimal variation from day to day and within each day, in the opinion of the subject.

(9) Willingness to complete the required visits including short stay for at least 12 hours at the investigational site for 2 separate visits.

(10) Subjects who use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens must have used the same product brands/types for a minimum period of 4 weeks prior to Baseline, must agree not to change brand/type or frequency of use throughout the study and must agree not to use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens on the

scheduled clinic visit day(s) before the visit.

(11) Subject must be willing to avoid the use of abrasive cleansers or washes (e.g., exfoliating facial scrubs), adhesive cleansing strips (e.g., Bioré® Pore Strips) and wax epilation on the face, during the entire duration of their study participation.

(12) Subject's willingness to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages).

(13) Subject must be in good health and free from any systemic or dermatological disorder (other than rosacea) that, in the opinion of the Investigator, will interfere with the study evaluations or increase the risk of AEs.

(14) Any skin type or race, providing the skin pigmentation will allow discernment of erythema.

Exclusion criteria

(1) Any of the following conditions: severe or unstable or uncontrolled cardiovascular disease, clinically unstable hypertension, orthostatic hypotension, and uncontrolled hypertension or hypotension, cerebral or coronary insufficiency, Raynaud's Syndrome, thromboangiitis obliterans, scleroderma, Sjögren's syndrome, renal or hepatic impairment.

(2) Subjects with narrow angle glaucoma.

(3) Females who are pregnant, breast feeding, or planning a pregnancy during the study.

(4) Females of childbearing potential who do not agree to utilize an adequate form of contraception during their participation in the study.

(5) Clinical signs of particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) on the face 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 that may interfere with the study evaluations, in the opinion of the Investigator.

(6) Presence of ≥3 facial inflammatory lesions of rosacea at screening and baseline.

(7) Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea, as determined by the Investigator.

(8) Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with the study treatments or study

assessments.

(9) History of drug or alcohol abuse within 12 months prior to the Screening visit.

(10) Known hypersensitivity or allergies to any component of the study treatment.

(11) Use within 12 hours prior to baseline of any topical products including, but not limited to, lotions, creams, ointments, and cosmetics applied to the face (facial cleanser is acceptable).

(12) Use 1 week prior to baseline of niacin ≥500 mg/day.

(13) Use within 2 weeks prior to baseline of products containing topical corticosteroids, topical retinoids, topical antibiotics, topical anti-inflammatory, topical treatment for rosacea, or topical treatment for acne.

(14) Use within 4 weeks prior to baseline of topical immunomodulators, systemic antibiotics, systemic corticosteroids, systemic anti-inflammatory agents, systemic treatment for rosacea, or systemic treatment for acne (other than oral retinoids, which require a 6-month washout).

(15) Undergone 4 weeks prior to baseline any dermatologic or surgical procedure on the face.

(16) Use within 3 months prior to baseline of any systemic immunomodulators known to have an effect on rosacea.

(17) Use within 6 months prior to baseline of any oral retinoids (e.g., isotretinoin) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).

(18) Undergone 6 months prior to baseline any laser, light-source (e.g. intense pulsed light, photodynamic therapy) or other energy-based therapy to the face.

(19) Exposed to excessive ultraviolet (UV) radiation within 1 week before Screening visit and/or subject is unwilling to refrain from excessive exposure to UV radiation during the course of the study.

(20) Current use of monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, or oxymetazoline (e.g., eye drops, nasal sprays).

(21) Subject has participated in a clinical trial within 30 days or in a biologics study within 6 months preceding admission of this study.

(22) Previous participation in this study.

(23) Inability to communicate well (i.e., language problem, poor mental development, psychiatric illness or poor cerebral function), that may impair the ability to provide written informed consent.

(24) Subject has any evidence of organ dysfunction, chronic infectious disease, system disorder or has a condition or is in a situation that, in the Investigator's opinion, that may put the subject at significant risk, may confound the study results, or may significantly interferes with the subject's participation in the study.

(25) Employees or family members of the research center or Investigator.

Study Design and Methodology

This is a multi-center, randomized, double-blind, parallel-group, three-arm, placebo-controlled, therapeutic equivalence study with clinical end-points. The study will compare the efficacy and safety of Test Product "Oxymetazoline hydrochloride Cream, 1%" (manufactured by Actavis Laboratories, Salt Lake City, UT) with that of an approved topical formulation RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%) marketed by Allergan, in healthy males and non-pregnant females diagnosed with moderate to severe persistent facial erythema of rosacea. Both the test and the reference formulations will also be compared to a placebo (vehicle) formulation to test for superiority.

Subjects with a confirmed diagnosis of moderate to severe persistent facial erythema of rosacea will be randomized to either Test Group (Oxymetazoline hydrochloride Cream, 1%); Reference Group (RHOFADE™, Oxymetazoline hydrochloride Cream, 1%); or Placebo Group (Vehicle Cream).

The study subject will receive treatment for approximately 29[redacted] days from the Baseline visit to the EoT visit. There will be 4 study visits, 3 to the study site and 1 telephone follow-up: Screening [redacted] visit, Baseline (Day 1[redacted]) visit, Telephone Follow-up (Day 14[redacted]) visit, and EoT (Day 29[redacted]) visit.

At screening a written Informed Consent Form (ICF) has to be signed by the subject and the eligibility criteria of the subject will be evaluated by clinical assessments. [redacted] Subjects should sign ICF prior to start of any study procedures, complete washout, and

return to the clinic to conduct the remainder of the screening procedures.

Study subject numbers will be assigned to study subjects sequentially in the order in which study subjects are enrolled into the study.

After the screening visit, each qualified subject will return to the clinic on Day 1 for confirmation of eligibility. Eligible subjects will be assigned to one of the three study treatment groups as per the computer-generated randomization schedule, and the assigned study medication will be dispensed by the study site staff. Since this is a double-blind study, neither the study team at the site nor the subjects will know the treatment the subject is assigned.

The subject will be instructed to apply a pea-size amount of the study treatment to cover the entire face (forehead, chin, nose, and each cheek [avoiding the eyes and lips]), once daily preferably, at the same time each day, up to and including the day before scheduled Visit 4 (Day 29±2). [redacted] On Day 1 visit and Day 29±2 visit, the subject will apply the assigned medication at the clinic under the supervision of an Independent Dispenser (unblinded to the treatment the subject is receiving). [redacted] From Day 2 up to and including the day before scheduled Visit 4 (Day 29[redacted]), the subject will be asked to apply the assigned medication once daily preferably, at the same time each day, and complete the subject diary, handed over by the study site staff at Baseline visit. [redacted] The subject will note the date and time of application of the study medication, any AE experienced, and any concomitant medication taken or changes from the existing ones, in the subject diary from Visit 2 (Day 1) to Visit 4 (Day 29[redacted]). A phone call will be made around Day 14 to follow up for any change in concomitant medications, and check on compliance of study medication usage.

Schedule of Events

Procedures	Visit				
	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4
	Screening [redacted]	Screening [redacted]	Day 1 (Baseline) [redacted]	Day 14 (Telephone Follow-up)[a] [redacted]	Day 29 (EoT) [redacted]
Written informed consent	X				
Demographics (height, weight, body mass index (BMI), gender, race, ethnicity)	X				
Pregnancy test (Urine)	X	X	X		X
Medical and surgical history	X	X			
Prior and concomitant medications and concurrent procedures	X	X	X	X	X
Vital signs measurements (blood pressure, heart rate, body temperature)	X	X	Pre-dose and 12 hrs		Pre-dose and 12 hrs
Clinician Erythema Assessment (CEA)	X	X	Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)		Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)
Subject Self-Assessment (SSA) for rosacea facial redness	X	X	Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)		Pre-dose, 3, 6, 9, and 12 hrs (± 30 minutes at each timepoint)
Physical examination	X				X
Review of Inclusion/Exclusion	X	X	Pre-dose (confirm eligibility)		
Randomization			X		
Dispense study medication tube			X		
Dosing (Days 1-29)[b]			X		X
Adverse event monitoring[c]	X	X	X	X	X
Subject diary review			X		X

Confinement in study clinic			≥12 hrs in clinic		≥12 hrs in clinic
Collection of study medication tube					X

[a]14 days after the first dose of study drug, a phone call will be made to follow-up on any changes in concomitant medications and check on compliance of study medication usage.

[b]Subject will apply study medication once daily preferably at the same time each day from Day 2 to Day 28 at home, as instructed.

[c]Including monitoring of application site dermatitis, application site pruritis, application site erythema, and application site pain, scaling or burning at Visit 2 and Visit 4.

Number of Subjects to be Enrolled and Randomized (Planned)

[redacted]

Additional subjects may be randomized to reach the planned number of evaluable subjects, if a higher drop out rate is experienced.

Variables

Efficacy variables:

- Scores obtained from the Clinical Erythema Assessment (CEA) scale
- Score obtained from the Self-Subject Assessment (SSA) scale

Safety variables:

- Serious Adverse Events (SAEs)
  - Non-SAEs

Primary Endpoints

The primary efficacy endpoint is the proportion of subjects with treatment success at all time-points 3, 6, 9, and 12 hours post application on Day 29. Treatment success is defined as having CEA score at least 2 grades lower than the baseline (Day 1 pre-dose) value.

Safety endpoints: Incidence of AEs.

Time point of Clinical Evaluations

Clinical Evaluations will be performed at:

- **Visit Screening A:** Demographics, vital signs, urine pregnancy test, physical examination, assessment of facial erythema using CEA scale (Investigator's assessment) and SSA scale (subject's assessment), AE monitoring, concomitant medications and concurrent procedures.
- **Visit Screening B:** Urine pregnancy test, assessment of facial erythema using CEA scale (Investigator's assessment) and SSA scale (subject's assessment), AE monitoring, concomitant medications and concurrent procedures.
- **Visit Day 1 (Baseline):** Vital signs, urine pregnancy test, assessment of facial erythema using CEA scale (Investigator's assessment) and SSA scale (subject's assessment), AE monitoring, concomitant medications and concurrent procedures.
- **Visit Day 14 (Telephone Follow Up):** Any changes in concomitant medications and concurrent procedures, and compliance with study medication usage.
- **Visit Day 29 (End of Treatment):** Vital signs, urine pregnancy test, assessment of facial erythema using CEA scale (Investigator's assessment) and SSA scale (subject's assessment), AE monitoring, concomitant medications and concurrent procedures.

Sample Size

[redacted]

Statistical Analysis

Three analysis populations will be used: Per protocol (PP) population, mITT population, and safety population.

Analysis of the primary endpoint

Analyses will be conducted with the PP population for equivalence determination, and analyses with the mITT population will be for supportive superiority purposes.

- *Equivalence testing*

Therapeutic equivalence will be concluded if the 90% confidence interval for the difference between test and reference products ($\pi T - \pi R$) of the treatment success rates at all timepoints 3, 6, 9, and 12 hours post-application on Day 29 falls within the acceptance range of [-0.20, +0.20] using PP population.

- *Superiority testing*

A two-sided exact Cochran-Mantel-Haenszel test, stratified by clinical site, will be applied to test the difference between treatment success rates at all timepoints 3, 6, 9, and 12 hours post-application on Day 29 of Test or Reference Product and Placebo. The sensitivity of the equivalence analysis (superiority of Test Product and Reference Product over Placebo) will be established if active treatment success rate is higher than and statistically significantly different from (p-value < 0.05) that of the Placebo group for each active treatment using the mITT population. No adjustment will be made for multiplicity.

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LIST OF ABBREVIATIONS

°C	Degree Celsius
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BA/BE	Bioavailability/Bioequivalence
BMI	Body mass index
Bpm	Beats per minute
CEA	Clinician Erythema Assessment
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EoS	End of Study
EoT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product

IRB	Institutional Review Board
IUD	Intra-uterine device
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mmHg	Millimeters of mercury
NA	Not applicable
NDA	New Drug Application
OTC	Over-the-counter
PhV	Pharmacovigilance
PP	Per-protocol
RLD	Reference Listed Drug
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SSA	Subject Self-Assessment
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
US/USA	United States/United States of America
WOCBP	Females of child bearing potential

1 INTRODUCTION AND BACKGROUND

1.1 Rationale for the Study

This therapeutic equivalence study with clinical endpoint is designed to determine the therapeutic equivalence of "Oxymetazoline hydrochloride Cream, 1%" (manufactured by Actavis Laboratories, Salt Lake City, UT) with the reference listed drug (RLD) RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%) marketed by Allergan, in healthy males and non-pregnant females diagnosed with moderate to severe persistent facial erythema of rosacea.

1.2 Overview of Study Indication

Rosacea is a common, chronic dermatological condition of uncertain etiology that is characterized by a myriad of clinical manifestations, including persistent erythema (which may be accompanied by facial stinging and burning), facial edema, superficial telangiectasias, recurrent papules and pustules, facial phymas (most commonly rhinophyma), and ocular manifestations.[1,2] In a recent meta-analysis, the global prevalence of rosacea was found to affect 5.46% of the adult population.[3] It is estimated to affect more than 16 million Americans, yet only a small fraction is being treated.[4] Its onset is typically between the ages of 30 and 50, and women are affected 2 to 3 times more often than men.[5] Of all the clinical manifestations of rosacea, facial flushing and persistent erythema are among the most common and are often associated with psychological distress.[6,7,8] Although the precise etiology and pathogenesis of erythematous rosacea remain uncertain, it is hypothesized that abnormal flushing and persistent erythema result from a progressive dysregulation in the cutaneous vasomotor response (i.e., persistently dilated facial blood vessels).[9]

While rosacea is not curable, it is a treatable condition; treatment goals include alleviation of signs and symptoms, improvement of appearance, and delay or prevention of advancement of the condition. Effective treatments have been developed to treat papulopustular rosacea using topical anti-infective agents such as sulfonamides, metronidazole, azelaic acid, ivermectin and tetracyclines.[2,10]

Conspicuous facial redness may have a deep impact on a patient's self-esteem and quality of life. Surveys of rosacea patients conducted by the National Rosacea Society indicate that more than 90% had lowered self-esteem and self-confidence; of rosacea patients with severe symptoms, 88% said the condition had adversely affected their professional interactions. Nearly 51% said they had even missed work because of their condition.[4]

Most topical pharmacologic agents approved by the United States Food and Drug Administration (US FDA) for treatment of papules and pustules of rosacea have no effect on persistent facial erythema. Oxymetazoline, an $alpha_{1A}$-adrenoceptor agonist, is approved by the US FDA to treat persistent facial erythema of rosacea. A long-term safety and dermal tolerability of once daily application of oxymetazoline over 52 weeks has been established. No clinically relevant rebound effect was observed; efficacy was observed at day 1 through 52 weeks and response rates increased throughout the study.[11]

1.3 Reference Product Information (RHOFADE™)[12]

Oxymetazoline is an $alpha_{1A}$-adrenoceptor agonist and vasoconstrictor of the cutaneous microvasculature that is US FDA approved for the topical treatment of persistent facial erythema associated with rosacea in adults. [12]

1.3.1 Dosage and administration

Oxymetazoline cream is for topical use only. A pea-sized amount of oxymetazoline cream, once daily should be applied in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) while avoiding the eyes and lips. Hands should be washed immediately after applying the cream. [12]

1.3.2 Pharmacokinetics

Absorption

The pharmacokinetics of oxymetazoline cream was evaluated following topical administration in a thin layer to cover the entire face in adult subjects with erythema associated with rosacea. The median weight of cream for each dose administration was 0.3 g. Plasma oxymetazoline concentrations were measurable in most of the subjects. Following the first dose application, the mean ± standard deviation (SD) peak concentrations (C_{max}) and area under the concentration-time curves from time 0 to 24 hours (AUC_{0-24h}) were 60.5 ± 53.9 pg/mL and 895 ±798 pg*hr/mL, respectively. Following once daily applications for 28 days, the mean ± SD C_{max} and AUC_{0-24h} were 66.4 ± 67.1 pg/mL and 1050 ± 992 pg*hr/mL, respectively. [12]

Distribution

An *in vitro* study demonstrated that oxymetazoline is 56.7% to 57.5% bound to human plasma proteins. [12]

Metabolism

In vitro studies using human liver microsomes showed that oxymetazoline was minimally metabolized, generating mono-oxygenated and dehydrogenated products of oxymetazoline. The percentage of parent drug oxymetazoline remaining was 95.9% after a 120-minute incubation with human liver microsomes. [12]

Excretion

The excretion of oxymetazoline following administration of oxymetazoline hydrochloride cream has not been characterized in humans. [12]

Pharmacokinetic Interactions

In vitro studies using human liver microsomes demonstrated that oxymetazoline up to the tested concentration of 100 nM had no inhibition on the activities of the cytochrome P450 (CYP) isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. Treatment of cultured human hepatocytes with up to 100 nM oxymetazoline did not induce CYP1A2, CYP2B6, or CYP3A4. [12]

1.3.3 Drug interactions

Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution should be taken in using drugs such as beta-blockers, anti-hypertensives and/or cardiac glycosides.

Caution should also be exercised in subjects receiving alpha 1 adrenergic receptor antagonists such as in the treatment of cardiovascular disease, benign prostatic hypertrophy, or Raynaud's disease. [12]

Monoamine Oxidase (MAO) Inhibitors

Caution should be taken with subjects taking MAO inhibitors that can affect the metabolism and uptake of circulating amines. [12]

1.3.4 Adverse effects

Clinical Studies Experience

A total of 489 subjects with persistent facial erythema associated with rosacea were treated with oxymetazoline cream once daily for 4 weeks in 3 controlled clinical trials. An additional 440 subjects with persistent facial erythema associated with rosacea were also treated with oxymetazoline cream once daily for up to one year in a long-term (open-label) clinical trial. Adverse reactions that occurred in at least 1% of subjects treated with oxymetazoline cream through 4 weeks of treatment are presented below. [12]

Table 1-1: Adverse reactions reported by ≥1% of subjects through 4 weeks of treatment in controlled clinical trials

Adverse Reaction	**Pooled controlled clinical trials**	
	Oxymetazoline hydrochloride cream (N=489)	**Vehicle cream** (N=483)
Application site dermatitis	9 (2%)	0
Worsening inflammatory lesions of rosacea	7 (1%)	1 (<1%)
Application site pruritus	5 (1%)	4 (1%)
Application site erythema	5 (1%)	2 (<1%)
Application site pain	4 (1%)	1 (<1%)

In the long-term (open-label) clinical trial, the rates of adverse reactions over a one-year treatment period were as follows: worsening inflammatory lesions of rosacea (3%), application site dermatitis (3%), application site pruritis (2%), application site pain (2%), and application site erythema (2%). Subjects with persistent erythema along with inflammatory lesions were allowed to use additional therapy for the inflammatory lesions of rosacea. [12]

1.3.5 Contraindications

None [12]

1.3.6 Warnings and precautions

Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. Oxymetazoline cream should be used with caution in subjects with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Subjects with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension should be advised to seek immediate medical care if their condition worsens. [12]

Potentiation of Vascular Insufficiency

Oxymetazoline cream should be used with caution in subjects with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Subjects should be advised to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop. [12]

Risk of Angle Closure Glaucoma

Oxymetazoline cream may increase the risk of angle closure glaucoma in subjects with narrow-angle glaucoma. Subjects should be advised to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop. [12]

1.3.7 Use in specific populations

Pregnancy

Risk Summary

There are no available data on oxymetazoline cream use in pregnant women to inform a drug associated risk for major birth defects and miscarriage. A literature article describing intranasal decongestant use in pregnant women identified a potential association between second-trimester exposure to oxymetazoline (with no decongestant exposure in the first trimester) and renal collecting system anomalies. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 3 times and 73 times, respectively, the exposure associated with the maximum recommended human dose. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. [12]

Fetal/Neonatal Adverse Reactions

Following repeated use of oxymetazoline hydrochloride solution nasal spray for the treatment of nasal congestion at a dose 5 times higher than recommended, one case of fetal distress was reported in a 41-week pregnant patient. The fetal distress resolved hours later, prior to the delivery of the healthy infant. The anticipated exposures for the case are 8- to18-fold higher than plasma exposures after topical administration of oxymetazoline cream. [12]

Human Data

No adequate and well-controlled trials of oxymetazoline cream have been conducted in pregnant women. Across all clinical trials of oxymetazoline cream, two pregnancies were reported. One pregnancy resulted in the delivery of a healthy child. One pregnancy resulted in a spontaneous abortion, which was considered to be unrelated to the trial medication. A literature article summarizing the results of exploratory analyses of intranasal decongestant use during pregnancy identified a potential association between second-trimester exposure to oxymetazoline hydrochloride solution (with no decongestant exposure in the first trimester) and renal collecting system anomalies. [12]

Lactation

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breastmilk production, or to establish the level of oxymetazoline present in human breastmilk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need

for oxymetazoline cream and any potential adverse effects on the breastfed child from oxymetazoline cream or from the underlying maternal condition. [12]

Pediatric Use

Safety and effectiveness of oxymetazoline cream have not been established in pediatric subjects below the age of 18 years. [12]

Geriatric Use

One hundred and ninety-three subjects aged 65 years and older received treatment with oxymetazoline cream (n = 135) or vehicle (n = 58) in clinical trials. No overall differences in safety or effectiveness were observed between subjects > 65 years of age and younger subjects, based on available data. Clinical studies of oxymetazoline cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. [12]

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this clinical study is to establish the **therapeutic equivalence** between Test Product (Oxymetazoline hydrochloride Cream, 1%, manufactured by Actavis Laboratories, Salt Lake City, UT) and Reference Product (RHOFADE™ Cream, 1%, Allergan) using the primary endpoint (proportion of subjects with treatment success at all time-points 3, 6, 9, and 12 hours post application on Day 29) , in subjects with moderate to severe persistent facial erythema of rosacea.

(1) To evaluate study sensitivity, the Test and Reference products will be statistically evaluated with regard to their superiority ($P < 0.05$) over placebo for the primary endpoints

2.2 Safety Objectives

(1) To monitor adverse events (AEs) and assess the safety and tolerability of Test Product and Reference Product in subjects with moderate to severe persistent facial erythema of rosacea.

3 STUDY DESIGN

3.1 Design Overview

This is a multi-center, randomized, double-blind, parallel-group, three-arm, placebo-controlled, therapeutic equivalence study with clinical end-point. The study will compare the efficacy and safety of Test Product "Oxymetazoline hydrochloride Cream, 1%" (manufactured by Actavis Laboratories, Salt Lake City, UT) with that of an approved topical formulation RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%) marketed by Allergan, in healthy males and non-pregnant females diagnosed with moderate to severe persistent facial erythema of rosacea. Both the test and the reference formulations will also be compared to a placebo (vehicle) formulation to test for superiority.

Subjects with a confirmed diagnosis of moderate to severe persistent facial erythema of rosacea will be randomized to one of the three treatment groups as follows:

Test Group: Oxymetazoline hydrochloride Cream, 1%, to be applied once daily preferably, and at the same time each day, for 29 days.

Reference Group: RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%), to be applied once daily preferably, and at the same time each day, for 29 days.

Placebo Group: Vehicle Cream, to be applied once daily preferably, and at the same time each day, for 29 days.

Planned sample size

[redacted]

Methodology

The study subject will receive treatment for approximately 29 days from the Baseline visit to the End of Treatment (EoT) visit. There will be 4 study visits, 3 to the study site and 1 telephone follow-up: Screening [redacted] visit (Visit 1), Baseline (Day 1[redacted]) visit (Visit 2), Telephone Follow-up (Day 14[redacted]) visit (Visit 3), and EoT (Day 29[redacted]) visit (Visit 4).

At screening, a written Informed Consent Form (ICF) has to be signed by the subject and the eligibility criteria of the subject will be evaluated by clinical assessments. If necessary, subjects will be allowed to conduct screening procedures on two separate days in order to allow for enough time to complete the adequate washout period required for medications, makeup use, etc. Subjects should sign ICF (prior to the start of any study procedures), complete washout, and return to the clinic to conduct the remainder of the screening procedures.

After the screening visit, each qualified subject will return to the clinic on Day 1 for confirmation of eligibility. Eligible subjects will be assigned to one of the three study treatment groups as per the computer-generated randomization schedule, and the assigned study medication will be dispensed by the study site staff. Since this is a double-blind study, neither the study team at the site nor the subjects will know the treatment the subject is assigned.

Treatment will be initiated at the clinic on Day 1 after collecting baseline measurements for both CEA and SSA for facial erythema as per the scales defined (Table 3-1).

The subject will be instructed to apply a pea-size amount of the study treatment to cover the entire face (forehead, chin, nose, and each cheek [avoiding the eyes and lips]), once daily preferably, at the same time each day, for 29 days. On Day 1 visit and Day 29 visit, the subject will apply the assigned medication at the clinic under the supervision of an Independent Dispenser, unblinded to the treatment the subject is receiving. [redacted] From Day 2 to Day 28, the subject will be asked to apply the assigned medication once daily preferably, at the same time each day, and complete the subject diary, handed over by the study site staff at Baseline visit. The subject will note the date and time of application of the study medication, any AE experienced, and any concomitant medication taken or changes from the existing ones, in the subject diary from Day 1 to Day 29.

A phone call will be made by the site to the subject around Day 14 to follow up for any change in concomitant medications, adherence to study restrictions, overall well-being of the subject, and check on compliance of study medication usage.

Key assessments

The schedule of visits and the assessments to be performed at each visit are presented in Table 6-1. Assessments should be performed by the same evaluator throughout the study whenever possible.

Efficacy Measurements

Efficacy measurements include Investigator's assessment of the severity of facial erythema using the CEA scale and subject's assessment of the severity of facial erythema using the SSA scale, at Pre-dose, 3, 6, 9, and 12 hours on Day 1 and Day 29. The CEA and SSA scales are shown in Table 3-1.

Table 3-1: Sample CEA and SSA Scale for Rosacea

Grade	CEA scale description	SSA scale description
0	Clear skin with no signs of erythema[a]	No sign of unwanted redness
1	Almost clear; slight redness	Almost clear of unwanted redness
2	Mild erythema; definite redness	Mild redness
3	Moderate erythema; marked redness	Moderate redness
4	Severe erythema; fiery redness	Severe redness

[a]Normal healthy skin color as observed in individuals without rosacea

CEA: Clinician Erythema Assessment; SSA: Subject Self-Assessment

Source: Draelos et al., 2018

Safety/Tolerability

Safety of the subject will be monitored and evaluated continuously throughout the study, after application of the first dose of assigned study treatment. Safety will be assessed by close monitoring and timely assessment of:

Vital signs: Blood pressure, heart rate and body temperature will be recorded at screening; at pre-dose and 12 hours on Day 1; and at pre-dose and 12 hours on Day 29.

Adverse event monitoring: Subjects will be questioned about any adverse events along with investigator evaluation of any application site reactions (including application site dermatitis, application site pruritis, application site erythema, and application site pain, scaling or burning) at, Day 1 and Day 29.

Pregnancy tests: A urine pregnancy test at screening visit and on Day 1 and Day 29 visits will be done for women of childbearing potential.

Physical examination: The Investigator will examine the subject for any physical abnormalities at screening and Day 29 for the following body systems: general appearance, head, eyes, ears, nose, throat, heart/cardiovascular, lungs, abdomen, neurologic, extremities, back, musculoskeletal, lymphatic, skin, and other findings. The subject's height and weight will be recorded at screening only.

3.2 Primary Endpoints

The primary efficacy endpoint will be used to address the primary objective, which aims at demonstrating therapeutic equivalence between Test Product and Reference products.

The primary efficacy endpoint is the proportion of subjects with treatment success at all time-points 3, 6, 9, and 12 hours post application on Day 29,which will be calculated for each subject as described in Section 6.4.2.

3.3 Safety Endpoints

- Incidence of AEs.

4 STUDY POPULATION

This multi-center study will enroll approximately [redacted] male or female subjects ≥18 years-of-age presenting with a clinical diagnosis of persistent facial erythema of rosacea.

4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study.

1. Study subjects must have provided IRB approved written informed consent using the latest version of the IRB informed consent form, (or assent in applicable state). In addition, study subjects must sign a HIPAA authorization, if applicable.
2. Healthy male or non-pregnant females, ≥18 years-of-age with a clinical diagnosis of rosacea with persistent (non-transient) facial erythema
3. Ability to follow study instructions and complete subject diary without assistance.
4. Females of child bearing potential (WOCBP*) must not be pregnant or lactating at screening visit (as documented by a negative urine pregnancy test) and at baseline visit (as documented by a negative urine pregnancy test).
   **All female subjects will be considered to be of childbearing potential unless they are postmenopausal. Female subjects of childbearing potential (WOCBP) are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti- estrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are NOT considered as surgically sterile.*
5. Female subjects of childbearing potential must be willing to use an acceptable form of birth control from the day of the first dose administration to 30 days after the last administration of IP. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (medroxyprogesterone acetate-stabilized for at least 3 months); vaginal contraceptive; contraceptive implant; double barrier methods (e.g. condom and spermicide); Nuvaring vaginal hormonal birth control, intra-uterine device (IUD), or abstinence with a second method of birth control should the subject become sexually active.
6. Moderate to severe persistent facial erythema associated with rosacea, defined as a grade of ≥3 on the CEA scale as assessed by the Investigator at Screening and on Baseline (Day 1) visit prior to study drug application (Table 3-1).
7. Moderate to severe persistent facial erythema associated with rosacea, defined as a grade of ≥3 on the Subject SSA scale as assessed by the subject at Screening and on Baseline (Day 1) visit prior to study drug application (Table 3-1).
8. Stable erythema (for at least 3 months prior to screening) associated with rosacea, with minimal variation from day to day and within each day, in the opinion of the subject.

9. Willingness to complete the required visits including short stay for at least 12 hours at the investigational site for 2 separate visits.
10. Subjects who use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens must have used the same product brands/types for a minimum period of 4 weeks prior to Baseline, must agree not to change brand/type or frequency of use throughout the study and must agree not to use make-up, facial moisturizers, creams, lotions and/or sunscreens on the scheduled clinic visit day before the visit.
11. Subject must be willing to avoid the use of abrasive cleansers or washes (e.g., exfoliating facial scrubs), adhesive cleansing strips (e.g., Bioré® Pore Strips) and wax epilation on the face, during the entire duration of their study participation.
12. Subject's willingness to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages).
13. Subject must be in good health and free from any systemic or dermatological disorder (other than rosacea) that, in the opinion of the Investigator, will interfere with the study evaluations or increase the risk of AEs.
14. Any skin type or race, providing the skin pigmentation will allow discernment of erythema.

4.2 Exclusion Criteria

Subjects are to be excluded from the study if they display any of the following criteria:

1. Any of the following conditions: severe or unstable or uncontrolled cardiovascular disease, clinically unstable hypertension, orthostatic hypotension, and uncontrolled hypertension or hypotension, cerebral or coronary insufficiency, Raynaud's Syndrome, thromboangiitis obliterans, scleroderma, Sjögren's syndrome, renal or hepatic impairment.
2. Subjects with narrow angle glaucoma.
3. Females who are pregnant, breast feeding, or planning a pregnancy during the study.
4. Females of childbearing potential who do not agree to utilize an adequate form of contraception during their participation in the study.
5. Clinical signs of particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) on the face 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 that may interfere with the study evaluations, in the opinion of the Investigator.
6. Presence of ≥3 facial inflammatory lesions of rosacea at screening and baseline
7. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea, as determined by the Investigator.
8. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with the study treatments or study assessments.
9. History of drug or alcohol abuse within 12 months prior to the Screening visit.

10. Known hypersensitivity or allergies to any component of the study treatment.
11. Use within 12 hours prior to baseline of any topical products including, but not limited to, lotions, creams, ointments, and cosmetics applied to the face (facial cleanser is acceptable).
12. Use 1 week prior to baseline of niacin ≥500 mg/day.
13. Use within 2 weeks prior to baseline of products containing topical corticosteroids, topical retinoids, topical antibiotics, topical anti-inflammatory, topical treatment for rosacea, or topical treatment for acne.
14. Use within 4 weeks prior to baseline of topical immunomodulators, systemic antibiotics, systemic corticosteroids, systemic anti-inflammatory agents, systemic treatment for rosacea, or systemic treatment for acne (other than oral retinoids, which require a 6-month washout).
15. Undergone 4 weeks prior to baseline any dermatologic or surgical procedure on the face.
16. Use within 3 months prior to baseline of any systemic immunomodulators known to have an effect on rosacea.
17. Use within 6 months prior to baseline of any oral retinoids (e.g., isotretinoin) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
18. Undergone 6 months prior to baseline any laser, light-source (e.g. intense pulsed light, photodynamic therapy) or other energy-based therapy to the face.
19. Exposed to excessive UV radiation within 1 week before Screening visit and/or subject is unwilling to refrain from excessive exposure to UV radiation during the course of the study.
20. Current use of monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, or oxymetazoline (e.g., eye drops, nasal sprays).
21. Subject has participated in a clinical trial within 30 days or in a biologics study within 6 months preceding admission of this study.
22. Previous participation in this study.
23. Inability to communicate well (i.e., language problem, poor mental development, psychiatric illness or poor cerebral function), that may impair the ability to provide written informed consent.
24. Subject has any evidence of organ dysfunction, chronic infectious disease, system disorder or has a condition or is in a situation that, in the Investigator's opinion, that may put the subject at significant risk, may confound the study results, or may significantly interferes with the subject's participation in the study.
25. Employees or family members of the research center or Investigator.

4.3 Restrictions and Prohibitions

The following treatments/applications will not be allowed before or during study participation as per the below schedule:

[redacted]

[redacted]

[redacted]

1. Niacin ≤500 mg/day if not at a stable dose or if it is known to cause flushing.
2. Vitamins in quantities above the recommended daily dose (e.g., Vitamin A above about 10,000 IU).
3. The use of anti-inflammatory medications (e.g., NSAIDs). NSAID use allowed on as needed basis for conditions such as headache, menstrual cramps, and minor injuries; Low dose aspirin is also allowed); Subjects will also be allowed to use acetaminophen for pain relief, as needed. The acceptable maximum dosage of acetaminophen should be 3,000mg/day.
4. Subject has to refrain from changing the use of any concomitant therapies after the screening visit until study completion.

4.4 Subject Withdrawal / Dropout

Study subjects will be discontinued from the study for any of the following reasons:

1. If the study subject withdraws his or her consent for any reason.
2. Subjects who discontinue treatment early due to insufficient or lack of treatment effect or whose condition worsens and require alternate or supplemental therapy for the treatment of moderate to severe persistent facial erythema of rosacea, the subjects should be discontinued, but included in the PP population analysis as treatment failures and provided with effective treatment.
3. Subjects that withdraw or discontinue early for reasons other than lack of treatment effect should be excluded from the PP population, but included in the mITT population, using last observation carried forward (LOCF).
4. If the study subject's drug code is un-blinded.
5. If an AE occurs for which the study subject desires to discontinue treatment or the Investigator determines that it is in the study subject's best interest to be discontinued.
6. If the subject experiences an SAE.
7. If there is a protocol violation.
8. If a concomitant therapy is reported or required which is prohibited or may interfere with the results of the study.
9. If the study subject is lost to follow-up.
10. If the study subject becomes pregnant (refer to Section 6.5.4)
11. [redacted]
12. Administrative reasons.
13. Any other reason that may affect the outcome of the study or the safety of study subjects.

**A protocol violation is defined as any study subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy that affects the rights, well-being or safety of the subject or the scientific integrity of the study data.*

If a subject discontinues participation in the study, every attempt will be made to complete the EoT as indicated in Table 6-1, and any outstanding data and study medication will be collected if possible. The reasons for a discontinuation and the date of removal from the study will be documented on the electronic Case Report Form (eCRF) and Sponsor will be notified.

Before a study subject is considered lost to follow-up, the Investigator will document all attempts to reach the study subject twice by telephone and will send a follow-up letter.

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

lost to follow-up. Should an SAE be noted, procedures stated in Section 6.5.1 must be followed.

When a study subject discontinues the study due to any of the above reasons, the study subjects should be prescribed appropriate treatment that he/she can continue to use as per the Investigator's clinical judgment.

5 TREATMENTS

5.1 Treatments to be Administered

The IPs supplied by the Sponsor will consist of the following:

Test Product		
Name of the product	:	Oxymetazoline hydrochloride Cream, 1%
Active ingredient(s)	:	Oxymetazoline hydrochloride
Pharmaceutical dosage form	:	Cream
Strength	:	1% (each gram of cream contains 10 mg [1%] oxymetazoline hydrochloride, equivalent to 8.8 mg [0.88%] of oxymetazoline free base)
Route of administration	:	Topical
Manufacturer	:	Actavis Laboratories, Salt Lake City, UT (a subsidiary of Teva Pharmaceuticals, USA)
Reference (R)		
Name of the product	:	RHOFADE™ (Oxymetazoline hydrochloride Cream, 1%)
Active ingredient(s)	:	Oxymetazoline hydrochloride
Pharmaceutical dosage form	:	Cream
Strength	:	1% (each gram of cream contains 10 mg [1%] oxymetazoline hydrochloride, equivalent to 8.8 mg [0.88%] of oxymetazoline free base)
Route of administration	:	Topical
Manufacturer/Marketed by	:	Manufactured by DPT Laboratories Ltd, for Allergan
Placebo (Vehicle)		
Name of the product	:	Vehicle to Oxymetazoline hydrochloride Cream
Active ingredient(s)	:	NA
Pharmaceutical dosage form	:	Cream
Strength	:	NA
Route of administration	:	Topical
Manufacturer	:	Actavis Laboratories, Salt Lake City, UT (a subsidiary of Teva Pharmaceuticals, USA)

5.2 Treatment Assignment (Randomization)

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

The study subject numbers will be assigned to study subjects sequentially in the order in which study subjects are enrolled into the study.

5.3 Dosage and Administration

The study medication will be dispensed to the subjects on Day 1 at the study site. Subjects will gently wash their face with a mild, non-medicated cleanser [redacted]), rinse with warm water and pat dry. The subjects will be asked to apply a pea-size amount of the assigned study treatment cream to cover the entire face [forehead, chin, nose, and each cheek (avoiding the eyes and lips)], once daily, preferably at the same time each day, for 29 days. Subjects will be instructed to avoid applying the study medication to the eyes, eyelids, lips, mouth, scalp, neck, ears, and any membrane of the inner nose, or open wounds. Subjects will be required to wash their hands before and after each application of study treatment.

On Day 1 and Day 29, the dose will be applied in the morning after completion of pre-dose study assessments and procedures. [redacted]

5.4 Receipt and Storage

Investigational Products (IPs) should be stored at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]; in a secured, authorized access area at the investigative site.

5.5 Packaging and Labeling

[redacted] The randomization will be pre-planned according to a computer-generated randomization schedule. The study medication will be blinded, packaged and delivered to the site in bulk. The study medication will be labeled and packaged such that neither the study subject nor the Investigator can identify the treatment. The labeling and packaging scheme will be outlined in a separate document by the Sponsor. The study medications will be shipped to the Investigator's site from a centralized location. The Principal Investigator will be responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study medication will be maintained in accordance with federal regulations.

5.6 Blinding

This is a double-blinded clinical end point bioequivalence study. Study medications will be provided in similar cartons to maintain study blinding.

If necessary, for the safety and proper treatment of the subjects, the Investigator can unblind the subject's treatment assignment to conduct appropriate follow-up care. Whenever possible, the Sponsor or medical monitor will be notified before unblinding the study medication. The date and signature of the person breaking the code as well as the reason for breaking the code and any associated AEs will be recorded in the subject's source documentation.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the treatment assigned to the subject. The study site will have at least one Independent Dispenser. The role of the unblinded Independent Dispenser will be to dispense and collect study medication to/from the subjects, maintain dispensing records, and ensure the study medication logs are complete and accurate. The Independent Dispenser will also be responsible for observing and supervising the administration of the study medication by the subject on clinic visits, Day 1 and Day 29. The subject will be requested not to discuss the appearance of the study medication with the Investigator or study staff outside of the Independent Dispenser. Independent dispenser should not participate in any activities other than the activities defined in this section. To ensure that information that could potentially bias handling of data is not disclosed, the packaging team will hold the randomization scheme until after database lock.

[redacted]

At the conclusion of the study, after the database has been locked, each site will be sent the study randomization scheme (respective to their site) that should be retained with the study documents in the event of an FDA inspection along with evidence of when the randomization scheme was provided.

5.7 Assessment of Compliance

A subject diary will be provided to all subjects on Day 1 where it is required to document the date and time of application of the study medication. In the subject diary, subjects will also note any AE observed and any concomitant medication taken or changes.

Compliance will be determined from the subject diary, which the subject will be trained and instructed to use to record the application of study medication each day, as well as all missed applications. The number of missed and additional applications will be captured on the compliance page of the CRF.

5.8 Study Medication Replacement

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

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

5.9 Accountability of Study Medication

It is the responsibility of the Investigator to ensure that the accountability of the IP is maintained at the study site where study medication is stored and dispensed.

A Drug Accountability Log will assist study site staff in maintaining inventory records of study medication.

The study medications will be dispensed only by an appropriately Independent dispenser. Study subjects must return used/unused IP to the Independent Dispenser. Any remaining drug supplies can be accounted for and noted in the Drug Accountability Log. The original Drug Accountability Log must remain at the study site and a copy should be provided to the study monitor after the study. See IMP manual for details.

5.10 Retention of Study Medication Samples

Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects.

5.11 Return of Drug Supplies

With the exception of the retention samples, all remaining IP will be returned by the Investigator or designee to the designated drug depot for storage and / or destruction after the close-out visit, [redacted].

6 STUDY PROCEDURES

6.1 Schedule of Events

The study will include the following scheduled visits: Screening visit [redacted] Baseline visit (Day 1[redacted]), Telephone Follow-up visit (Day 14[redacted]) and EoT visit (Day 29[redacted]). The schedule of visits and the study assessments at each visit are presented in Table 6-1. The assessments will be performed by, or under the supervision of, an Investigator or a qualified delegate. Evaluations should be performed by the same evaluator throughout the study whenever possible. Additional examinations may be performed as necessary to ensure the safety and well-being of subjects during the study.

[redacted]

Signs and symptoms that existed before signing informed consent should be recorded as medical history findings. Signs and symptoms that worsen after the informed consent is signed as well as any sign or symptom that begins after the ICF is signed (even if before start of study treatment) should be recorded on an AE page of the eCRF using Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (see Section 6.5.1).

Table 6-1: Schedule of Events

Procedures	Visit: Screening A	Screening B	Day 1 (Baseline)	Day 14 (Telephone Follow-up)[a]	Day 29 (EoT)
Written informed consent	X				
Demographics (height, weight, body mass index (BMI), gender, race, ethnicity)	X				
Pregnancy test (Urine)	X	X	X		X
	X				
Medical and surgical history	X	X			
Prior and concomitant medications and concurrent procedures	X	X	X	X	X
Vital signs measurements (blood pressure, heart rate, body temperature)	X	X	Pre-dose and 12 hrs		Pre-dose and 12 hrs
Clinician Erythema Assessment (CEA)	X	X	Pre-dose, 3, 6, 9, and		Pre-dose, 3, 6, 9, and

			12 hrs		12 hrs
Subject Self-Assessment (SSA) for rosacea facial redness	X	X	Pre-dose, 3, 6, 9, and 12 hrs		Pre-dose, 3, 6, 9, and 12 hrs
Physical examination	X				X
Review of Inclusion/Exclusion	X	X	Pre-dose (confirm eligibility)		
Randomization			X		
Dispense study medication tube and subject diary			X		
Dosing (Days 1-29)[b]			X		X
Adverse event monitoring[c]	X	X	X	X	X
Subject diary review			X		X
Confinement in study clinic			≥12 hrs in clinic		≥12 hrs in clinic
Collection of study medication tube					X

[a]14 days after the first dose of study drug, a phone call will be made to follow-up on any changes in concomitant medications and check on compliance of study medication usage.

[b]Subject will apply study medication once daily, preferably at the same time each day, from Day 2 to Day 28 at home, as instructed.

[c]Including application site dermatitis, application site pruritis, application site erythema, and application site pain, scaling, burning at Visit 2 and Visit 4.

6.2 Visit Description

Screening visit

The following is a list of all tests and procedures at the screening visit: (If necessary, subjects will be allowed to conduct screening procedures on two separate days in order to allow for enough time to complete the adequate washout period required for medications, makeup use, etc. Subjects should sign ICF, complete washout, and return to the clinic to conduct the remainder of the screening procedures.)

- Signed informed consent must be obtained prior to performing any study-specific tests or assessments.

  Note: A unique study subject number will be assigned to the subject at the time of the screening visit and will serve as subject identification on all study documents throughout the study.

- Obtain demographic information (age, gender, height, weight, BMI, race and ethnicity).
- Conduct urine pregnancy test (subjects of childbearing potential only).
- Document primary clinical diagnosis of facial rosacea
- Obtain current and past medical and surgical history including drug and alcohol use.
- Collect information on all prior (within 6 months of screening visit) and current medications.
- Record vital signs (blood pressure, heart rate and oral body temperature).
- Investigator's assessment of the severity of facial erythema using the CEA scale.
- Subject's assessment of the severity of facial erythema using the SSA scale.
- Complete physical examination.
- Screen the subject for protocol inclusion and exclusion criteria.
- Adverse event monitoring

  If necessary, subjects will be allowed to conduct screening procedures on two separate days in order to allow for enough time to complete the adequate washout period required for medications, makeup use, etc.

Screening B visit

In the event that the subject requires a Screening B visit, the following procedures should be performed:

- Conduct urine pregnancy test (subjects of childbearing potential only).
- Review of Medical and Surgical History
- Review of Prior and concomitant medications and concurrent procedures
- Record vital signs (blood pressure, heart rate and oral body temperature).
- Investigator's assessment of the severity of facial erythema using the CEA scale

- Subject's assessment of the severity of facial erythema using the SSA scale
- Screen the subject for protocol inclusion and exclusion criteria.
- Adverse event monitoring

Day 1 (Baseline) visit

The following is a list of all tests and procedures at Day 1 :

Pre-dose procedures

- Confirm subject's eligibility (check of inclusion / exclusion criteria) and randomize to treatment.
- Record vital signs (blood pressure, heart rate and oral body temperature).
- Investigator's assessment of the severity of facial erythema using the CEA scale at pre-dose.
- Subject's assessment of the severity of facial erythema using the SSA scale at pre-dose.
- Conduct urine pregnancy test (subjects of childbearing potential only).
  Review of Prior and concomitant medications and concurrent procedures
- Dispense the assigned study medication tube (to be done by Independent Dispenser).
- Hand over subject diary (to be done by study site staff).

Dosing

- Subjects will gently wash their face with a mild, non-medicated cleanser , rinse with warm water and pat dry.
- Subject should wash their hands with soap and water before and after applying treatment and to avoid contact of the study product with the eye or lips.
- Subject will apply a pea-size amount of the assigned study medication to cover the entire face (forehead, chin, nose, and each cheek [avoiding the eyes and lips]), under the supervision of the unblinded Independent Dispenser. The Independent Dispenser will be a designated site staff; unblinded to the treatment and will not be involved in any other clinical assessment activities.
- Subject will note the date and time of application of the study medication in the subject diary.

Post-dose procedures

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- Subjects will be questioned about how they are feeling and if any AE experienced this will be recorded in the subject diary.
- Subject will be advised to apply a pea-size amount of the assigned study medication to cover the entire face (forehead, chin, nose, and each cheek [avoiding the eyes and lips]), once daily preferably, at the same time each day, from Day 2 to Day 28 at home.
- Subject will be instructed to wash his/her hands before and after each application of study treatment and to avoid applying the study medication to the eyes, eyelids, lips, mouth, scalp, neck, ears, and any membrane of the inner nose, or open wounds.
- Subject will be instructed to refrain from using restricted/prohibited medications.
- Subjects who use make-up, facial moisturizers, creams, lotions, cleansers and/or sunscreens, will be instructed to use the same product brands/types, and not change the brand/type or frequency of use throughout the study, and not to use make-up, facial moisturizers, creams, lotions, and sunscreens on the scheduled clinic visit day before the visit. However, the use of facial cleanser will be acceptable.
- Subjects will be instructed to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages) throughout the study.
- Subject will be asked to return to the study site on the morning of Day 29 without applying the assigned study medication and to refrain from using restricted/prohibited medications prior to the clinic visit. [redacted]

Day 2 to Day 28 (At home)

The following is a list of procedures subject should follow at home.

- Subject will apply study medication once daily, preferably, at the same time each day, as instructed.
- Subject will note the date and time of application of the study medication daily in the subject diary. The subject will also note any AE observed and any concomitant medication taken or changes.

Telephone Follow-up (Day 14[redacted]) visit

- The follow-up visit will be performed via a phone call contact at Day 14 [redacted] after the first dose of study drug, to follow-up for any changes in concomitant medications and concurrent procedures and check on compliance of study medication usage.

Day 29[redacted] (End-of-Treatment) visit

The following is a list of the tests and procedures to be performed at Day 29[redacted]:

Pre-dose procedures

- Review of subject diary for compliance, AEs and concomitant medication.

- [redacted]
- Investigator's assessment of the severity of facial erythema using the CEA scale at pre-dose.
- Subject's assessment of the severity of facial erythema using the SSA scale at pre-dose.
- Record vital signs (blood pressure, heart rate and body temperature).
- Conduct urine pregnancy test (subjects of childbearing potential only).

Dosing

- Subjects will gently wash their face with a mild, non-medicated cleanser [redacted] rinse with warm water and pat dry.
- Subject should wash their hands with soap and water before and after applying treatment and to avoid contact of the study product with the eye or lips.
- Subject will apply a pea-size amount of the assigned study medication to cover the entire face [forehead, chin, nose, and each cheek (avoiding the eyes and lips)], under the supervision of designated staff (who is not involved in any other clinical assessment activities).
- Subject will note the date and time of application of the study medication in the subject diary.

Post-dose procedures

- The study medication tube will be collected by the study site staff.
- [redacted]
- Perform complete physical examination.

Unscheduled Visit and Early Discontinuation Visit

Unscheduled visit may occur as necessary, for any reason, if in the Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Investigator will determine whether additional visits are needed. Relevant and clinically significant laboratory data and AEs obtained at the unscheduled visits should be entered into the eCRF and recorded in the source documentation as necessary.

If a study subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Day 29 Visit will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the study subject will continue to take part in the study), then the reason for unscheduled visit is documented and required procedures at the discretion of Investigator considering the reason for visit, will be performed.

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

6.3 Population Characteristics

6.3.1 Demographics

For demographic assessment, the following parameters will be recorded: year of birth (for age), sex, ethnicity/race, weight, height and BMI.

6.3.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the Investigator:

- Not pertaining to the study indication;
- Start before signing of the informed consent;
- Considered relevant for the subject's study eligibility.

Complete medical history includes prior surgeries (including dermal surgeries), prior and concomitant medications, concomitant diseases and allergy history.

6.4 Efficacy

The primary efficacy variable will be derived from the efficacy measures: the Investigator's assessment of the severity of facial erythema using the 5-point CEA scale (Table 3-1).

6.4.1 Efficacy variables

The efficacy variable will be the following:

- Score on the Clinical Erythema Assessment (CEA) scale

6.4.2 Primary Efficacy Endpoints

The primary efficacy endpoint will be used to address the primary objectives, which aims at demonstrating therapeutic equivalence between Test Product and Reference Product.

The primary efficacy endpoint is the proportion of subjects with treatment success at all time-points 3, 6, 9, and 12 hours post application on Day 29. Treatment success is defined as having CEA score at least 2 grades lower than the baseline (Day 1 pre-dose) value..

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6.5 Safety

6.5.1 Safety Variables

The safety variables will be as follows:

- Serious Adverse Events (SAEs)
- Non-SAEs

6.5.2 Adverse events

Incidence of all AEs reported during the study will be summarized using the current version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary by treatment group, body system, severity, and relationship to the study drug. No inferential statistical analyses are planned.

6.5.2.1 Definitions

Adverse event (AE)

An AE is any untoward medical occurrence in a subject, regardless of whether it has a causal relationship with this treatment.

In this study, any AE occurring after the subject has signed the ICF until the end of follow-up period should be recorded and reported as an AE.

An AE can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered AEs.

Accordingly, an AE can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study

Worsening of the disease under study will be measured by evaluation of pain, inflammation lesions of rosacea, dermatitis, pruritus and erythema at the application site. The evaluation of pain and inflammation should be recorded as an AE only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular subject.

A treatment-emergent AE (TEAE) is any AE that occurs after initiation of study medication, or any event already present that worsens in either intensity or frequency following exposure to study medication.

Serious adverse event (SAE)

A SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening AE (i.e., the subject was at immediate risk of death from the event as it occurred; does not include an event that, had it occurred in a more severe form, might have caused death)

- in-subject hospitalization or prolongation of existing hospitalization means that hospital in-subject admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered SAEs, unless there was worsening of the preexisting condition during the subject's participation in this study.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.
- An AE that does not meet any of the criteria for seriousness listed above will be regarded as a non-SAE.

Other significant adverse events

When tested, marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/IP treatment, dose reduction, or significant additional concomitant therapy, other than those reported as SAEs, should be collected in the CRF and summarized in the Clinical Study Report (CSR).

6.5.2.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the Investigator according to the categories detailed below.

Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 6.5.2.1.

Intensity

The severity of each adverse event must be recorded as 1 of the choices on the following scales.

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

Causality should be assessed separately for each study treatment as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g., owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

Adverse events will be assessed for the relationship to the study drug (causality) according to the following scale:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered "No Reasonable Possibility" if it is clearly due to extraneous causes or when (must have two): • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable Possibility (related)	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered "Reasonable Possibility related" if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. • It follows a known pattern of response to the test drug.

Expectedness

An AE which is not included in the adverse events section of the relevant Safety Information Reference by its specificity, severity, outcome or frequency is considered an unexpected adverse event.

The reference safety information for this study is to be found in Appendix II.

When applicable, the sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events. CRO and investigators will not determine the expectedness.

Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

Outcome

The outcome of the AE is to be documented as follows:

- Recovered / resolved
- Recovering / resolving
- Recovered / resolved with sequelae
- Not recovered / not resolved
- Fatal
- Unknown

6.5.2.3 Recording and Reporting of adverse events

In this study, safety will be assessed by qualified study personnel by evaluating reported AEs, vital signs measurements, physical examination findings (including body weight and height measurements) and use of concomitant medication.

For AE recording, the study period is defined for each subject as that time period from signature of the ICF through the end of the study.

All AEs that occur during the defined study period must be recorded on the source documentation, regardless of the severity of the event or judged relationship to the study drug. For SAEs, the SAE Form must also be completed, and the SAE must be reported immediately (see Section 12). The Investigator does not need to actively monitor subjects for AEs once the study has ended. However, SAEs occurring in a subject after the treatment of that subject has ended should be reported to the Sponsor if the Investigator becomes aware of them.

At each contact with the subject, the Investigator or designee must question the subject about AEs by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings may be recorded collectively as a single diagnosis on the CRF and, if it is a SAE, on the SAE Form.

The onset and end dates and times, action taken regarding study drug, treatment administered, and outcome for each AE must be recorded on the source documentation.

The relationship of each AE to study drug treatment and study procedures, and the severity and seriousness of each AE, as judged by the Investigator, must be recorded as described above.

Subjects will be evaluated at each site visit for any signs/symptoms of application site dermatitis, application site pruritus, application site erythema, application site pain, and application site scaling or burning. The Investigator's assessment of Application Site Reactions will be captured in the following format within the source documents:

The clinical course of each AE will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the subject is referred for continued care to a health care professional or until a determination of a cause unrelated to the study drug or study procedure is made.

Adverse events will be coded according to MedDRA and reported with respect to severity, duration, relationship to study medication(s), seriousness and action taken.

6.5.2.4 Reporting of serious adverse events

To satisfy regulatory requirements, all SAEs (as described in Section 6.5.2.1) that occur during the study period, regardless of judged relationship to treatment with the study drug, must be reported to the Sponsor or CRO by the Investigator. The event must be reported within 24 hours of when the Investigator learns about it. Completing the SAE form and reporting the event must not be delayed, even if not all the information is available.

[redacted]

PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.

The CRO should inform the Pharmacovigilance (PhV) unit if the whole study is early discontinued due to safety reasons.

It is the responsibility of the CRO to report a SAE to the FDA within proper time constraints as per the Guidance for Industry and Investigator's Safety Reporting Requirements for Investigational New Drugs (INDs) and Bioavailability/Bioequivalence (BA/BE) Studies – DEC 2012. Confirmation of submission of this report must then be provided to Actavis, Inc. (Teva)'s study representative as well as their Pharmacovigilance department (contact info below).

The timeliness for submission of expedite reports should be 15 days or 7 days (death cases) or as otherwise specified in local regulations.

All SAE of the study due to safety reasons must be reported in parallel to the following persons:

[redacted]

<u>Sponsor's Contact person for this Biostudy (copy of the SAE details for information purposes only)</u>

[redacted]

These SAE reports must contain the following information, preferably using the template provided by the Sponsor:

A. Study name/number

B. Study Drug

C. Investigator details (name, phone, fax, e-mail)

D. Subject Number

E. Subject Initials when appropriate

F. Subject Demographics

G. Clinical Event

1) Description

2) Date of onset

3) Treatment (drug, dose, dosage form)

4) AE Relationship to study drug

5) Action taken regarding study drug in direct relationship to the AE

H. If the AE was Fatal:

1) Cause of death (whether or not the death was related to study drug)

2) Autopsy findings (if available)

The SAE form and supportive documents should be filled/ written in English. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded within 24 hours of the information becoming available to the same address as the initial report. Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Each report of an SAE will be reviewed and evaluated by the Investigator and the Sponsor pharmacovigilance to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

The CRO will take on the responsibility of reporting SAEs to the Investigators and/or to the IRB/Ethics Committee (EC).

The Investigator does not need to actively monitor subjects for AEs once the study has ended. Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the Sponsor if the Investigator becomes aware of them.

Submission of SAEs

Any SAE will be reported to competent authority and EC according to the country specific requirements and the responsibilities defined in the abovementioned section. All AEs will be reported in the CSR with the complete information named above according to the requirements of the Note for Guidance on Structure and Content of CSRs (CPMP/ICH/137/95).

Investigator Reporting of SAEs

Adverse events which are evaluated by the Investigator as "Serious" will be reported to the CRO designated below and IRB within 24 hours of notice whether or not they are considered expected or drug-related. All SAEs will be reported as per the FDA regulations.

Any SAEs should be reported to [redacted] within 24 hours to:

[redacted]

The Investigator or the Investigator's designee must be prepared to supply minimum details needed in the SAE reporting with the following information:

a. Investigator Name and Site Number

b. Subject ID Number

c. Subject initials and date of birth

d. Subject Demographics

e. Clinical Event

1) Description

2) Date of onset

3) Severity

4) Treatment (including hospitalization)

5) Relationship to study drug

6) Action taken regarding study drug

f. If the AE was Fatal or Life-threatening

1) Cause of death (whether or not the death was related to study drug)

2) Autopsy findings (if available)

3) Death Certificate

g. Concomitant medication log

h. AE log

i. Relevant tests with dates

j. IP Unblinding information, if applicable

CRO Reporting of SAEs

TCTM will report any SAE to Actavis Inc. drug safety team and the medical monitor within 1 business day.

Drug Safety Department:

Sponsor Study Manager:

Medical Monitor:

6.5.2.5 Submission of SAEs

The Principal Investigator or the Principal Investigator's designee must complete the provided SAE Form (Appendix III).

6.5.3 Follow-up of subjects after AE

The staff of the clinical facility has to monitor the clinical trial subject's safety from the occurrence of an AE until satisfactory recovery.

Any AE which remains unresolved at the time point of subject's last visit requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found; in case of AEs related to the IPs every effort has to be made to follow-

up clinical trial subjects in order to determine the final outcome. If follow-up cannot be completed until release of CRF by the Investigator the individual CRF will be released and transferred to the Clinical Data Management. In this case, follow-up information will be documented separately in the subject's record and outcome including a short description on follow-up procedures performed must be sent to the Sponsor.

It is the Investigator's responsibility to assure that subjects experiencing adverse reactions will receive definitive treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e., if treatment or hospitalization is required).

6.5.4 Pregnancy

If a subject becomes pregnant during the study, the Investigator will notify the Sponsor immediately after the pregnancy is confirmed and the subject exits from the study after appropriate safety follow-up.

All pregnancies of women participating in the study that occur during the study, or within 30 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the Investigator must provide the Sponsor with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a SAE (also see Section 6.5.2.4).

Any female subject becoming pregnant during the study will discontinue treatment. The Investigator will notify the subject's physician that the subject may have been treated with an investigational medication (oxymetazoline or vehicle), follow the progress of the pregnancy to term, and document the outcome of the pregnancy (including spontaneous or voluntary termination).

If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the Sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the Investigator becomes aware of after termination from the study will be reported as an AE or SAE, as appropriate.

If the pregnancy does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as an SAE.
- For an elective abortion due to developmental anomalies, report as an SAE.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an AE.

6.6 Other Procedures and Variables

6.6.1 Physical examination

The physical examination (by means of inspection, palpation, auscultation) will be performed by the Investigator or the designated physician at the study site on the day of screening and Day 29. All clinical signs and symptoms that can be brought into context with the underlying

disease, the treatment to be administered or any relevant comorbidities (if present) should be assessed during the physical examination.

At a minimum, the subject will be examined for the following aspects/symptoms but will not be commented on, unless there is an issue:

- General appearance
- Skin (paleness, jaundice, redness / rash, acneiform changes)
- Hand and feet (signs of hand-foot syndrome / palmar-plantar erythrodysesthesia)
- Eyes (accommodation, double images, abnormal sensitivity to light, jaundice)
- Ears, nose, throat (presence of petechial bleedings, gingiva bleeding)
- Head and neck
- Lungs
- Heart/ cardiovascular
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Lymph nodes
- Musculoskeletal system and spine
- Arms and legs (petechial bleedings, ulcer, signs of thrombosis)
- Neurological examination

Other clinical signs and symptoms may be investigated as well if clinically indicated. The subject's height and weight will be recorded at screening only.

6.6.2 Vital signs

Blood pressure, heart rate and body temperature will be recorded by a member of the Investigator's team at screening; at pre-dose and 12 hours on Day 1; and at pre-dose and 12 hours on Day 29.

Blood pressure (millimeters of mercury [mmHg]) and heart rate (beats per minute [bpm]) will be measured during the physical examination after 5 minutes rest in sitting position. Blood pressure and heart rate will be obtained preferably using the same arm and same equipment each time. If one arm has higher blood pressure than the other, that arm should be used for further blood pressure measurements (all further blood pressure measurements should be done in the same arm).

Body temperature will be measured using the oral or tympanic thermometer with digital display and recorded in the eCRF in degree Celsius (°C). Preferably the same method will be used each time.

If clinically indicated at the Investigator's discretion, additional vital sign assessments may be performed at unscheduled time points.

6.6.3 Laboratory evaluations

Urine pregnancy testing at Screening and Day 1 and Day 29 visits will be done for women of childbearing potential. A negative result will be required prior to receiving assigned study treatment. Further urinary pregnancy tests could be performed at any time during the study at the discretion of the Investigator.

6.7 Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the eCRF, regardless of whether an AE occurs as a result.

6.8 Follow up of Subjects after AE

The staff of the clinical facility has to monitor the clinical trial subject's safety from the occurrence of an AE until satisfactory recovery.
Any AE which remains unresolved at the time point of subject’s last visit requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found; in case of AEs related to the IPs every effort has to be made to follow-up clinical trial subjects in order to determine the final outcome. If follow-up cannot be completed until release of CRF by the investigator the individual CRF will be released and transferred to the Clinical Data Management. In this case, follow-up information will be documented separately in the subjects’ record and outcome including a short description on follow-up procedures performed must be sent to the sponsor.

It is the investigator's responsibility to assure that subjects experiencing adverse reactions will receive definitive treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e. if treatment or hospitalization is required). The responsibility to provide adequate follow-up for AEs includes periodically repeating laboratory tests (if required) yielding clinically abnormal results at the end of study evaluation.

6.9 Reconciliation of SAEs

Upon completion of the study, it is the responsibility of [redacted] to perform a reconciliation of the SAEs in the study with those in the Pharmacovigilance database. An email with this confirmation should be sent to [redacted]

6.10 Appropriateness of Procedures / Measurements

All efficacy and safety parameters, as well as the methods to measure them are standard variables/methods in clinical studies and/or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant for this therapeutic area.

7 STATISTICAL AND ANALYTICAL PLANS

The sections described here highlight the sample size determinations and planned analyses for this study. SAS Version 9.4 or higher will be used to perform all the statistical analyses. A Statistical Analysis Plan (SAP) that expands the statistical section of the protocol will be approved prior to locking the database. The SAP will provide descriptions of the statistical methods, hypotheses, analysis populations to be analyzed, and text with table and listing shells. The SAP will serve as a companion to the protocol and will serve as the de facto documentation of the proposed statistical evaluation.

The continuous data will be summarized by treatment groups using descriptive statistics (number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be summarized by treatment groups using frequency count (n) and percentages (%).

All statistical tests will be conducted at the 5% significance level, unless indicated otherwise.

7.1 Sample Size Rationale

[redacted]

The assumptions used to estimate this sample size were based on the efficacy data presented in the [redacted] were as follows:

- [redacted]
- [redacted]

[redacted]

7.2 Randomization Procedures

[redacted]

7.3 Significance Level

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

7.4 Datasets to be Analyzed

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

- [redacted]

7.5 Comparability of Study Groups at Baseline

The number and percentage of all the subjects entering and completing the study will be provided across treatment groups. Similarly, summarization of the primary reasons for discontinuation will be provided. The listing of subjects who discontinued from analysis population along with reasons of discontinuation will be presented. Descriptive statistics for various continuous demographic variables age (in years), height (in cm) and weight (in kg) will be provided. The frequency count (n) and percentages (%) for categorical variables will be provided by treatment groups for intent-to-treat (ITT) population. Other baseline data will be tabulated and listed appropriately. Medical history will be coded using MedDRA terms. The frequency count and percentage of subjects will be summarized according to the coded terms of System Organ Class (SOC) and preferred term across all the treatment groups for

safety population. Listing for all the demographic and baseline characteristics will be provided. No inferential analyses are planned.

7.6 Safety Assessment

Safety analyses will be performed on the safety population. No inferential analyses are planned.

The extent of exposure will be summarized using descriptive statistics. Subject exposure to the study medication will be characterized by study duration and treatment duration. Study duration will be defined as number of days from the date of first dosing to the date of EoT visit (Day 29); if the date of EoT visit is missing, the date of the last visit will be used (i.e., date of study visit minus date of first dosing plus 1). Treatment duration will be defined as number of days from the date of first dosing to last dose (i.e., date of last dose minus date of first dose plus 1). Study duration and treatment duration will be summarized using descriptive statistics by treatment group.

Adverse events will be coded using preferred terms and primary SOC from the current version of MedDRA. The AEs and SAEs are considered to be treatment-emergent if they have started or worsened after first application of any study drug up until the EoT visit. The incidence of TEAEs, treatment-emergent SAEs (TESAEs) and drug-related TEAEs and TESAEs will be summarized by treatment group in frequency tables. The maximum severity of a TEAE/TESAE experienced by a subject will be determined by the most severe rating recorded on the eCRF for the subject's given TEAE. TEAEs leading to study discontinuation and treatment-related TEAEs leading to study discontinuation will be summarized by preferred term within primary SOC. Individual subject listings will be generated for TEAEs and TESAEs, including subject age, sex, and race, sorted by primary SOC, preferred term, onset and stop date, onset day relative to the most recent dose, relationship, and severity.

Adverse events will also be collected both for the screening and baseline period (which will be referred to as pretreatment AEs). A listing of pretreatment AEs (including any SAEs) will be presented.

Incidence of concomitant medications will be summarized by treatment group. A listing by subject of all abnormal physical examination values will be provided. The vital signs (body temperature, systolic blood pressure, diastolic blood pressure and heart rate), will be reviewed by the Investigator or qualified delegate and will be summarized by descriptive statistics.

7.7 Efficacy Assessment

The efficacy analysis will be performed on all the subjects in mITT and PP population. Analyses will be conducted with the PP population for equivalence determination, and analyses with the mITT population will be for supportive superiority purposes. The SAP will provide descriptions of the statistical methods, hypotheses, and analysis populations to be analyzed.

7.7.1 Analysis of primary endpoint

- *Equivalence testing*

Therapeutic equivalence will be concluded if 90% continuity-corrected confidence interval for the difference between test and reference products ($\pi T - \pi R$) of the treatment success rates at all timepoints 3, 6, 9, and 12 hours post-application on Day 29 falls within the acceptance range of [-0.20, +0.20] using PP population.

- *Superiority testing*

A frequency distribution of subjects with at least a 2-grade decrease (improvement) on CEA scores by time point on Day 1 and Day 29 and by treatment group will be tabulated. A two-sided exact Cochran-Mantel-Haenszel test, stratified by clinical site, will be applied to test the difference between treatment success rates at all post-application timepoints on Day 29 of Test or Reference Product and Placebo. The sensitivity of the equivalence analysis (superiority of Test Product and Reference Product over Placebo) will be established if active treatment success rate is higher than and statistically significantly different from (p-value < 0.05) that of the Placebo group for each active treatment, using the mITT population. No adjustment will be made for multiplicity.

Detailed statistical methods will be explained in SAP.

8 ETHICS

This study will be performed in accordance with the ethical principles that have their origin in the current Declaration of Helsinki (Appendix I) and will be consistent with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study subjects are the most important considerations and should prevail over interests of society and science.

8.1 Informed Consent

The Investigator must ensure that study subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent, according to FDA Regulations and ICH-GCP will be followed. A copy of the proposed consent form must be submitted to the IRB, together with the protocol, for approval. Prior to beginning of the study, the Investigator must have the IRB's written approval of the written ICF and any other information to be provided to study subjects.

Informed consent will be obtained from all study subjects using the following procedure: Study subjects must have provided IRB approved written informed consent. Each study subject's signed informed consent must be kept on file by the Investigator. A copy of the signed consent form will be given to the study subject. A notation will be made in the study subject's medical record indicating the date the informed consent was obtained. In addition, the Investigator or the Investigator's designee will provide a HIPAA authorization form (if applicable) for the study subject to review and sign. Both the ICF and the HIPAA form (if applicable) must be signed by the study subject before any protocol assessments can be undertaken.

8.2 Institutional Review Board

Before study initiation, the Investigator must have, including but not only, written and dated approval from the IRB for the protocol, consent form, study subject recruitment materials and any other written information to be provided to study subjects. The Investigator or Sponsor name/CRO will also provide the IRB with a copy of the package insert.

Any changes to the protocol as well as a change of the Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents

pertaining to this study must be kept on file by the Investigator and are study subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

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

8.3 Study Subject Confidentiality

As of 14 APR 2003, the federal medical Privacy Rule authorized by the HIPAA requires most health care providers to take new measures to protect the privacy of individually identifiable health information. The Privacy Rule's requirements extend to identifiable health information used or disclosed in research.

The HIPAA Privacy Rule reinforces clinical Investigator's existing obligations to protect the privacy of identifiable health information under state law, codes of medical ethics and the federal regulations governing research.

Please be advised that the Privacy Rule compliance obligations include the following:

1. Treating individually identifiable health information as confidential in accordance with HIPAA and other federal, state and local laws and regulations governing the confidentiality and privacy of such information
2. Using or disclosing individually identifiable health information for study subject recruitment purposes only as permitted by HIPAA, applicable laws and regulations and institutional policies
3. Obtaining each study subject's written authorization for the use or disclosure of individually identifiable health information in research, where applicable, in a form that meets the requirements of HIPAA and identifies all uses, disclosures and data recipients
4. Disclosing identifiable health information created or maintained in connection with the research only for the purposes and to the parties described in the authorization form or as necessary to communicate with the FDA and other regulatory authorities or as otherwise permitted or required by law
5. Employing appropriate physical and technical safeguards to protect the privacy of individually identifiable health information
6. Obtaining a HIPAA waiver of authorization, or where applicable, providing representations and/or entering data use agreements as required under the HIPAA Privacy Rule for any secondary data analyses or activities preparatory to research and referencing these and other research uses and disclosures in your HIPAA notice of privacy practices.

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

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

9 DOCUMENTATION

9.1 Site Regulatory Documents Required for Initiation

A minimum of the following set of documents will be received by [redacted] prior to the initiation of the study:

1. Fully executed protocol
2. Completed and signed FDA Form 1572
3. Current curricula vitae, signed and dated for the Investigator and each Sub- Investigator named in the FDA Form 1572 (current within 2 years)
4. Current medical licenses of the Investigator and Sub-Investigators named in FDA Form 1572
5. Documentation of "No Objection" to proceed from the local regulatory agency, wherever applicable.
6. Documentation of IRB approval of this study protocol, Investigator, and ICFs
7. Current IRB membership list or roster and EC Standard Operating Procedures (SOPs)
8. Original Non-disclosure Agreements for the Investigator and Sub-Investigators named in FDA Form 1572
9. Financial Disclosure Statement for the Investigator and each Sub-Investigator named in FDA Form 1572

9.2 Maintenance and Retention of Records

It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB, informed consent, source documents, as well as CRFs (paper or electronic files). No documents shall be transferred from the site or destroyed without first notifying the Sponsor. The Sponsor will archive the data for the lifetime of the product. If the Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the IP or entered as a control in the investigation. Data reported on the eCRF, which are derived from source documents, must be consistent with the source documents.

9.3 Case Report Forms (CRFs)

Electronic Data Capture (EDC) technology will be utilized. Electronic CRFs (eCRFs) will be prepared for all data collection fields. Study subjects will be identified by initials, birth date and subject number, if applicable. Corrections to the CRF will generate an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The user will document the reason for the change which is also maintained in the audit trail. CRFs may be reviewed and signed manually / electronically by properly trained and authorized individuals. The EDC platform will be compliant with 21 CFR (Code of Federal Regulations) part 11 security and audit trail requirements.

CRFs must be kept current to reflect the study subject's status at each phase during the course of the study. Study subjects are not to be identified on CRFs by name; appropriately coded identification (i.e., study subject study number) and the study subject's initials must be used. The Investigator must keep a separate log of the study subject's names and addresses.

Source documents such as the clinic chart are to be maintained separately from the eCRF (in order to allow data verification. Due to the potential for errors and inaccuracies in entering data into CRFs, originals of laboratory and other test results must be kept on file with the study subject's source document. Source documents and copies of test results must be available at all times for inspection by the study monitor.

9.4 Primary Source Documents

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

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

The Investigator must also retain all study subject specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to validate data in the CRFs against these sources of data.

9.5 Study Monitoring

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

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

The following should also be available for review:

1. Study Subject Screening/Enrollment Log – reflecting the reason any study subject screened for the study was found to be ineligible and start and end dates for all study subjects
2. Delegation of Authority / Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/designee will be documented
4. Drug Inventory/Packing Slip – reflecting the total amount of drug shipped to the site and received and signed for by the Investigator
5. Drug Accountability Log – reflecting the total amount of IP dispensed to and returned by each study subject
6. Informed Consent Form – which must be available for each study subject and be verified for proper documentation
7. All correspondence

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

At the end of the study, a closeout monitoring visit will be performed.

9.6 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations. Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the study or after the study.

9.7 Modifications to the Protocol

The procedures defined in the protocol and in the eCRF/paper CRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no deviations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB prior to implementation. All amendments to the protocol, which involve substantial changes in study design, procedure or analyses, will be submitted to appropriate regulatory authority for prior approval.

The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a study subject or study subjects. However, the Investigator must notify the Sponsor and the IRB as soon as possible.

9.8 Completion of Study

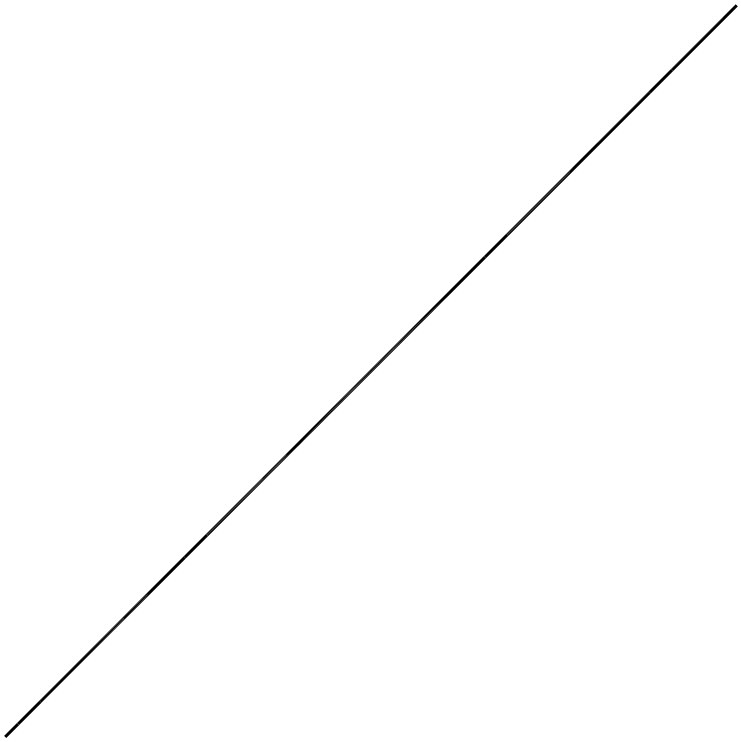
The Investigator is required to forward CRFs and all other relevant data and records to CRO. The Investigator will complete and report (submission of CRFs) his/her study in satisfactory compliance with the protocol as soon as possible after the completion of the study.

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

A CSR will be prepared in accordance with ICH-GCP and Sponsor requirements. In the event the study is prematurely terminated for medical reasons, the principal Investigator or his/her authorized designee will produce an abbreviated safety report.

10 STUDY SUBJECT INSURANCE

All study subjects will be covered by adequate insurance for any trial related injuries. This insurance covers cost of medical treatment, discomfort or injury to the study subject as a result of drug administration or any of the procedures carried out during the study.



11 CONFIDENTIALITY, USE OF INFORMATION, AND PUBLICATION

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

The information developed during the course of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of the drug. The information may be disclosed as deemed necessary by the Sponsor. To allow the use of the information derived from this clinical study, the Investigator is obliged to provide the Sponsor with complete test results and all data developed in the study. The information obtained during this study may be made available to other Investigators who are conducting similar studies.

12 PREMATURE TERMINATION OF STUDY/SUBJECT

A subject may terminate from the study early for any reason at any time without any disadvantages. In this case, the Investigator should make every effort to have the subject return to the next scheduled visit to perform all required Study Completion/Early Termination visit activities and to collect and reconcile all test articles. If the subject does not return for the Study Completion/Early Termination visit, the site should fully document the reason for early termination. All data, including the date and primary reason for termination, must be recorded on the Study Completion/Early Termination CRF, and source document.

Any subject who experiences an AE may be terminated from the study or from study treatment at any time at the discretion of the Investigator. In this case, the subject should be followed at the discretion of the Investigator until the resolution or stabilization of the AE. All applicable data should be recorded in the AEs section of the CRF. If a subject terminates from the study early for multiple reasons that include AEs, the Study Completion/Early Termination CRF should indicate that early termination was related to an AE.

An exception to this requirement will be the occurrence of an AE that in the opinion of the Investigator is not severe enough to warrant early termination but that requires the use of a prohibited medication, thereby requiring discontinuation of the subject. In such a case, the reason for discontinuation would be the need to take a prohibited medication, not the AE.

The Investigator must inform the clinical project physician/clinical leader/Principal Investigator as soon as possible of all subjects who are being considered for early termination due to AEs. Additional reports must be provided when requested.

The Sponsor reserves the right to terminate the study at any time for administrative reasons. The study may also be terminated by regulatory authorities or by the Investigator for his/her site following consultation with the Sponsor. Following a decision to discontinue the trial, the Investigator will immediately inform both the study subjects and the IRB responsible for this trial within 10 working days, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is Sponsor's responsibility to report the premature termination of the study to the regulatory agencies within 15 days providing them with the reasons for the trial discontinuation and advising them in writing of any potential risks to the health of study subjects or other persons. The CRO may notify the regulatory agency on behalf of the Sponsor.

13 REFERENCES

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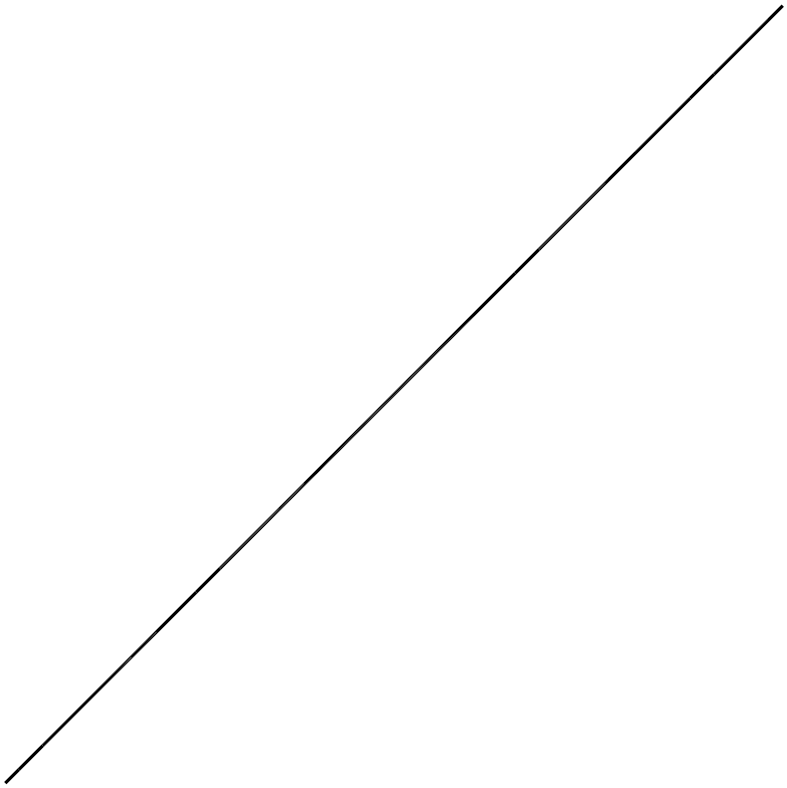
14 LIST OF APPENDICES

Appendix-I: Declaration of Helsinki

Appendix-II: Reference Safety Information (Prescribing Information: RHOFADE™)

Appendix-III: SAE Form

Appendix-IV: Pregnancy Form



APPENDIX – 1 DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest,

institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix-II: Reference Safety Information (Prescribing Information: RHOFADE™)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RHOFADE™ topical cream safely and effectively. See full prescribing information for RHOFADE™ topical cream.

RHOFADE™ (oxymetazoline hydrochloride) cream, for topical use

Initial U.S. Approval: 1964

----------INDICATIONS AND USAGE----------

RHOFADE™ is an alpha1A adrenoceptor agonist indicated for the topical treatment of persistent facial erythema associated with rosacea in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Not for oral, ophthalmic, or intravaginal use. (2)
- Prime pump bottle before initial use and discard product from first three pumps. (2)
- Apply a pea-sized amount once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips. (2)
- Wash hands after application. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Cream, 1%. Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8 mg (0.88%) of oxymetazoline free base. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Alpha-adrenergic agonists as a class may impact blood pressure. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens. (5.1)
- Use with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome and advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop. (5.2)
- Advise patients to seek immediate medical care if signs and symptoms of acute narrow-angle glaucoma develop. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1%) are application site dermatitis, worsening inflammatory lesions of rosacea, application site pruritis, application site erythema, and application site pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RHOFADE™ cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

2 DOSAGE AND ADMINISTRATION

For topical use only. RHOFADE is not for oral, ophthalmic, or intravaginal use.

Prime the RHOFADE pump before using for the first time. To do so, with the pump in the upright position, repeatedly depress the actuator until cream is dispensed and then pump three times. Discard the cream from priming actuations. It is only necessary to prime the pump before the first dose.

RHOFADE tubes do not require priming.

Apply a pea-sized amount of RHOFADE cream, once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips. Wash hands immediately after applying RHOFADE cream.

3 DOSAGE FORMS AND STRENGTHS

RHOFADE (oxymetazoline hydrochloride) cream, 1% is a white to off-white cream. Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8 mg (0.88%) of oxymetazoline free base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. RHOFADE should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

5.2 Potentiation of Vascular Insufficiency

RHOFADE should be used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

5.3 Risk of Angle Closure Glaucoma

RHOFADE may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 489 subjects with persistent facial erythema associated with rosacea were treated with RHOFADE once daily for 4 weeks in 3 controlled clinical trials. An additional 440 subjects with persistent facial erythema associated with rosacea were also treated with RHOFADE once daily for up to one year in a long-term (open- label) clinical trial. Adverse reactions that occurred in at least 1% of subjects treated with RHOFADE through 4 weeks of treatment are presented in Table 1 below.

Table 1: Adverse Reactions Reported by ≥1% of Subjects through 4 Weeks of Treatment in Controlled Clinical Trials

Adverse Reaction	Pooled Controlled Clinical Trials	
	RHOFADE Cream (N = 489)	**Vehicle Cream** (N = 483)
Application site dermatitis	9 (2%)	0
Worsening inflammatory lesions of rosacea	7 (1%)	1 (<1%)
Application site pruritus	5 (1%)	4 (1%)
Application site erythema	5 (1%)	2 (<1%)
Application site pain	4 (1%)	1 (<1%)

In the long-term (open-label) clinical trial, the rates of adverse reactions over a one-year treatment period were as follows: worsening inflammatory lesions of rosacea (3%), application site dermatitis (3%), application site pruritis (2%), application site pain (2%), and application site erythema (2%). Subjects with persistent erythema along with inflammatory lesions were allowed to use additional therapy for the inflammatory lesions of rosacea.

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha$_1$ adrenergic receptor antagonists such as in the treatment of cardiovascular disease, benign prostatic hypertrophy, or Raynaud's disease.

7.2 Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on RHOFADE use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. A literature article describing intranasal decongestant use in pregnant women identified a potential association between second-trimester exposure to oxymetazoline (with no decongestant exposure in the first trimester) and renal collecting system anomalies *[see Data]*. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 3 times and 73 times, respectively, the exposure associated with the maximum recommended human dose (MRHD) *[see Data]*. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Following repeated use of oxymetazoline hydrochloride solution nasal spray for the treatment of nasal congestion at a dose 5 times higher than recommended, one case of fetal distress was reported in a 41-week pregnant patient. The fetal distress resolved hours later, prior to the delivery of the healthy infant. The anticipated exposures for the case are 8-to18-fold higher than plasma exposures after topical administration of RHOFADE.

Data

Human Data

No adequate and well-controlled trials of RHOFADE have been conducted in pregnant women. Across all clinical trials of RHOFADE, two pregnancies were reported. One pregnancy resulted in the delivery of a healthy child. One pregnancy resulted in a spontaneous abortion, which was considered to be unrelated to the trial medication. A literature article summarizing the results of exploratory analyses of intranasal decongestant use during pregnancy identified a potential association between second-trimester exposure to oxymetazoline hydrochloride solution (with no decongestant exposure in the first trimester) and renal collecting system anomalies.

Animal Data

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogeneisis (3 times the MRHD on an AUC comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogeneisis (73 times the MRHD on an AUC comparison basis). Maternal toxicity, such as decreased maternal body weight, was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of delayed skeletal ossification.

In a rat perinatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (3 times the MRHD on an AUC comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 and 0.2 mg/kg/day (2 times the MRHD and 3 times the MRHD on an AUC comparison basis, respectively). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of

0.05 mg/kg/day (one-half of the MRHD on an AUC comparison basis).

8.2 Lactation

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breastmilk production, or to establish the level of oxymetazoline present in human breastmilk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOFADE and any potential adverse effects on the breastfed child from RHOFADE or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of RHOFADE have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use

One hundred and ninety-three subjects aged 65 years and older received treatment with RHOFADE (n = 135) or vehicle (n = 58) in clinical trials. No overall differences in safety or effectiveness were observed between subjects ≥ 65 years of age and younger subjects, based on available data. Clinical studies of RHOFADE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

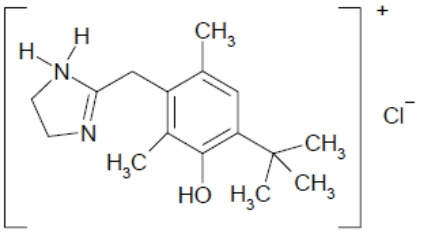
10 OVERDOSAGE

RHOFADE is not for oral use. If oral ingestion occurs, seek medical advice. Monitor patient closely and administer appropriate supportive measures as necessary. Accidental ingestion of topical solutions (nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep RHOFADE out of reach of children.

11 DESCRIPTION

RHOFADE (oxymetazoline hydrochloride) cream 1% contains oxymetazoline hydrochloride, an alpha$_{1A}$ adrenoceptor agonist. RHOFADE is a white to off-white cream. It has a chemical name of 3-[(4,5-Dihydro- 1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethyl-phenol hydrochloride and a molecular weight of

296.8. It is freely soluble in water and ethanol and has a partition coefficient of 0.1 in 1-octanol/water. The molecular formula of oxymetazoline HCl is $C_{16}H_{25}ClN_2O$ and its structural formula is:



Each gram of RHOFADE (oxymetazoline hydrochloride) cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8 mg (0.88%) of oxymetazoline free base. The cream contains the following inactive ingredients: sodium citrate dihydrate, citric acid anhydrous, disodium edetate dihydrate, butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, PEG-6 stearate, glycol stearate, PEG-32 stearate, cetostearyl alcohol, ceteareth-6, stearyl alcohol, ceteareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymetazoline is an alpha$_{1A}$ adrenoceptor agonist. Oxymetazoline acts as a vasoconstrictor.

12.2 Pharmacodynamics

The pharmacodynamics of RHOFADE has not been studied.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of oxymetazoline was evaluated following topical administration of RHOFADE in a thin layer to cover the entire face in adult subjects with erythema associated with rosacea. The median weight of cream for each dose administration was 0.3 g. Plasma oxymetazoline concentrations were measurable in most of the subjects. Following the first dose application, the mean ± standard deviation (SD) peak concentrations (C_{max}) and area under the concentration-time curves from time 0 to 24 hours (AUC_{0-24hr}) were 60.5 ± 53.9 pg/mL and 895 ±798 pg*hr/mL, respectively. Following once daily applications for 28 days, the mean ± SD C_{max} and AUC_{0-24hr} were 66.4 ± 67.1 pg/mL and 1050 ± 992 pg*hr/mL, respectively. Following twice daily applications (twice the recommended frequency of application) for 28 days, the mean ± SD C_{max} and AUC_{0-24hr} were 68.8 ± 61.1 pg/mL and 1530 ± 922 pg*hr/mL, respectively.

Distribution

An in vitro study demonstrated that oxymetazoline is 56.7% to 57.5% bound to human plasma proteins.

Metabolism

In vitro studies using human liver microsomes showed that oxymetazoline was minimally metabolized, generating mono-oxygenated and dehydrogenated products of oxymetazoline. The percentage of parent drug oxymetazoline remaining was 95.9% after a 120-minute incubation with human liver microsomes.

Excretion

The excretion of oxymetazoline following administration of RHOFADE has not been characterized in humans.

Drug Interaction

In vitro studies using human liver microsomes demonstrated that oxymetazoline up to the tested concentration of 100 nM had no inhibition on the activities of the cytochrome P450 (CYP) isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. Treatment of cultured human hepatocytes with up to 100 nM oxymetazoline did not induce CYP1A2, CYP2B6, or CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oxymetazoline hydrochloride was not associated with an increased incidence of neoplastic or proliferative changes in transgenic mice given oral doses of 0.5, 1.0, or 2.5 mg/kg/day oxymetazoline hydrochloride for 6 months.

Oxymetazoline hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and human lymphocyte chromosomal aberration assay) and one in vivo gentoxicity test (mouse micronucleus assay).

Effects on fertility and early embryonic development were evaluated in rats following oral administration of 0.05, 0.1, or 0.2 mg/kg/day oxymetazoline hydrochloride prior to and during mating and through early pregnancy. Decreased number of corpora lutea and increased post-implantation losses were noted at 0.2 mg/kg/day oxymetazoline hydrochloride (3 times the MRHD on an AUC comparison basis). However, no treatment related effects on fertility or mating parameters were noted at 0.2 mg/kg/day oxymetazoline hydrochloride (3 times the MRHD on an AUC comparison basis).

14 CLINICAL STUDIES

RHOFADE was evaluated for the treatment of persistent erythema associated with rosacea in two identical, randomized, double-blind, vehicle-controlled, parallel-group clinical trials. The trials enrolled 885 subjects aged 18 years and older. Overall, 90% of subjects were Caucasian and 79% were female. Subjects applied either RHOFADE or vehicle once daily for 29 days.

Disease severity was graded by the clinician using a 5-point clinician erythema assessment (CEA) scale and by the subject on a similar 5-point subject self-assessment (SSA) scale, on which subjects scored either “moderate” or “severe” on both scales.

CEA and SSA were measured over a 12-hour period at equally-spaced timepoints (hours 3, 6, 9, and 12) post- dose on Days 1, 15, and 29. The primary efficacy endpoint was defined as the proportion of subjects with at least a 2-grade reduction in erythema (improvement) from baseline (pre-dose on Day 1) on both the CEA and SSA measured at hours 3, 6, 9, and 12 on Day 29. The results from both trials on the composite endpoint for Day 29 are presented in Table 2.

Table 2: Proportion of Subjects Achieving Composite Success* on Day 29

Time-point (Hour)	Trial 1		Trial 2	
	RHOFADE Cream (N=222)	Vehicle Cream (N=218)	RHOFADE Cream (N = 224)	Vehicle Cream (N=221)
3	12%	6%	14%	7%
6	16%	8%	13%	5%
9	18%	6%	16%	9%
12	15%	6%	12%	6%

*Composite success is defined as the proportion of subjects achieving at least a 2-grade improvement on both CEA and SSA.

16 HOW SUPPLIED/STORAGE AND HANDLING

RHOFADE (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. The product is available in a laminated tube and an airless pump polypropylene bottle in the following packaging configurations, each with a child-resistant closure:

NDC 0023-5300-30	30 gram tube
NDC 0023-5300-60	60 gram tube
NDC 0023-5300-35	30 gram pump
NDC 0023-5300-65	60 gram pump

Storage: Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30ºC (59°F-86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Patient Information* and *Instructions for Use).*

Important Administration Instructions
Advise patients of the following:

- RHOFADE is for topical use only.
- RHOFADE pumps require priming before initial use and discard product from the first three pumps.
- Do not to apply RHOFADE to irritated skin or open wounds.
- Avoid contact with the eyes and lips.
- Wash hands immediately after application.
- Keep RHOFADE out of reach of children.

Manufactured for Allergan, Irvine, CA 92612, U.S.A. by
DPT Laboratories, Ltd, San Antonio, TX 78215

Made in the U.S.A.

73141US10

PATIENT INFORMATION
RHOFADE™ (roe' fayd)
(oxymetazoline hydrochloride)

Important: RHOFADE cream is for skin (topical) use on the face only. Do not use RHOFADE cream in your eyes, mouth, or vagina.

Keep RHOFADE cream out of the reach of children.

Get medical help right away if you, a child, or anyone else swallows RHOFADE cream.

What is RHOFADE cream?

RHOFADE cream is a prescription medicine used on the skin (topical) to treat facial redness due to rosacea that does not go away (persistent) in adults.

It is not known if RHOFADE cream is safe and effective in children under 18 years of age.

Before you use RHOFADE cream, tell your healthcare provider about all of your medical conditions, including if you:

- have heart, blood vessel, or blood pressure problems. Call your healthcare provider or get medical help if these conditions worsen.
- have problems with blood circulation or have had a stroke
- have Sjögren's Syndrome
- have scleroderma
- have Raynaud's phenomenon
- have thromboangiitis obliterans
- have narrow-angle glaucoma. Call your healthcare provider or get medical help if your glaucoma worsens.
- have irritated skin or open sores on the face
- are pregnant or plan to become pregnant. It is not known if RHOFADE cream will harm your unborn baby.
- are breastfeeding. It is not known if RHOFADE cream passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use RHOFADE cream.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, skin products, vitamins, and herbal supplements. Using RHOFADE cream with certain other medicines may affect each other and can cause serious side effects.

How should I use RHOFADE cream?

- See the detailed Instructions for Use that comes with your RHOFADE cream tube or pump for information about how to apply RHOFADE cream correctly.
- Use RHOFADE cream exactly as your healthcare provider tells you. Do not use more RHOFADE cream than prescribed.
- RHOFADE cream is for use on your skin only. **Do not** use RHOFADE cream in your eyes, mouth, or vagina. Avoid contact with your lips and eyes.
- **Do not** apply RHOFADE cream to irritated skin or open wounds.

What are the possible side effects of RHOFADE cream?

The most common side effects of RHOFADE cream include application site reactions of:

- skin reactions (dermatitis)
- itching
- pain
- worsening of rosacea pimples
- redness

These are not all the possible side effects of RHOFADE cream.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RHOFADE cream?

- Store RHOFADE cream at room temperature between 68°F to 77°F (20°C to 25°C).

Keep RHOFADE cream and all medicines out of the reach of children.

General information about the safe and effective use of RHOFADE cream
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use RHOFADE cream for a condition for which it was not prescribed. Do not give RHOFADE cream to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about RHOFADE cream that is written for health professionals.

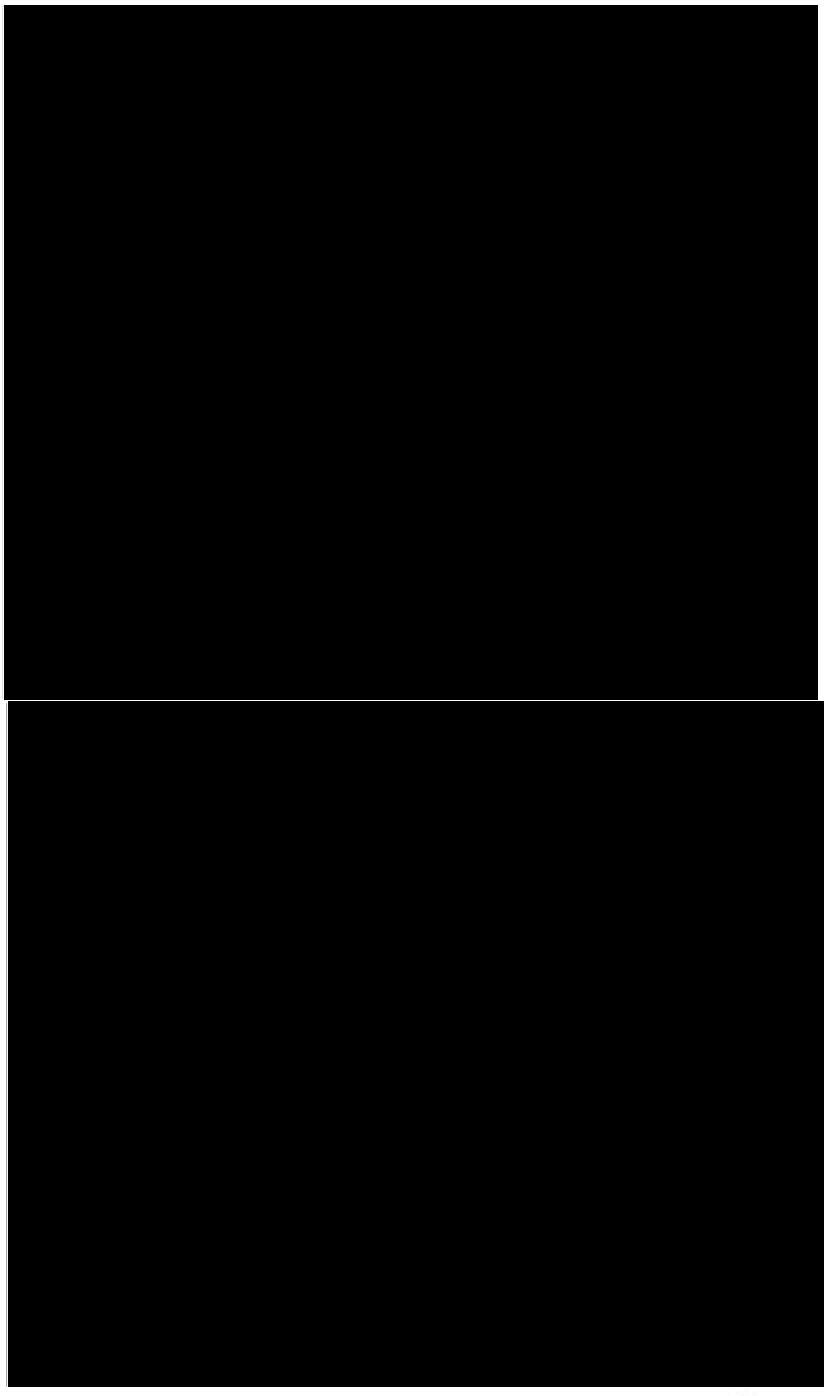
What are the ingredients in RHOFADE cream? Active ingredient: oxymetazoline hydrochloride
Inactive ingredients: sodium citrate dihydrate, citric acid anhydrous, disodium edetate dihydrate, butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, PEG-6 stearate, glycol stearate, PEG-32 stearate, cetostearyl alcohol, ceteareth-6, stearyl alcohol, ceteareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water

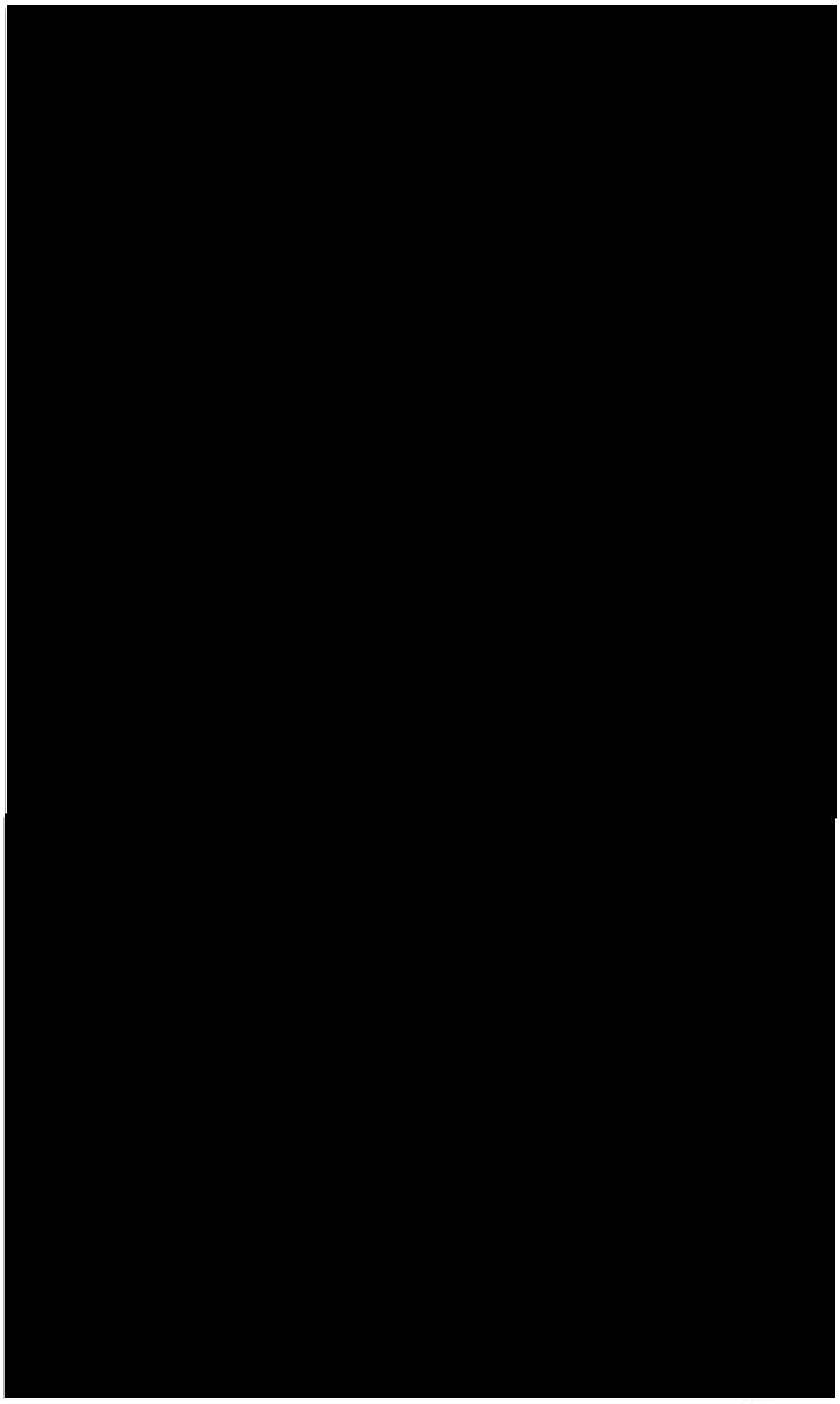
Manufactured for Allergan, Irvine, CA 92612, U.S.A. by
DPT Laboratories, Ltd, San Antonio, TX 78215

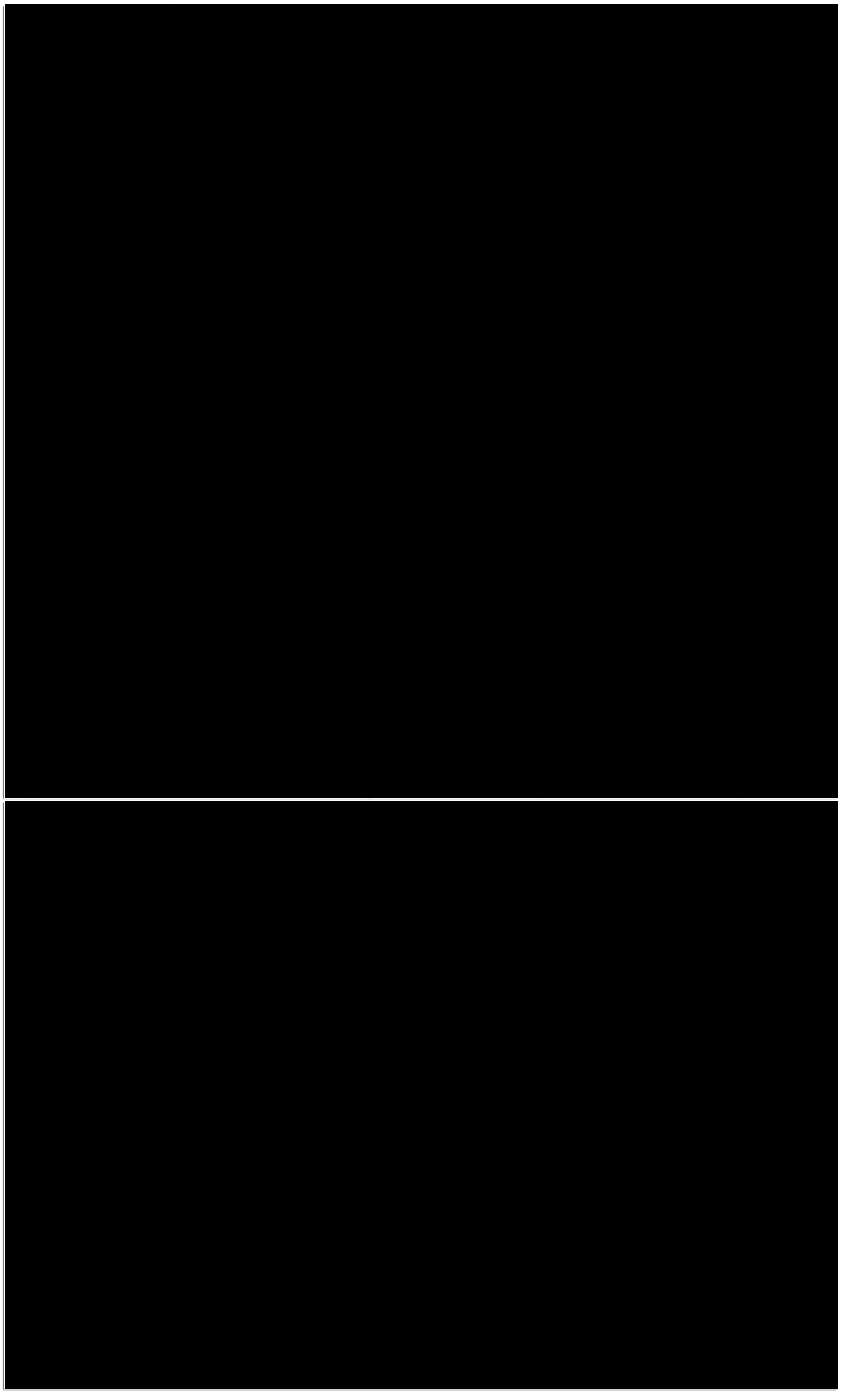
This Patient Information has been approved by the U.S. Food and Drug Administration Approved: 01/2017

73141US10

Appendix-III: SAE Form







Appendix-IV: Pregnancy Form