16. APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

CLINICAL STUDY PROTOCOL

Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea

Protocol Number:	CMO-MA-MED-0530
Investigational Product:	Rhofade (Oxymetazoline Hydrochloride [HCl] cream) 1.0%
Phase:	Phase 4
Sponsor:	Allergan Morris Corporate Center III 400 Interpace Parkway Parsippany, NJ 07054 United States
Contract Research Organization:	INC Research 3201 Beechleaf Court Suite 600 Raleigh, NC 27604 United States
Protocol Date:	06 Feb 2018
Protocol Version:	Version 2

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea

Protocol Number: CMO-MA-MED-0530

This study will be conducted in compliance with the clinical study protocol International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

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February 9, 2018
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2 STUDY PERSONNEL

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3 SYNOPSIS

Protocol Number:

CMO-MA-MED-0530

Title:

Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea

Investigational Product:

Rhofade (Oxymetazoline Hydrochloride [HCl] cream) 1.0%

Study Centers:

4

Phase:

Phase 4

Objectives:

Primary objective: To evaluate the safety and tolerability of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

Exploratory objective: To evaluate preliminary measures of efficacy of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

Study Design:

This is a multicenter, interventional, open-label safety and tolerability study.

Number of Subjects:

Approximately 45 subjects in total

Treatment:

All subjects will receive one of the following energy-based therapies: Potassium Titanyl Phosphate [KTP], Pulsed Dye Laser [PDL], or Intense Pulsed Light [IPL] twice during the study (Day 1 and Day 29). Once-daily application of oxymetazoline HCl cream 1.0% will be initiated on Day 3 and continued until Day 56. Subjects will be washed out from study drug 24 hours prior to the energy-based therapy session on Day 29 and will recommence study drug administration on Day 31.

Study Duration:

The duration of the entire study for each subject is 10 weeks. This includes a screening period of up to 2 weeks, a treatment period of 8 weeks, comprising of daily dosing of study drug and 2 energy-based therapy sessions, followed by a final exit visit at Week 8 (Day 56).

Study Population:

To be eligible for study entry subjects must satisfy all the following inclusion criteria:

1. Subject has provided written consent prior to any study-related procedures.
2. Male or female aged ≥ 18 years.
3. Clinical diagnosis of rosacea.
4. Moderate to severe persistent facial erythema associated with rosacea at baseline, as determined by a grade of ≥ 3 on the Clinician Erythema Assessment (CEA) scale with photonumeric guide.

5. Written informed consent prior to any study-related procedures
6. Written Authorization for Use and Release of Health and Research Study Information
7. Females of childbearing potential must not be lactating, must have a negative urine pregnancy test at screening and Day 1, and must agree to practice a reliable method of contraception throughout the study (See Section 5.6.9).
8. The ability to follow study instructions and complete study assessments without assistance and have a willingness and ability to comply with all scheduled visits, treatment plan, and other study procedures.

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Any uncontrolled systemic disease
2. History of any of the following conditions: Raynaud's syndrome, narrow angle glaucoma, orthostatic hypotension, cerebral or coronary insufficiency, thromboangiitis obliterans, scleroderma, Sjögren's syndrome, severe or unstable or uncontrolled cardiovascular disease, or any other current uncontrolled systemic disease.
3. Diagnosis or presence of any of the following conditions within the treatment area: rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin, peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or chronic recurring facial acne.
4. The presence of facial hair, tattoos, or other facial characteristics such as actinic damage (eg, actinic lentigines, mottled hyperpigmentation or hypopigmentation, yellowish discoloration, excessive telangiectasia) that could interfere with the assessments of erythema in the opinion of the investigator.
5. Current treatment with monoamine oxidase (MAO) inhibitors.
6. Current treatment with niacin ≥ 500 mg/day.
7. Any of the following treatments occurring within the specified period prior to Day 1:
    - 14 days: products containing oxymetazoline (eg, eye drops, nasal sprays), topical glucocorticosteroids applied to the face, systemic or nasal corticosteroids, any prescription or over-the-counter (OTC) product for the treatment of acne.
    - 28 days: Systemic antibiotics that are known to have an effect on rosacea such as erythromycin or doxycycline.
    - 180 days: isotretinoin.
8. Prior dermal adverse reaction to using Mirvaso® (brimonidine) topical gel, 0.33% or current use of marketed Mirvaso® (brimonidine) topical gel, 0.33%.
9. Previous participation in clinical trials associated with oxymetazoline cream for facial rosacea
10. Known hypersensitivity or allergies to any component of the study drug.
11. Greater than 3 inflammatory lesions on the face.
12. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.
13. History or current evidence of drug or alcohol abuse within 12 months prior to the screening visit.
14. Condition or situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
15. An employee (or a relative of an employee) of the investigators, Allergan, or representative of Allergan.

Primary Endpoints:

Safety and tolerability of oxymetazoline HCl 1.0% cream as an adjunctive treatment to energy-based therapy as determined by:

- The incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).
- The number and percentage of subjects with at least a 1-grade worsening from baseline in the Dermal Tolerability Assessment at any timepoint over the treatment period.
- The number and percentage of subjects with at least a 1-grade worsening from baseline in the Clinician's Telangiectasia Assessment (CTA) at any timepoint over the treatment period.

Exploratory Endpoints:

Exploratory measures of efficacy of oxymetazoline HCl 1.0% cream as an adjunctive treatment to energy-based therapy as determined by:

- The number and percentage of subjects with at least a 1-grade improvement on the CEA from baseline over a 6-hour period (measured at hours 1, 3, and 6) following study drug application.
- Percentage change from baseline in rosacea facial redness using Digital Image Analysis (DIA) of standardized facial photographs during the treatment period.
- Proportion of subjects indicating Satisfied or Very Satisfied with treatment on the Items from Satisfaction Assessment for Rosacea Facial Redness and proportion of subjects indicating Somewhat Satisfied or Very Satisfied with treatment on the FACE-Q Satisfaction with Skin Scale.

Safety:

The following safety assessments will be performed:

- Adverse event (AE), TEAE, and SAE monitoring
- Urine pregnancy test (female subjects of child bearing potential only)
- Vital signs (blood pressure, pulse rate, and oral body temperature)
- Physical examination
- CTA
- Dermal Tolerability Assessment

Efficacy:

The following assessments will be performed as preliminary measures of efficacy:

- CEA
- Items from Satisfaction Assessment for Rosacea Facial Redness Scale
- FACE-Q Satisfaction with Skin Scale
- Photography of facial treatment area for DIA

Statistical Analysis:

The following analysis populations will be used:

- Enrolled – all subjects who signed an informed consent form (ICF) and enrolled in the study.
- Modified intent-to-treat (mITT) – all subjects treated with both study drug and energy-based therapy who had at least one post-treatment efficacy assessment between Day 3 and Day 56.
- Safety – all subjects who received at least one dose of study drug as treatment in this study.

The enrolled population will be used for subject disposition, demographics, and baseline characteristics summaries; the modified intent-to-treat population will be used for the efficacy analyses, and the safety population will be used for safety analyses.

For safety analysis, all AEs will be coded from the verbatim text to the lower level term (LLT) and mapped to preferred term (PT) and primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). For pretreatment AEs (PTAEs), the number and percentage of subjects reporting at least 1 PTAE will be tabulated by descending order of incidence rate, by primary SOC and PT, and by primary SOC, PT, and severity. TEAEs regardless of causality, application-site AEs, and treatment-related TEAEs will be analyzed in the same manner. Maximum severity of each dermal tolerability measure over the treatment period will be summarized using a frequency distribution. The same analysis will be performed for at least a 1-grade worsening from baseline (ie, predose on day 1) over the treatment period for each tolerability measure.

Physical examination data will be tabulated. Raw data and change from baseline in each vital sign measure will be summarized using descriptive statistics.

The CTA will be summarized using a frequency distribution by visit.

Concomitant medications will be recorded throughout the study and be coded to the trade or preferred name using the World Health Organization Drug Dictionary (WHODrug). More detailed analyses will be described in the analysis plan.

For exploratory efficacy analysis the proportion of subjects with at least a 1-grade decrease (improvement) on the CEA from baseline (ie, predose on Day 1) will be summarized by visit and timepoint using frequency distributions. In addition, the raw CEA data will be summarized by visit and timepoint using descriptive statistics. Each item in the Items from Satisfaction Assessment for Rosacea Facial Redness and FACE-Q Satisfaction with Skin Scale will be summarized using frequency distributions by visit and timepoint.

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LIST OF ABBREVIATIONS

AE	adverse event
CEA	Clinician Erythema Assessment
CTA	Clinician Telangiectasia Assessment
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
cGCP	current Good Clinical Practice
HCl	Hydrochloride
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IPL	Intense Pulsed Light
IRB	institutional review board
KTP	Potassium Titanyl Phosphate
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MAO	monoamine oxidase
n	number of subjects with an observation
N	number of subjects in the dataset or population
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OTC	over-the-counter
PP	per protocol
PDL	Pulsed Dye Laser
PT	preferred term
PTAE	pretreatment AEs
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WMA	World Medical Association

4 INTRODUCTION

4.1 Background

Rosacea is primarily an adult condition, with onset of symptoms generally occurring after the age of 30, often having a deep impact on a patient's self-esteem and quality of life. The diagnosis of rosacea is made based on the presence of 1 or more primary features centrally distributed on the face, including flushing (transient erythema), persistent (nontransient) erythema, papules and pustules, and/or telangiectasia. Persistent redness is the most common individual sign of rosacea and is defined as stable central facial erythema that is not transient flushing or blushing. Various secondary features may also be present including burning or stinging, plaque, dry appearance, edema, phymatous changes, and ocular manifestations.[1] For many individuals with rosacea, symptoms are triggered or exacerbated by external stimuli leading to the theory that the vasodilation and immune dysregulation seen in rosacea is neurogenic in nature.[2] Rosacea is not curable, and it generally requires long-term treatment to alleviate symptoms and delay or prevent disease progression. Rosacea has been classified into 4 standard subtypes, reflecting common patterns of signs and symptoms. Many patients may experience characteristics of more than one subtype at the same time, and these often may develop in succession. In many individuals with Subtype 1 rosacea (where persistent erythema is the predominant symptom), small blood vessels become visible on the skin. While rosacea may or may not evolve from one subtype to another, each individual sign or symptom may progress from mild to moderate to severe. Early diagnosis and treatment are therefore recommended.[1]

Moderately effective topical treatments such as sulfonamides, metronidazole, azelaic acid, and oral tetracyclines are ineffective in managing persistent erythema associated with rosacea.[3,4]

Alpha agonists have been approved for topical dermal application to reduce persistent erythema associated with rosacea. An α2-adrenoceptor agonist, brimonidine gel 0.33%, received United States Food and Drug Administration (US FDA) approval in 2013 for use in facial erythema of rosacea; however, it has been fraught with tolerability issues.[5,6]

Oxymetazoline hydrochloride (HCl) is a highly-specific α1A-adrenoceptor receptor agonist, and a vasoconstrictor of the cutaneous microvasculature. Oxymetazoline topical cream 1.0% has recently been approved by the US FDA under the name Rhofade™ for the topical treatment of persistent facial erythema associated with rosacea in adults.[7]

4.2 Nonclinical Studies

Repeat-dose dermal toxicology studies, including microscopic pathology evaluation of systemic tissues, were conducted in rats for up to 6 months and minipigs for up to 9 months. The no observed adverse effect level (NOAEL) in minipigs following 9 months of treatment was 2.5%, which was the highest dose tested. This NOAEL is approximately 17-fold higher than that estimated for facial dose in human subjects at the 1.0% concentration with once-daily application.

Oxymetazoline was shown to be not genotoxic, carcinogenic, nor phototoxic in nonclinical test systems. Maternal systemic exposures observed at the NOAEL or no observed effect level (NOEL) doses in reproductive and developmental toxicity studies in rats and rabbits were at least 2-fold higher than those observed in subjects given the 1.0% concentration once daily.

4.3 Clinical Studies

To date thus far there have been 4 human dermal safety studies and 10 clinical studies (including 3 pivotal Phase 3 studies) of topical dermal oxymetazoline for the treatment of persistent facial erythema associated with rosacea. All clinical studies have been conducted with the same cream formulation with varying concentrations of oxymetazoline.

In the first 2 Phase 3 studies oxymetazoline HCl cream 1.0% was applied topically for 29 days, once daily, to the faces of patients with persistent, moderate, or severe facial erythema associated with rosacea, followed by a 28 day post-treatment period. The results from these 2 pivotal studies consistently demonstrated that oxymetazoline HCl cream 1.0% was safe and well tolerated based upon multiple safety evaluations, and was significantly more effective than vehicle in reducing facial erythema associated with rosacea over a 12-hour evaluation period (hours 3, 6, 9, and 12) following a 29 day treatment period. In the most recent Phase 3 study the long-term safety and efficacy of oxymetazoline HCl cream 1.0% (applied topically, once daily) was evaluated in 440 patients with moderate to severe persistent facial erythema associated with rosacea over a period of 52 weeks. Improvement in erythema was consistently observed 3 and 6 hours after study drug application compared with predose assessments from Day 1 through to Week 52 of the treatment period.

In the most recent Phase 3 study the most commonly reported TEAEs (reported by ≥ 2% of patients) were upper respiratory tract infection (3.6%), rosacea (3.2%), application site dermatitis (3.0%), nasopharyngitis (3.0%), hypertension (2.5%), headache (2.3%), sinusitis (2.3%), application site pain (2.0%), and application site pruritus (2.0%). A majority of TEAEs were considered to be of mild or moderate severity; severe TEAEs reported by 2 or more patients included application site dermatitis (0.7%, 3/440) and application site erythema, basal cell carcinoma, and rosacea (0.5%, 2/440 each). Treatment-related TEAEs were reported during the entire study period by 8.2% (36/440) of patients. The most commonly reported treatment-related TEAEs (reported by ≥ 1% of patients) were application site dermatitis (1.8%), application site paresthesia (1.6%), application site pain (1.1%), and application site pruritus (1.1%). A majority of treatment-related TEAEs were considered to be of mild or moderate severity. Severe treatment-related TEAEs included application site dermatitis (0.7%, 3/440) and application site pain, application site erythema, and photosensitivity reaction (0.2%, 1/440 each).

4.4 Energy-Based Therapies for the Treatment of Rosacea

For more than 2 decades, lasers and non-laser light-based therapies have become increasingly popular in dermatology for the management of clinical conditions such as rosacea, namely Pulsed Dye Laser (PDL), Long-Pulsed Nd:YAG Laser, Potassium Titanyl Phosphate (KTP) Laser, and Intense Pulsed Light (IPL).[8,9] These therapies emit wavelength of light in a range absorbed by the hemoglobin chromophore, resulting in targeted vessel wall destruction.[10] Moreover, these devices are able to target vascular abnormalities without significant epidermal and dermal dysruption.[11]In the most recent Cochrane review of treatments for rosacea (published in 2015),[12] PDL was found to be more effective than Nd:YAG laser therapy (and of comparable effect with IPL).[13] However, the evidence for the effectiveness of these therapies on all signs and symptoms of skin conditions were rated of low quality based on the study design and data.

In an effort to address the multiple signs and symptoms of skin conditions, there has been increased use of a multi-modal approach with non-ablative lasers (ie, KTP, PDL) or non-laser light sources (ie, IPL) with pre-existing topical medications. Pharmaceutical treatments that are

routinely being used in conjunction with these devices include topical 0.33% brimonidine (Mirvaso®) and 0.75% metronidazole (MetroCream®, MetroLotion™) for rosacea, retinoids for acne and actinic damage (Differin®, Retin-A®, Avage®, Avita®, Renova®), and the prescription triple-combination cream (Tri-Luma®) for melasma and other pigmentary disorders.[11,14,15] Furthermore, Mirvaso® gel is an alpha adrenoceptor agonist that is in the same class as the topical drug product in this study.

4.5 Rationale for Study Design

Oxymetazoline has been shown in 3 pivotal Phase 3 studies to be effective in treating persistent facial erythema in subjects with rosacea. Energy-based therapies have also been seen to be efficacious in reducing erythema and telangiectasia in rosacea patients.[16] This Phase 4 study is the first to investigate the safety, tolerability, and preliminary measurements of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy (ie, KTP, IPL, and PDL) for patients with moderate to severe persistent facial erythema associated with rosacea.

The side effects of energy-based therapy can include transient pupura and immediate post-treatment erythema, which normally resolve within a day or 2.[12] In a recent publication, energy-based therapy was performed the same day as Mirvaso® application for the treatment of rosacea with no safety concerns reported related to concurrent treatment.[14] As an additional safety precaution we are delaying oxymetazoline treatment for 48 hours post energy-based therapy (and 24 hours prior to re-treatment with energy-based device) to limit any potential interaction between the device and drug. Any potential AEs that may arise from the use of a device will be noticeable within a 48-hour window, which will alert the physician as to whether oxymetazoline treatment should be applied.

There are 6 safety determinations in the current study (adverse events, urine pregnancy in females of childbearing potential, physical examination, vital signs, Clinician's Telangiectasia Assessment [CTA], and Dermal Tolerability Assessment). Four assessments will be used as measures of efficacy: Clinician Erythema Assessment [CEA], Items from Satisfaction Assessment for Rosacea Facial Redness, FACE-Q Satisfaction with Skin Scale, and Digital Image Analysis [DIA] of standardized photography of the treatment area).

STUDY OBJECTIVES

4.6 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

4.7 Exploratory Objective

The exploratory objective of the study is to evaluate preliminary measures of efficacy of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

5 STUDY ENDPOINTS

5.1 Primary Endpoints

The primary endpoints of the study are:

- The incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).
- The number and percent of subjects with at least a 1-grade worsening from baseline in the Dermal Tolerability Assessment at any timepoint over the treatment period.
- The number and percentage of subjects with at least a 1-grade worsening from baseline in the CTA at any timepoint over the treatment period.

5.2 Exploratory Endpoints

The exploratory endpoints of the study are:

- The number and percentage of subjects with at least a 1-grade improvement on the CEA from baseline over a 6-hour period (measured at hours 1, 3, and 6) following study drug application.
- Percentage change from baseline in rosacea facial redness using DIA of standardized facial photographs during the treatment period.
- Proportion of subjects indicating Satisfied or Very Satisfied with treatment on the Items from Satisfaction Assessment for Rosacea Facial Redness and proportion of subjects indicating Somewhat Satisfied or Very Satisfied with treatment on the FACE-Q Satisfaction with Skin Scale.

Investigational Plan

5.3 Overall Study Design and Plan: Description

This is a Phase 4, multicenter, interventional, open-label study to evaluate the safety and tolerability of once-daily oxymetazoline HCl 1.0% cream when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe facial erythema associated with rosacea. The study will enroll approximately 45 subjects at 4 study centers within the United States.

All subjects will receive 1 of the following energy-based therapies (Potassium Titanyl Phosphate [KTP], Pulsed Dye Laser [PDL] or Intense Pulsed Light [IPL]) on Day 1 and Day 29 of the treatment period. Once-daily application of oxymetazoline HCl cream 1.0% will be initiated on Day 3 of the treatment period and will continue until the final exit visit (excluding a 3-day washout period that begins 24 hours prior to the second energy-based therapy session on Day 29).

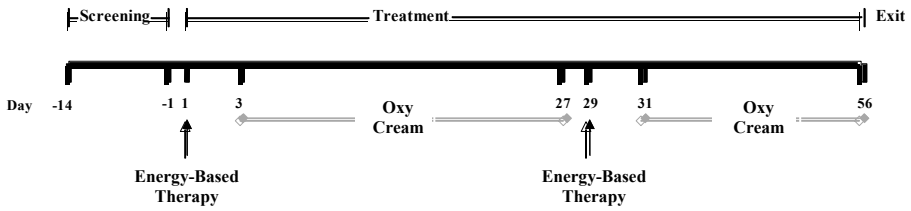
Study Duration:

The duration of the clinical phase is approximately 10 weeks for each subject. This includes a screening period of up to 2 weeks, a treatment period of 8 weeks, and a final exit visit at Week 8 (Day 56).

5.3.1 Study Design

The overall study design is shown in Figure 1. The schedule of assessments for individuals is shown in Table 1.

Figure 1 Overall Study Design



Oxy Cream - Oxymetazoline HCl Cream 1.0% once daily
Energy-Based Therapy - Potassium Titanyl Phosphate (KTP), Pulsed Dye Laser (PDL) or Intense Pulsed Light (IPL) Therapy

Table 1 Schedule of Assessments and Procedures

Study Period	Screening*	Day 1/ Baseline*	Day 3	Day 29	Day 31	Day 56/ Exit Visit
Visit Window	Day -14 to Day -1	N/A	N/A	± 3 Days	+2 days from Day 29	± 3 Days
Informed Consent	X					
Demographics	X					
Fitzpatrick Skin Phototype	X					
Inclusion/Exclusion Criteria	X	X[a]				
Medical History	X	X[b]				
Physical Examination	X					X
Vital Sign Measurement	X	X[a]	X[c]	X[a]	X[c]	X
Urine Pregnancy Test (if applicable)	X	X[a,b]				X
Energy-Based Therapy (KTP, PDL, or IPL)		X		X		
Onsite Study Drug Treatment/Dispensing			X		X	X[d]
Standardized Photography		X[e]	X[f]	X[e]	X[f]	X[f]
Clinician Erythema Assessment (CEA)		X[e]	X[f]	X[e]	X[f]	X[f]
Clinician's Telangiectasia Assessment (CTA)	X	X[a,b]	X[a]	X[a]	X[a]	X[a]
Items From Satisfaction Assessment for Rosacea Facial Redness	X	X[a,b]	X[g]		X[g]	X[g]
FACE-Q Satisfaction With Skin Scale	X	X [a,b]		X[a]		X[a]
Dermal Tolerability Assessment (Investigator and Subject)		X[e]	X[h]	X[e]	X[h]	X[h]
Adverse Events/Reactions	◄----------					----------►
Concomitant Medications and Concurrent Procedures	◄----------					----------►

[*] Screening and baseline may occur on same day
[a] predose (Oxymetazoline HCl)/pretreatment (Energy-based therapy [KTP, PDL, or IPL])
[b] repeated only if screening/Day1 occur on separate days
[c] predose/pretreatment and 6 hr
[d] Study drug application only. No study drug will be dispensed
[e] predose/pretreatment and 1 hr
[f] predose, 1 hr, 3 hr, and 6 hr
[g] 6 hr
[h] predose/pretreatment 1 hr and 6 hr

Acceptable Time Window Deviations
Predose – all predose assessments on Day 1 and Day 29 should occur within 90 minutes prior to energy-based treatment. All predose assessments on Day 3, Day 31, and Day 56 should occur within 90 minutes prior to study drug administration.
Postdose – all assessments performed at the 1 hour, 3 hour, and 6 hour postdose timepoints should be performed within 15 minutes (ie, 1 h ±15min, 3 h±15min, 6 h ±15min).

5.4 Discussion of Study Design

The study will take place in subjects with moderate to severe persistent facial erythema of rosacea in order to ascertain whether once-daily application of oxymetazoline HCl 1.0% cream is safe and well tolerated when used as an adjunct to energy-based therapies known to improve erythema and telangiectasia in rosacea subjects. For further details on study drug and energy-based therapy dose and treatment design refer to Section 5.6.

5.5 Selection of Study Population

5.5.1 Number of Planned Subjects

The total planned number of subjects is 45.

5.5.2 Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following inclusion criteria:

1. Subject has provided written consent prior to any study-related procedures.
2. Male or female aged ≥ 18 years.
3. Documented clinical diagnosis of rosacea.
4. Moderate to severe persistent facial erythema associated with rosacea at baseline, as determined by a grade of ≥ 3 on the CEA scale with photonumeric guide.
5. Females of childbearing potential must not be lactating, must have a negative urine pregnancy test at screening and Day 1, and must agree to practice a reliable method of contraception throughout the study (see Section 5.6.9).
6. The ability to follow study instructions and complete study assessments without assistance and have a willingness and ability to comply with all scheduled visits, treatment plan, and other study procedures.

5.5.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Any uncontrolled systemic disease.
2. History of any of the following conditions: Raynaud's syndrome, narrow angle glaucoma, orthostatic hypotension, cerebral or coronary insufficiency, thromboangiitis obliterans, scleroderma, Sjögren's syndrome, severe or unstable or uncontrolled cardiovascular disease, or any other current uncontrolled systemic disease.
3. Diagnosis or presence of any of the following conditions within the treatment area: rosaceaconglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin, peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or chronic recurring facial acne.
4. The presence of facial hair, tattoos, or other facial characteristics such as actinic damage (eg, actinic lentigines, mottled hyperpigmentation or hypopigmentation, yellowish

discoloration, excessive telangiectasia) that could interfere with the assessments of erythema in the opinion of the investigator.

5. Current treatment with monoamine oxidase (MAO) inhibitors.
6. Current treatment with niacin ≥ 500 mg/day.
7. Any of the following treatments occurring within the specified period prior to Day 1:
    - 14 days: products containing oxymetazoline (eg, eye drops, nasal sprays), topical glucocorticosteroids applied to the face, systemic or nasal corticosteroids, any prescription or over-the-counter (OTC) product for the treatment of acne.
    - 28 days: Systemic antibiotics that are known to have an effect on rosacea such as erythromycin or doxycycline.
    - 180 days: isotretinoin.
8. Prior dermal adverse reaction to using Mirvaso® (brimonidine) topical gel, 0.33% or current use of marketed Mirvaso® (brimonidine) topical gel, 0.33%.
9. Previous participation in clinical trials associated with oxymetazoline cream for facial rosacea
10. Known hypersensitivity or allergies to any component of the study drug.
11. Greater than 3 inflammatory lesions on the face.
12. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.
13. History or current evidence of drug or alcohol abuse within 12 months prior to the screening visit.
14. Condition or situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
15. An employee (or a relative of an employee) of the investigators, Allergan, or representative of Allergan.

5.5.4 Removal of Subjects From Therapy or Assessments

Subjects may stop study drug for any of the following reasons:

- Subject request
- Use of non-permitted concurrent therapy
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs that are not compatible with the continuation of subject participation in the study, in the investigator's opinion, or are unacceptable to the subject to continue
- Investigator request
- Intercurrent illness
- Sponsor request
- Treatment failure

- Pregnancy

Subjects who do not comply with the protocol, withdraw consent, or stop study drug for any other reason will not be replaced. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Upon withdrawal from the study, any time after dosing has taken place, all efforts should be made to invite the subject to complete the early withdrawal visit. The same procedures should be performed as on the Day 56 (exit visit). The aim is to record data in the same way as for subjects who completed the study, particularly safety data.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts should be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the study drug/energy therapy or the company itself occur, making further treatment of subjects impossible. In this event, the investigators will be informed of the reason for study termination.

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or female partners of male subjects, should be confirmed and reported to the investigator, who will then withdraw the female subject from the study without delay. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page of the eCRF, and a Pregnancy Data Form should be completed and faxed/emailed to Allergan within 24 hours of awareness of the event using the contact details in Section 7.1.2.1.1.

5.6 Investigational Products and Therapies

5.6.1 Investigational Products Administered

Oxymetazoline HCl cream 1.0% will be applied in a thin layer topically to the entire face including forehead, nose, each cheek, and chin, once daily. Subjects will be instructed to apply study drug to their clean, dry face in the morning, at approximately the same time each day, starting on Day 3 through Day 56. There will be a 3 day washout period from the study drug beginning 24 hours prior to the second energy-based therapy session on Day 29 (subjects will not apply the study drug on Day 28, Day 29, and Day 30) to ensure that energy-based therapy and treatment with oxymetazoline are clearly separated in the case of any treatment-related adverse events. The Investigator should assess if any adverse events resulting from treatment with the energy-based device (eg, treatment site skin irritation or wounding) would present a risk for treatment with oxymetazoline and either delay or discontinue treatment.

For study visits, subjects will be instructed to apply the study drug at the study site. The dose will be applied after predose study assessments and procedures are completed. Site personnel

will observe subject dosing in the clinic to ensure proper study drug application technique and retrain if necessary. Detailed instructions on study drug application will be provided to subjects (see Section 5.6.12).

5.6.2 Identity of Investigational Products

Oxymetazoline cream 1.0% (Rhofade) contains oxymetazoline HCl, methylparaben, propylparaben, phenoxyethanol, sodium citrate dihydrate, citric acid anhydrous, disodium edetate, butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol (PEG)-300, PEG-6 (and) PEG-32 (and) glycol stearate, cetostearyl alcohol, ceteareth-6 (and) stearyl alcohol, ceteareth-25, and purified water.

5.6.3 Packaging and Labelling

All study drug will be supplied by Allergan. The study drug will be packaged in identically appearing containers consistent with all applicable regulations. The medication will be supplied in the approved commercial packaging. The study drug container will have a child-resistant feature. Labelling on the container and the carton will include the following statements: “For Topical Use Only” and “Keep Out of Reach of Children.”

5.6.4 Energy-Based Therapies

Subjects will receive one of the following 3 types of energy-based therapy at the timepoints indicated in Table 1 during the study:

Pulsed Dye Laser (PDL): The following 2 PDL devices will be utilized for this study: Cynergy (Cynosure) and Vbeam Perfecta (Syneron-Candela). The Pulsed Dye Laser (PDL) delivers pulsed laser energy at a wavelength that targets hemoglobin and results in the destruction of superficial blood vessels, reducing both erythema and telangiectasia.[17]

Potassium Titanyl Phosphate Laser (KTP): The KTP utilized for this study will be the Excel V (Cutera). The KTP laser has been shown to improve telangiectasia to a greater extent than erythema in rosacea patients.[18]

Intense Pulsed Light Therapy (IPL): The IPL utilized for this study will be the Palomar Icon (Cynosure). IPLs emit polychromatic light and are commonly used to treat vascular lesions associated with rosacea.[19]

Each study center will be assigned one or more devices from the list above to utilize during the study. Each study center will utilize only the specific devices assigned for use at their site. The devices will be assigned based on the current expertise and devices present at the study center.

Approximately 11 subjects will be treated with each energy-based therapy device type. The method for treatment with laser at each site will be based on the Investigator’s current standard of practice. The details of the study treatment (ie, wavelength, pulse duration, number of pulses, and fluence) will be recorded in the eCRF for each subject.

5.6.5 Methods of Assigning Subjects to Treatment Groups

Subjects who meet all inclusion/exclusion criteria will be assigned a subject enrolment number that will serve as the subject identification number on all study documents.

All eligible subjects will receive oxymetazoline HCl cream 1.0%.

There is no stratification of randomization associated with this study. Subjects will be assigned to 1 of 3 types of energy-based therapy, based on the assigned devices at the site they attend. Enrolment at each study center will be monitored to ensure that a minimum of 11 subjects will receive each type of energy-based therapy.

5.6.6 Selection of Doses in the Study

Oxymetazoline HCl cream 1.0% applied once daily for treatment of persistent facial erythema of rosacea has been evaluated by Allergan in 3 Phase 3 studies, with duration of application extending from 29 days to 52 weeks. The results from these studies consistently demonstrated that oxymetazoline HCl cream 1.0% was safe and well tolerated based upon multiple safety evaluations, and demonstrated consistent trends in efficacy, with improvements from baseline observed throughout the treatment period.

5.6.7 Selection and Timing of Energy Therapy

Laser and light therapy have been shown to reduce erythema and telangiectasia in patients with rosacea.[17] Subjects will be allocated to one of KTP, PDL, or IPL treatments and undergo 2 sessions (Day 1 and Day 29) during the study. The 28-day period between the 2 treatments is standard in current practice allowing for efficacious results.

Subjects will begin study drug administration on Day 3 (2 days after the first energy-based therapy session) and will washout study drug from 24 hours prior to the second energy-based therapy session on Day 29, until 2 days after (Day 31). This will ensure that the study drug will not be present on the skin during the energy-based therapy or during the immediate recovery period during which there may be irritation to the skin. Any post-treatment skin irritation will be identified by the physician during this washout period and oxymetazoline treatment will not recommence until deemed safe to do so.

5.6.8 Blinding

This study will be an open-label study, therefore blinding of the study drug or treatments is not required.

5.6.9 Contraceptive Requirements

Females of child bearing potential are defined as any female subject post-puberty. Females that are postmenopausal (defined as having 12 months of consecutive spontaneous amenorrhea) or surgically sterile (6 months post-surgical bilateral oophorectomy with or without hysterectomy, 6 months post-hysterectomy, or 6 months post-tubal ligation) are exempt from the contraceptive requirements of the study.

Females of childbearing potential are required to use effective contraception from the time of signing the ICF until the end of the study. Acceptable methods of contraception are intrauterine devices, hormonal contraceptives (eg, oral, patch, or injectable), partner's vasectomy (if this is the sole partner and vasectomy was medically confirmed), a double barrier protection method (eg, condom or diaphragm with spermicide cream, foam, or gel), or sexual abstinence. Periodic abstinence [calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.

5.6.10 Prior and Concomitant Therapy

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator, including but not limited to medications for other conditions (ie, hypertension, diabetes, etc.), treatment of AEs, estrogens, androgens, anti-androgenic agents, vitamins, iron supplements, folate, and herbal supplements. Medications should be taken consistently throughout the study and at the investigator's discretion.

Concomitant medications as defined for this study include dietary supplements, OTC medications, and oral herbal preparations, as well as changes in dosages of current prescription medications. Concomitant medications will be documented for each subject at each scheduled visit. A detailed history of medications will be documented at screening. Subsequently, at each study visit, subjects will be asked what medication, if any, they have taken since the previous visit. All concomitant medications will be recorded in the eCRF.

5.6.10.1 Prohibited Medication/Therapy

The decision to administer a prohibited medication/treatment is done with the safety of the subject as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

The following products are prohibited under this study:

1. Products containing oxymetazoline, except for study drug.
2. Any prescription, OTC, or herbal topical and/or systemic product that has a known effect on rosacea (eg, Mirvaso [brimonidine] topical gel, 0.33%, metronidazole-containing products, azelaic acid-containing products, systemic antibiotics such as erythromycin or doxycycline).
3. Any prescription, OTC, or herbal product applied to the face that causes vasoconstriction.
4. Any prescription, OTC, or herbal product that is primarily used to decrease facial redness.
5. Any topical facial treatment that may affect erythema or cause skin irritation.
6. New topical facial regimens.
7. Topical glucocorticosteroids applied to the face.
8. MAO inhibitors.
9. Isotretinoin.
10. Any new use of systemic or inhaled glucocorticosteroids, cardiac glycosides, alpha-1 adrenergic receptor antagonists, β-adrenergic blocking agents (topical or systemic), β-adrenergic agonists, antihypertensive agents, or ≥ 500 mg/day niacin.
11. Medications that the subject knows may increase their facial erythema or cause flushing.

5.6.10.2 Prohibited Treatments

Laser, light-source, or other energy-based therapies to the face, other than those treatments performed as part of the study, are not permitted during the study.

Dermatological treatments on the face (eg, facial peels, microdermabrasion, exfoliating treatments) are prohibited for the duration of the study.

5.6.10.3 Prohibited Activities

Twenty-four hours before all study visits, the following activities are prohibited:

1. Consumption of any food, alcohol, or other beverage that the subject knows increases their facial erythema.
2. Use of saunas, steam rooms, and hot tubs, or any other activities that the subject knows will increase their facial erythema.

During all study visits, application of any facial products (eg, sunscreen, moisturizer, makeup) is prohibited from 2 hours before the first assessment until all assessments are complete. Facial cleansers are allowed; however, application of study drug and study assessments should occur at least 20 minutes after the cleanser is used.

5.6.10.4 Dietary Requirements at Site

Subjects will remain at the investigational site for at least 6.5 hours during the Day 3, Day 31, and Day 56 Visits. The study site will provide meals and beverages during these visits. Subjects may only consume the food and beverages provided by the study staff, unless they require a special diet that they bring from home, under study site supervision. The meals should not include items that may increase any of the subjects' facial erythema, such as certain spices, caffeine, nicotine, hot beverages, or alcohol. Subjects may consume water at their discretion.

5.6.11 Treatment Compliance

At each visit after Day 1 subjects will be asked if they have used any concomitant medications, had any concurrent procedures, used any prohibited medications/treatments, or participated in any prohibited activities since the previous visit. At each visit after Day 3 subjects will also be asked if they have applied the study drug every day in the morning. Any breach of compliance will be recorded in the eCRF.

5.6.12 Instructions for the Subjects

Subjects will be instructed to avoid all prohibited medications, treatments, and activities, as described in Section 5.6.10. They will be instructed that the application of any facial products (eg, sunscreen, moisturizer, makeup) is prohibited during all study visits from 2 hours before the first assessment and until all assessments are complete.

Use of facial products is permitted on all other dosing days; however, the products must be removed before study drug application and may be re-applied no sooner than 20 minutes after study drug application.

If a subject routinely shaves his/her face, they will be instructed to use a consistent shaving habit as much as possible (eg, same time each day, use of same shaving products), and on study visit days they must shave at least 2 hours prior to the first assessment and refrain from shaving until all assessments are complete.

When the patients arrive at the study center on Days 3, 31, and 56, they will be instructed to wait approximately 30 minutes for acclimation to the study site environment before any assessments are made.

For application of study drug, subjects will be instructed by the study staff and by an instructional video:

1. To apply the study cream at approximately the same time every day (in the morning).
2. To wash their hands before and after each application of study drug.
3. To dispense approximately a pea size amount of study drug in the palm of the hand or fingertip.
4. To dab the study drug onto each of the 5 areas of the face (ie, forehead, nose, each cheek, and chin).
5. To gently spread the study drug to cover their entire face (hairline to mandibular ridge and from ear to ear).
6. Care must be taken to avoid applying the study drug to the eyes, eyelids, scalp, neck, ears, and any membrane of the inner nose, mouth, lips, or open wounds.

Detailed subject instructions on study drug application will be provided to subjects. Subject instructions will include the statements “For Topical Use Only” and “Keep Out of Reach of Children.” Subjects will be instructed on the proper storage of study drug and to keep it out of the reach of children. Subjects will be instructed to return all used and unused study drug containers to the site.

Twenty-four hours before each visit, subjects should avoid any foods, beverages, or activities that they know trigger an increase in their facial erythema. Subjects will be asked to recall any missed applications of study drug.

6 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are performed. The planned schedule of study assessments are in Table 1. When the subjects arrive at the study center on Days 3, 31, and 56, they will be instructed to wait approximately 30 minutes for acclimation to the study site environment before any assessments are made.

6.1 Pretreatment

6.1.1 Screening Visit (Day -14 to Day -1)

During the screening visit the following assessments will be performed:

- Obtain informed consent.
- Assess for eligibility (against inclusion and exclusion criteria).
- Record demographic data, such as ethnic origin, date of birth, and sex.
- Collect full medical history.
- Record any AEs and concomitant medications or procedures.
- Perform a physical examination.
- Vital sign measurement (blood pressure, pulse rate, oral body temperature).
- Urine pregnancy test (for women of childbearing potential only).

- CTA.
- Fitzpatrick Skin Phototype.
- Items from Satisfaction Assessment for Rosacea Facial Redness.
- FACE-Q Satisfaction with Skin Scale.

6.1.2 Baseline Visit (Day 1)

The Day 1 Baseline Visit will take place up to 14 days after the Screening Visit. The screening and Day 1 baseline assessments may be performed on the same day. The following procedures will be performed at the Day 1 Baseline Visit (at the timepoints indicated in Table 1):

- Reconfirm inclusion/exclusion criteria.*
- Record any AEs/TEAEs and changes in concomitant medication or concomitant procedures.
- Collect updated medical history.*
- Vital sign measurement (blood pressure, pulse rate, oral body temperature).
- Urine pregnancy test (for women of childbearing potential only).*
- CTA.*
- Energy-Based Therapy (KTP, PDL, or IPL).
- Standardized photography of treatment area.
- CEA.
- Dermal Tolerability Assessment (investigator and subject).
- Items from Satisfaction Assessment for Rosacea Facial Redness.*
- FACE-Q Satisfaction with Skin Scale.*

* only performed if screening and baseline assessments performed on separate visits.

6.1.3 Day 3

The subject will return to the site on Day 3 and the following procedures will be performed (at the timepoints indicated in Table 1):

- Record any AEs/TEAEs and changes in concomitant medication or concomitant procedures.
- Vital sign measurement (blood pressure, pulse rate, oral body temperature).
- CTA.
- Standardized photography of treatment area.
- CEA.
- Dermal Tolerability Assessment (investigator and subject).
- Items from Satisfaction Assessment for Rosacea Facial Redness.
- Application and dispensing/collection of study drug.

The subject will be instructed how to apply the study drug at this visit and will be given a sufficient supply to enable once-daily application from Day 4 until Day 27. The subject will be instructed not to apply study drug on Day 28, Day 29, and Day 30.

6.1.4 Day 29

The subject will return to the site on Day 29 and the following procedures will be performed (at the timepoints indicated in Table 1):

- Record any AEs/TEAEs and changes in concomitant medication or concomitant procedures.
- Vital sign measurement (blood pressure, pulse rate, oral body temperature).
- CTA.
- Standardized photography of treatment area.
- CEA.
- Dermal Tolerability Assessment (investigator and subject).
- Energy-Based Therapy (KTP, PDL, or IPL).
- FACE-Q Satisfaction with Skin Scale.

6.1.5 Day 31

The subject will return to the site on Day 31 and the following procedures will be performed (at the timepoints indicated in Table 1):

- Record any AEs/TEAEs and changes in concomitant medication or concomitant procedures.
- Vital sign measurement (blood pressure, pulse rate, oral body temperature).
- CTA.
- Standardized photography of treatment area.
- CEA.
- Dermal Tolerability Assessment (investigator and subject).
- Items from Satisfaction Assessment for Rosacea Facial Redness.
- Application and dispensing/collection of study drug.

The subject will be given sufficient study drug to enable once-daily application from Day 32 to the Day 56 exit visit.

6.1.6 Day 56 (Exit Visit)

The subject will return to the site on Day 56 (±3 days) for the study exit visit and the following procedures will be performed (at the timepoints indicated in Table 1):

- Record any AEs/TEAEs and changes in concomitant medication or concomitant procedures.
- Physical Examination.
- Urine pregnancy test (for women of childbearing potential only).
- Vital sign measurement (blood pressure, pulse rate, oral body temperature).
- CTA.
- Application of study drug.
- Standardized photography of treatment area.
- CEA.
- Dermal Tolerability Assessment (investigator and subject).
- Items from Satisfaction Assessment for Rosacea Facial Redness.
- FACE-Q Satisfaction with Skin Scale.

6.1.7 Early Withdrawal (or Discontinuation) Visit

If a subject's participation in the study is prematurely terminated for any reason or if the subject fails to return for a scheduled visit, every effort should be made to determine the reason. This information will be recorded in the subject's eCRF.

Upon withdrawal from the study, at any time after the first dose of study drug has taken place, all efforts should be made to invite the subject to return to the site for an early withdrawal visit and complete the exit visit procedures (Section 6.1.6). If for any reason the subject does not agree to return to the site for the exit visit, the reason and/or efforts made will be recorded.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.2 Duration of Study

The duration of the entire study for each subject is 10 weeks. This includes a screening period of up to 2 weeks, a treatment period of 8 weeks, comprising of daily dosing of study drug and 2 energy-based therapy sessions, followed by a final exit visit at Week 8 (Day 56).

6.3 Acceptable Time Window Deviations

Allowed time window deviations are (assessments at screening are not described here):

Predose – all predose assessments on Day 1 and Day 29 should occur within 90 minutes prior to energy-based treatment. All predose assessments on Day 3, Day 31, and Day 56 should occur within 90 minutes prior to study drug administration.

Post dose – all assessments performed at the 1 hour, 3 hour, and 6 hour post dose timepoints should be performed within 15 minutes (ie, 1 h ±15min, 3 h ±15min, 6 h ±15min).

7 EFFICACY AND SAFETY ASSESSMENTS

7.1 Efficacy and Safety and Other Measurements Assessed

The planned schedule of all study assessments is listed in Table 1.

7.1.1 Efficacy Assessments

The measures of efficacy are:

- Investigator's assessment of the subject's overall severity of persistent erythema associated with rosacea in the treatment area as measured by a 5-point CEA scale with photonumeric guide (Section 7.1.1.1).
- Patient's self-assessment of satisfaction using patient-reported outcomes (PROs):
    - Items from Subject Satisfaction Assessment for Rosacea Facial Redness (Section 7.1.1.2)
    - FACE-Q Satisfaction with Skin Scale (Section 7.1.1.3).
- Standardized photography of treatment area (Section 7.1.1.4).

7.1.1.1 Clinician Erythema Assessment

The CEA scale is the following:

Clinician Erythema Assessment (CEA) Scale	
Grade	**Descriptions**
0	Clear skin with no signs of erythema[a]
1	Almost clear of erythema, slight redness
2	Mild erythema, definite redness
3	Moderate erythema, marked redness
4	Severe erythema, fiery redness

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

The CEA photonumeric guide is provided in Appendix 14.1. Prior to screening subjects, investigators will be trained in grading erythema severity using the CEA with photonumeric guide. The investigator should report the grade that best describes the average overall severity of persistent facial erythema associated with rosacea. All CEA and subject satisfaction assessments should be performed under consistent lighting conditions. The investigator may refer to the baseline (predose Day 1) facial photographs at each post-treatment timepoint to aid their assessment. The investigator must not discuss the results of the CEA with the subject, nor compare the results of assessments with previous assessments (other than the Day 1 predose assessment).

7.1.1.2 Items From Subject Satisfaction Assessment for Rosacea Facial Redness

The Subject Satisfaction Assessment for Rosacea Facial Redness, a PRO measure, was developed in accordance with the FDA PRO Guidance.[20] Two questions from this assessment will be answered by subjects in the study at the timepoints listed in Table 1. These 2 questions are contained in the Items From Subject Satisfaction Assessment for Rosacea Facial Redness (Appendix 14.2). The subject will be allowed to view their baseline (predose Day 1) facial photographs during each assessment to aid their assessment.

7.1.1.3 FACE-Q Satisfaction With Skin Scale

The FACE-Q Satisfaction with Skin Scale (Appendix 14.3) is another PRO measure. The questionnaire should be completed by the subjects at the timepoints listed in Table 1. The subject will be allowed to view their baseline (predose Day 1) facial photographs during each assessment to aid their assessment.

7.1.1.4 Standardized Photography

Standardized photographs will be taken of the treatment area by trained study staff. Three photographs will be taken for each subject's face (right oblique, left oblique and frontal view) at the timepoints indicated in Table 1. Full details of the photography procedures are described in the Study Manual. Digital Image Analysis of the facial photographs for redness will be performed by a central laboratory (Canfield Scientific Inc.). The baseline (predose Day 1) photographs obtained can be used by the investigator and subject during post-treatment CEA

and PRO assessments (Items from Subject Satisfaction Assessment for Rosacea Facial Redness and FACE-Q Satisfaction with Skin Scale) to allow comparison with the current condition of the treatment area.

7.1.2 Safety Assessments

The following safety measures will be collected:

- AEs and TEAEs (Section 7.1.2.1)
- Urine pregnancy tests (for women of childbearing potential only, Section 7.1.2.2)
- Vital sign measurements (blood pressure, pulse rate, and oral body temperature) (Section 7.1.2.3)
- Physical examination (Section 7.1.2.4)
- CTA (Section 7.1.2.5)
- Dermal Tolerability Assessment (Section 7.1.2.6)

7.1.2.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Adverse event collection will commence from the time the subject signs the ICF. It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” Adverse events should be reported on the appropriate page of the eCRF.

A TEAE is any event not present prior to the initiation of the study treatments or any event already present that worsens in either intensity of frequency following exposure to the study treatments. Any AEs reported after signing the ICF and prior to study treatment are considered pretreatment AEs (PTAEs).

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Unlikely:	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable:	Clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Very Likely/Certain:	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- Study drug stopped
- Study drug temporarily interrupted
- Energy-based therapy stopped
- Energy-based therapy temporarily interrupted
- Concomitant medication

Follow-up of Adverse Events

All investigators should follow up on subjects with SAEs and AEs of special interest until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. All other non-serious AEs will be followed until the subject exits the study. Details of AE resolution must be documented in the eCRF.

Documentation and Reporting of Adverse Events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

7.1.2.1.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF).
- Results in persistent or significant disability/incapacity. An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- Results in a congenital anomaly/birth defect.

Allergan considers all cancer AEs as SAEs. Any abortion (spontaneous or nonspontaneous) is also considered a SAE.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study drug.

Reporting of Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the study drug. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be faxed **within 24 hours** for the attention of the medical monitor at:

Fax: +1 714 796 9504
Back-Up Fax: +1 714 246 5295
E-mail: IR-Clinical-SAE@allergan.com

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor and/or INC Research will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, INC Research, on behalf of the sponsor, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 5.5.4.

7.1.2.1.2 Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reaction Definition

An adverse event is considered “unexpected” if it is not listed in the Reference Safety Information (RSI), such as Investigator Brochure, Prescription Information (eg, the current package insert for Rhofade),[7] or it is not consistent with the risk information described in any of the RSI. If an unexpected AE is serious and suspected, it is a suspected unexpected serious adverse reaction (SUSAR).

All SUSARs will be the subject of expedited reporting. The sponsor and/or INC Research shall ensure that all relevant information about a SUSAR is reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up on SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

7.1.2.2 Urine Pregnancy Test (Females of Childbearing Potential Only)

Females of child bearing potential will have urine pregnancy tests performed at the timepoints indicated in Table 1. A negative test result must be obtained during screening and prior to energy-based treatment at the baseline visit. If a positive pregnancy test is obtained at any visit during the study the subject will be withdrawn from the study.

Females of childbearing potential are defined as any female subject after puberty. Females that are postmenopausal (defined as having 12 months of consecutive spontaneous amenorrhea) or surgically sterile (6 months post-surgical bilateral oophorectomy with or without hysterectomy, 6 months post-hysterectomy, or 6 months post-tubal ligation) are exempt from this requirement.

7.1.2.3 Vital Signs

Vital signs (blood pressure, pulse rate, and oral body temperature) will be recorded (at the timepoints listed in Table 1) in a standardized manner (ie, after the subject has rested in the sitting position for 5 minutes).

Changes in vital signs determined by the investigator to be clinically significant will be noted as an AE in the eCRF. Such abnormalities will be closely monitored until stabilized or resolved.

7.1.2.4 Physical Examination

Physical examinations (evaluating eyes, ears, nose, mouth, throat, thyroid, lungs, heart, abdomen, extremities, neuromuscular system, skin, and lymph nodes) will be performed at the timepoints specified in Table 1.

Significant changes from baseline examination on screening will be recorded as AEs.

7.1.2.5 Clinician's Telangiectasia Assessment

The investigator will use the CTA to evaluate the average overall severity of telangiectasia on the subject's face using the 5 point scale below (at the timepoints specified in Table 1). The investigator performing the assessment should record the results in the eCRF and should not compare the current assessment to previous assessments to prevent bias.

Clinician Telangiectasia Assessment (CTA)	
Grade	**Description**
0	Clear skin with no signs of telangiectasia
1	Almost clear, a few barely visible telangiectasia
2	Mild, a few visible telangiectasia
3	Moderate, with presence of clearly visible telangiectasia
4	Severe, with the presence of many visible telangiectasia

7.1.2.6 Dermal Tolerability Assessment

Dermal Tolerability Assessments will be performed by both investigator and subject at the timepoints specified in Table 1.

Investigator's Assessments: Dryness and Scaling of the Treatment Area

Investigators will assess dryness and scaling in the treatment area using the 4-point scales below. The results will be recorded in the eCRF and should not be discussed with the subject.

Dryness: skin roughness		
Score	**Grade**	**Description**
0	None	No dryness
1	Mild	Slight but definite roughness
2	Moderate	Moderate roughness
3	Severe	Marked roughness

Scaling: abnormal peeling of the stratum corneum		
Score	**Grade**	**Description**
0	None	No peeling
1	Mild	Barely perceptible peeling, noticeable only on light scratching or rubbing
2	Moderate	Obvious, but not profuse peeling
3	Severe	Heavy scale production

Subject's Assessments: Stinging/Burning and Pruritus of the Treatment Area

The investigator will ask the subject if he/she is experiencing burning/stinging and pruritus (itching) using the 4-point scales below. The results will be recorded in the eCRF.

Stinging/Burning: prickling pain sensation		
Score	**Grade**	**Description**
0	None	No stinging/burning
1	Mild	Slight warm, tingling/stinging sensation; not really bothersome
2	Moderate	Definite warm, tingling/stinging sensation; somewhat bothersome
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

Pruritus: itching in the application area		
Score	**Grade**	**Description**
0	None	Normal, no itching in the application area
1	Mild	Noticeable discomfort causing intermittent awareness
2	Moderate	Noticeable discomfort causing continuous awareness
3	Severe	Definite, continuous discomfort interfering with normal daily activities

7.1.3 Other Assessments

7.1.3.1 Demographic Information and Medical History

At the screening visit, subject demographic data will be collected. These data include date of birth, age, gender, race, and ethnicity. A medical history will also be obtained from each subject at this visit. Medical history includes a detailed history of prior cosmetic and surgical procedures, with start and stop dates, if applicable, as well as any discontinuations due to intolerability or toxicity.

7.1.3.2 Fitzpatrick Phototyping Scale

Each subject's skin phototype will be assessed at screening by the investigator using the Fitzpatrick Phototyping Scale in the table below:

Fitzpatrick skin type	Constitutive or unexposed skin color	Sunburn and tanning history[a]
I	Ivory white (pale white) Extremely fair skin	Burns easily, strongly; never tans
II	White or fair skin	Burns easily; tans minimally with difficulty
III	Medium white skin	Burns moderately; tans moderately and uniformly
IV	Beige or lightly tanned or olive skin	Burns minimally; tans easily and moderately
V	Moderate brown or tanned brown skin	Rarely burns; tans profusely (dark brown)
VI	Dark brown or black skin	Never burns, tans profusely (dark brown or black)

[a] Sunburn and tanning history is based on what subjects say their responses are to an initial sun exposure (eg, about 45 to 60 minutes of noon exposure in early summer). The subject response should be based on the following 2 specific questions:

1. "How painful is your sunburn (intensity of erythema, edema, skin peeling and discomfort) after 24 hours?"
2. "How much tan will you develop in a week?"

8 STATISTICAL METHODS

8.1 General Statistical Considerations

A brief summary of the general statistical analysis methods is provided below; full details will be provided in a separate statistical analysis plan, which will be finalized prior to database lock.

Data will be summarized using descriptive statistics (number of observations [n], mean, standard deviation, median, minimum, and maximum for continuous variables; and n and percentage for categorical variables).

Two critical timepoints, baseline and end of study, will be referenced in most of statistical analyses for this study. Baseline is defined as the latest assessment prior to any study treatments for each subject (Day 1). End of study is the last clinical visit an enrolled subject has in this study (Day 56 exit visit). Subjects who discontinue will be asked to return for the last clinical visit (Day 56 exit visit) for end-of-study data collection.

8.1.1 Datasets or Populations Analyzed

The following analysis populations will be used:

- Enrolled – all subjects who signed an ICF and enrolled in the study.
- Modified intent-to-treat (mITT) – all subjects treated with both study drug and energy-based therapy who had at least one post-treatment efficacy assessment between Day 3 and Day 56.
- Safety – all subjects who received at least one dose of study drug as treatment in this study.

The enrolled population will be used for subject disposition, demographics, and baseline characteristics summaries; the modified intent-to-treat population will be used for the efficacy analyses, and the safety population will be used for safety analyses.

8.1.2 Demographic and Other Baseline Characteristics

The number of subjects in each of the analyzed study populations will be described. Subjects who discontinue study drug or are removed from the study prematurely will also be reported. Reasons for study drug and/or energy-based therapy discontinuation, and time of withdrawal from the study will be described.

Subject characteristics at entry into the study will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables.

Concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODrug) dictionary into Anatomical Therapeutic Chemical (ATC) classification codes. The type and timing of use of specific concomitant medications will be listed and summarized. The type and duration of pre-study use will be described on the safety population. The type, dose, schedule, duration of use, dose modifications, dose omissions, and reasons for deviations from initial therapy will be described.

8.1.3 Efficacy Variables and Analysis

The efficacy variables are:

- The number and percentage of subjects with at least a 1-grade decrease (improvement) on the CEA, from baseline over a 6-hour period following study drug application at each study visit and timepoint (specified in Table 1).
- Percentage change from baseline at each visit in rosacea facial redness using DIA of standardized facial photographs.
- Proportion of subjects indicating Satisfied or Very Satisfied (score of 3 or 4) with treatment on the Items from Subject Satisfaction Assessment for Rosacea Facial Redness and proportion of subjects indicating Somewhat Satisfied and Very Satisfied with treatment on the FACE-Q Satisfaction with Skin Scale at each visit and timepoint specified in Table 1.

The proportion of subjects with at least a 1-grade decrease (improvement) on the CEA from baseline (ie, predose on Day 1) will be summarized by visit and timepoint using frequency distributions. In addition, the raw CEA data will be summarized by visit and timepoint using descriptive statistics. Each item from the PROs (Items from Subject Satisfaction Assessment for Rosacea Facial Redness and FACE-Q Satisfaction with Skin Scale) will be summarized using frequency distributions by visit and timepoint.

8.1.4 Safety Variables and Analysis

The safety variables are PTAEs, treatment emergent adverse events (TEAEs), application site adverse events, investigator and subject dermal tolerability assessments, physical examination, vital signs (blood pressure pulse rate, and oral temperature) and CTA.

All AEs will be coded from the verbatim text to the lower level term (LLT) and mapped to preferred term (PT) and primary system organ class (SOC) using the Medical Dictionary for

Regulatory Activities (MedDRA). For PTAEs, the number and percentage of subjects reporting at least 1 PTAE will be tabulated by descending order of incidence rate, by primary SOC and PT, and by primary SOC, PT, and severity. TEAEs regardless of causality, application site AEs, and treatment-related TEAEs will be analyzed in the same manner. Maximum severity of each dermal tolerability measure over the treatment period will be summarized using a frequency distribution. The same analysis will be performed for at least a 1-grade worsening from baseline (ie, predose on day 1) over the treatment period for each tolerability measure.

Physical examination and vital signs data will be tabulated. Raw data and change from baseline in each vital sign measure will be summarized using descriptive statistics.

Clinician's Telangiectasia Assessment will be summarized using a frequency distribution by visit. More detailed analyses will be described in the analysis plan.

8.1.5 Interim Analyses

No interim analysis is planned for this study.

8.1.6 Handling of Missing Data

Missing data strategy will be documented in the statistical analysis plan.

8.2 Determination of Sample Size

Sample size for this study was calculated using estimated incidence rate of treatment-related AEs for daily application of oxymetazoline HCl cream 1% in conjunction with energy-based therapy. A conservative estimate of the empirical incidence rate of study drug related adverse events (p_0) was 8.2% (based on the oxymetazoline arm of 3 Allergan pivotal studies). In the scenario of improved overall efficacy outcomes resulting from the combination of oxymetazoline treatment with energy-based devices, a 14% increase (less than 15%) in the treatment-related adverse event rate may still be tolerable or warrant further clinical development. Thus, we choose to use $\delta = 0.14$ as the margin of indifference.

Sample size calculation for this study is based on one proportion equivalence test for testing (2-sided) the null hypothesis H_0: $|p - p_0| > \delta$ against the alternative hypothesis H_1: $|p - p_0| < \delta$. A sample size of N = 43 is required for attaining a power of 80% while controlling Type-I error rate of the test at 5%. To allow for a small percentage of potential subject withdrawal, approximately 45 subjects will be enrolled into this study.

8.3 Protocol Deviations

Major protocol deviations may include, but are not limited to:

- Inclusion/Exclusion criteria violations.
- Inadequate compliance with study drug.
- Prohibited medications taken.
- Significant deviations from the study drug administration schedule.
- Other protocol deviations that could affect subjects' outcomes.

The final list of major protocol deviations will be defined during the data review meeting.

9 QUALITY ASSURANCE AND QUALITY CONTROL

9.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

9.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with current Good Clinical Practice (cGCP) and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. Monitoring will be performed both on site and remotely, for further details, refer to the Monitoring Plan.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

9.3 Data Management and Coding

INC Research will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of INC Research.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA Code of Federal Regulations (CFR) 21 Part 11 compliant.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHODrug for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

10 RECORDS AND SUPPLIES

10.1 Drug Accountability

On receipt of the study drug, the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of unused study drug returned by the subject. The study monitor will also perform an inventory of study drug at the end of the study. Accountability may be performed remotely (refer to Monitoring Plan for further detail). All discrepancies must be accounted for and documented.

10.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between INC Research and the sponsor.

11 ETHICS

11.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

11.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

11.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject.

Photographs of the subject's face will be taken as part of this study. If a subject does not consent to have the photographs taken, they cannot participate in the study. Subjects will also have the option of indicating whether or not they give permission for the use of their study photographs for advertising, publicity, and promotional purposes. If subjects do not consent to their photographs being used, they will be excluded from participating in the study.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

11.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act,[21] applicable to national and/or local laws and regulations on personal data protection.

12 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the study drug. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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14 APPENDICES

14.1 Clinician Erythema Assessment Photonumeric Guide

Clinician Erythema Assessment Scale with Photonumeric Guide

The Clinician Erythema Assessment (CEA) Scale with Photonumeric Guide is a tool used for the static assessment of overall facial erythema. The CEA scale uses a 5-point ordinal scale representing each grade of erythema from 0-4. Each grade includes a brief description of erythema, accompanied by representative frontal view photographs. This scale is a tool for the assessment of overall facial erythema based on appearance the day of evaluation, without relying on prior memory, perception or assessment of change as compared to previous assessments.

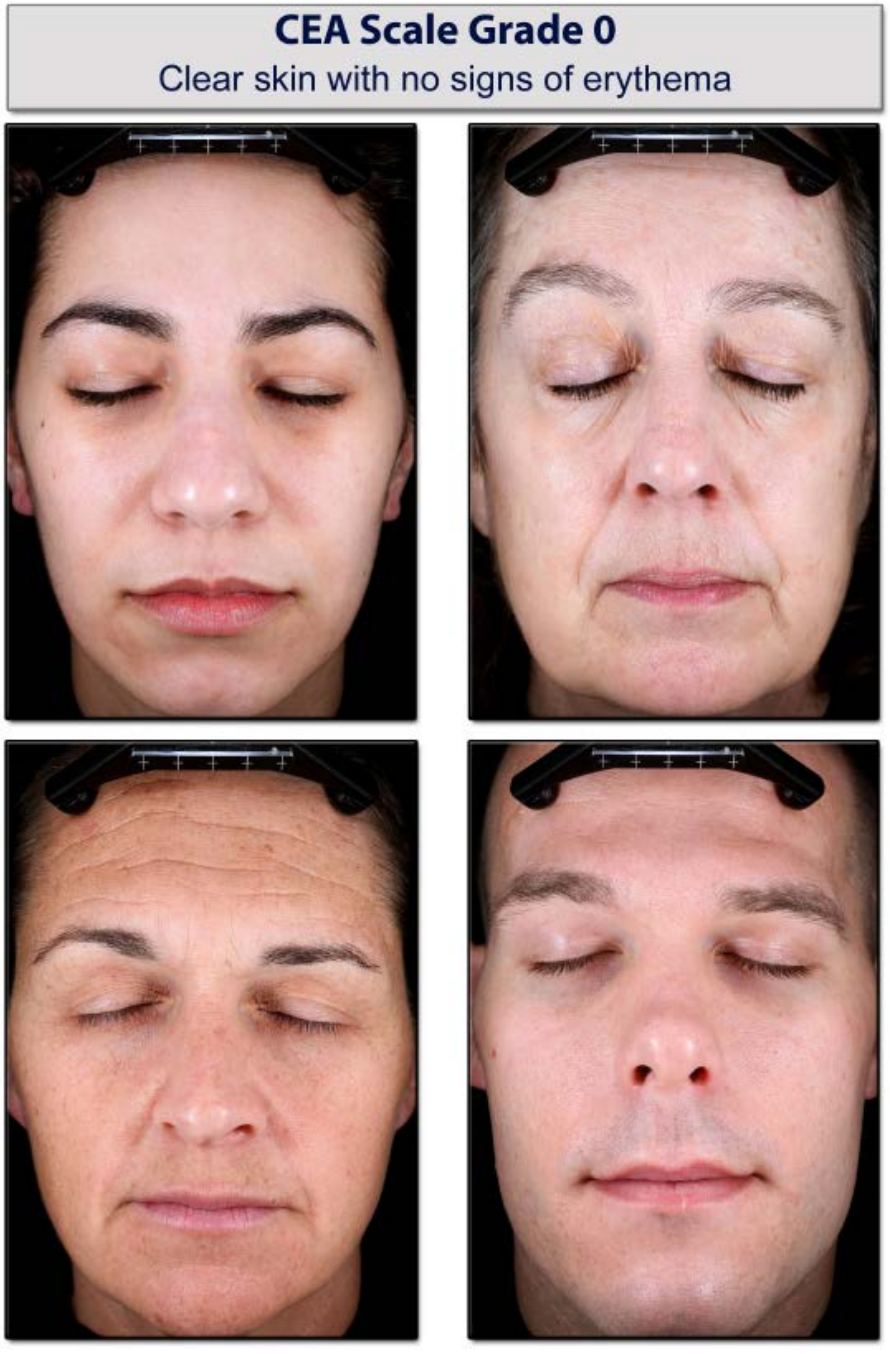
Using the CEA scale with photonumeric guide, the clinician should select one of the following CEA grades which best describes the severity of facial erythema:

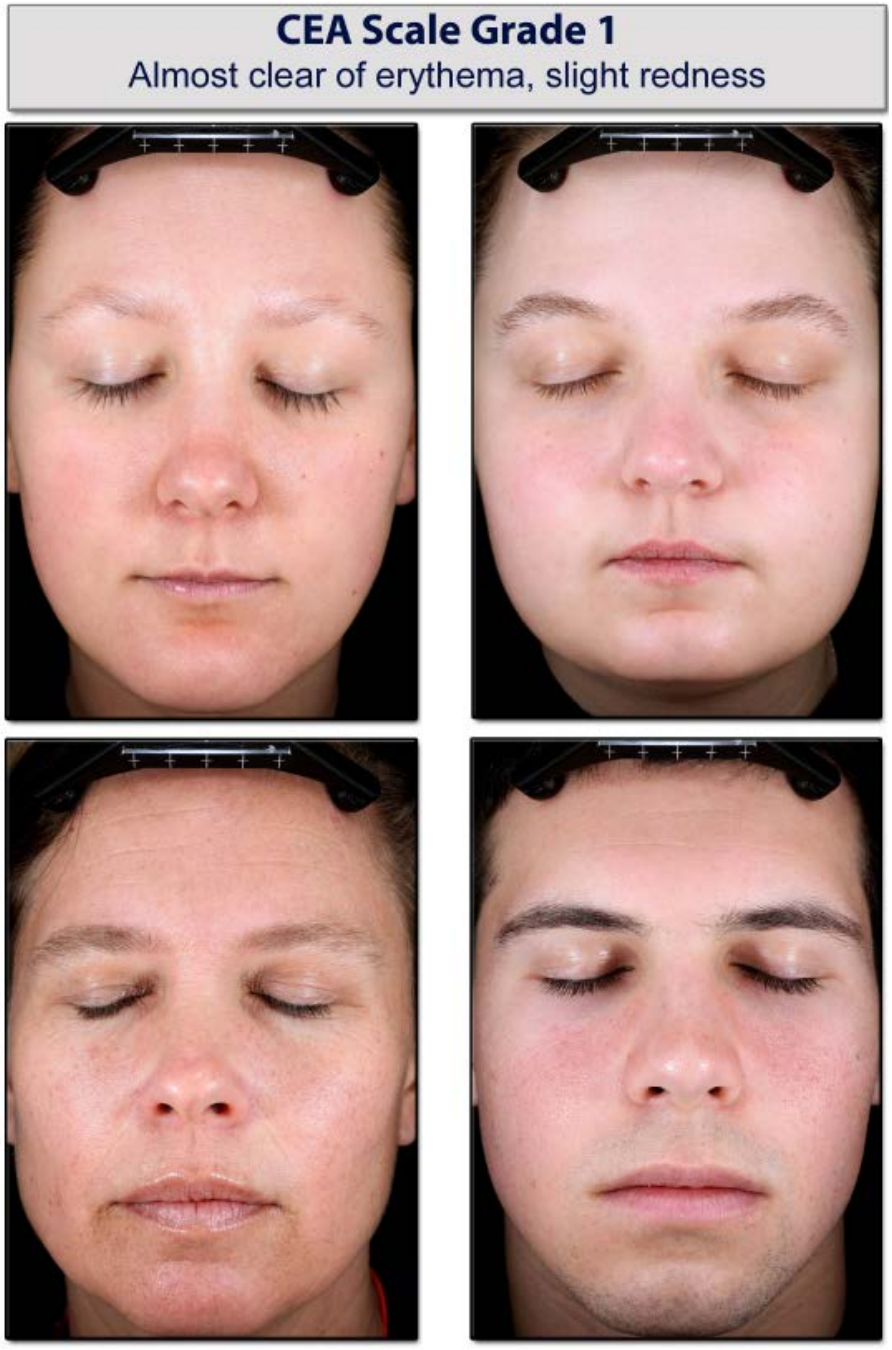
Grade	Descriptions
0	Clear skin with no signs of erythema[a]
1	Almost clear of erythema, slight redness
2	Mild erythema, definite redness
3	Moderate erythema, marked redness
4	Severe erythema, fiery redness

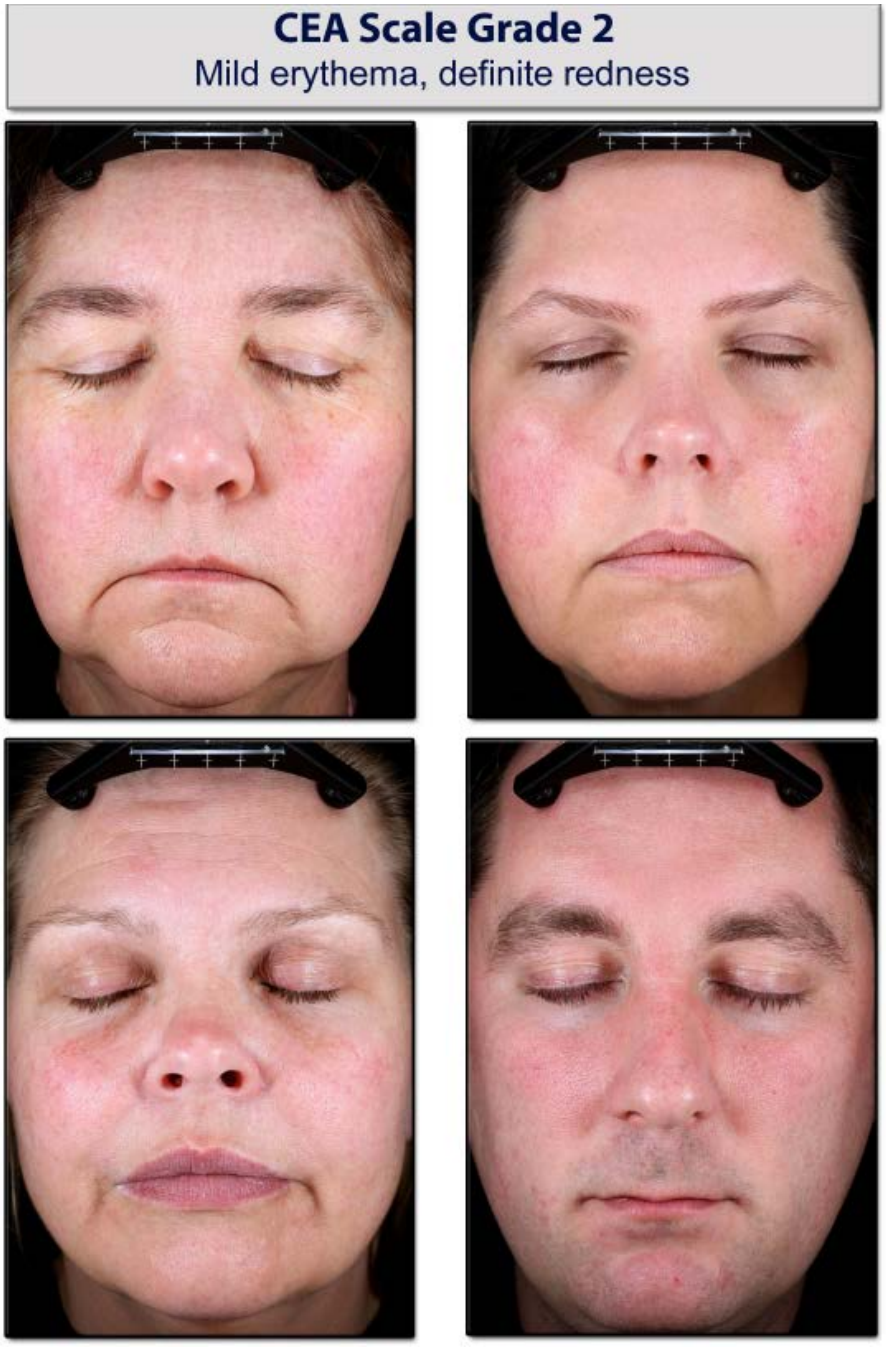
a – Normal healthy skin color as seen in individuals without rosacea

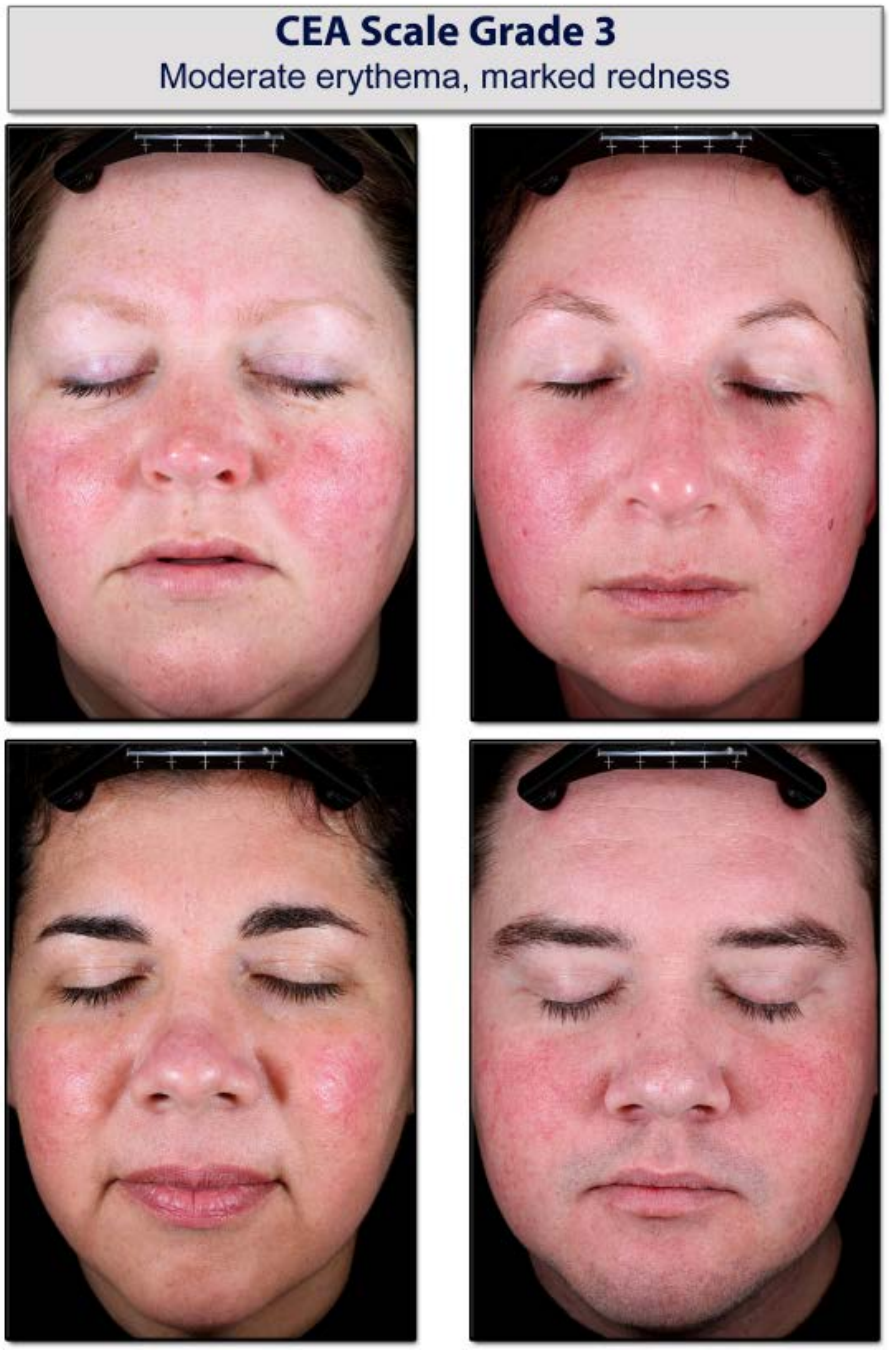
In determining the appropriate CEA grade the clinician should evaluate the degree of facial erythema the patient presents with at the time of evaluation. If the patient has diffuse facial erythema the clinician should assign a CEA grade based on the overall facial erythema. If the patient has localized erythema the clinician should assign a CEA grade for the erythematous area of the face.

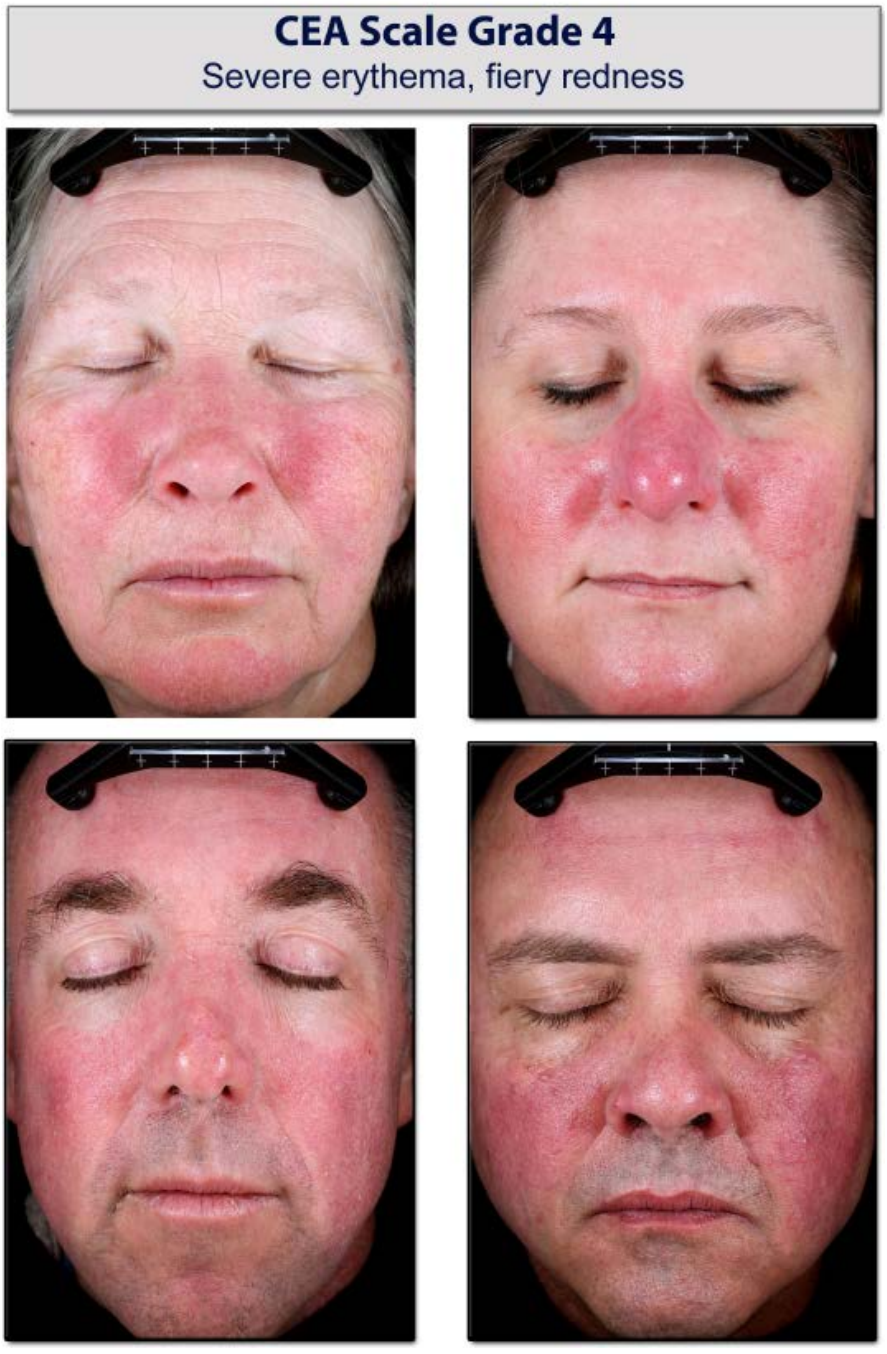
This photonumeric guide will serve as a tool to assist the clinician in assigning a CEA grade that is the best representation of facial erythema.


CEA Scale Grade 0
Clear skin with no signs of erythema


CEA Scale Grade 1
Almost clear of erythema, slight redness


CEA Scale Grade 2
Mild erythema, definite redness


CEA Scale Grade 3
Moderate erythema, marked redness


CEA Scale Grade 4
Severe erythema, fiery redness

14.2 Items From Satisfaction Assessment for Rosacea Facial Redness

INSTRUCTIONS

This questionnaire includes two questions about how satisfied you are with the facial redness caused by your rosacea.

Before answering each question, please look in the mirror and think about the redness on your **whole face** caused by your rosacea. Please mark ONE **"X" in the box (☒)** that best describes your satisfaction **right now**.

There are no right or wrong answers to any of the questions.

1. Right now, how satisfied are you with the appearance of your facial redness?

Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
▼	▼	▼	▼	▼
☐0	☐1	☐2	☐3	☐4

2. Right now, how satisfied are you with the amount of redness on your face?

Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
▼	▼	▼	▼	▼
☐0	☐1	☐2	☐3	☐4

14.3 FACE-Q™ - Satisfaction With Skin

FACE-Q™ - SATISFACTION WITH SKIN

For each question, circle only one answer. With your facial skin (complexion) in mind, in the past week, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How your facial skin looks at the end of your day?	1	2	3	4
b. How healthy your facial skin looks?	1	2	3	4
c. How attractive your facial skin makes you look?	1	2	3	4
d. How smooth your facial skin looks?	1	2	3	4
e. How clear your facial skin (complexion) looks?	1	2	3	4
f. How refreshed your facial skin makes you look?	1	2	3	4
g. How hydrated your facial skin looks?	1	2	3	4
h. How your facial skin looks when you first wake up?	1	2	3	4
i. How radiant your facial skin looks?	1	2	3	4
j. How the tone (color) of your facial skin looks?	1	2	3	4
k. How your pores look?	1	2	3	4
l. How even-colored your facial skin looks?	1	2	3	4

Note to Investigators: This scale can be used independently of the other scales. A REDCap Data Dictionary file is available (http://projectredcap.org/).

Psychometric Paper: Klassen AF, Cano SJ, Schwitzer J, Baker SB, Carruthers A, Carruthers J, Chapas A, Pusic AL. Development and Psychometric Validation of the FACE-Q Skin, Lips and Facial Rhytides Appearance Scales and Adverse Effect Checklists for Cosmetic Procedures. JAMA Dermatol. 2016 Apr 1;152(4):443-51.

FACE-Q™ - SATISFACTION WITH SKIN CONVERSION TABLE

Instructions: Higher scores reflect a better outcome. If missing data is less than 50% of the scale's items, insert the mean of the completed items. Use the Conversion Table below to convert the raw scale summed score into a score from 0 (worst) to 100 (best).

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
12	0
13	3
14	9
15	14
16	18
17	21
18	24
19	26
20	29
21	32
22	34
23	36
24	39
25	41
26	43
27	45
28	47
29	49
30	51
31	53
32	55
33	57
34	59
35	61
36	63
37	65
38	67
39	69
40	72
41	74
42	76
43	79
44	81
45	84
46	88
47	93
48	100

Investigator Signature Page

Protocol Title: Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea

Protocol Number: CMO-MA-MED-0530

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Allergan and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Allergan and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Allergan, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____
Investigator Signature Date

_____
Printed Name

_____
Institution