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APPLICATION NUMBER:

208552Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 208552
Priority or Standard Standard

Submit Date(s) March 23, 2016
Received Date(s) March 23, 2016
PDUFA Goal Date January 23, 2017
Division / Office DDDP/ ODE III

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M.S.
Review Completion Date 01/09/2016

Established Name Oxymetazoline
(Proposed) Trade Name Rhofade
Therapeutic Class Sympathomimetic agonist
Applicant Allergan, Inc.

Formulation(s) Cream, (b) (4) %
Dosing Regimen Once daily
Indication(s) For the topical treatment of
persistent facial erythema
associated with rosacea
Intended Population(s) Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends approval of this application.

1.2 Risk Benefit Assessment

Rhofade (oxymetazoline HCl) Cream, 1% is an alpha adrenergic receptor agonist, and the applicant proposed the product for “the topical treatment of the facial erythema of rosacea in adults 18 years of age or older.” It is proposed for once daily application.

Rosacea is a chronic dermatological condition that predominantly affects the central region of the face, e.g., cheeks nose, chin, mid forehead. It may be characterized by flushing (transient erythema), persistent (nontransient) erythema, telangiectasias, and inflammatory acneiform lesions (papules, pustules). Ocular involvement may occur (e.g., blepharitis, conjunctivitis). Onset is typically between the approximate ages of 30 and 50 years, and it is most frequently seen in Caucasians with lighter skin. While it is more common in women, it may be more severe in men. The disease is reported to be rare in children, although it may be underreported.

The applicant conducted two adequate and well-controlled Phase 3 trials which evaluated their product in individuals with non-transient, facial erythema of rosacea. In the trials 446 subjects were randomized to the oxymetazoline group, and 439 subjects were randomized to the vehicle group. Primary efficacy was evaluated by two-grade improvement on a composite endpoint which reflected the clinician (objective) and the subject (subjective) assessment of treatment effect. Primary efficacy was measured at hours 3, 6, 9, and 12 on Day 29. Oxymetazoline HCl cream, 1% was superior to vehicle on the primary efficacy endpoint in both trials, and the results were statistically significant. The applicant established that once daily use of oxymetazoline HCl cream, 1% was effective for the topical treatment of the facial erythema of rosacea.

The clinical development program of oxymetazoline for the treatment of persistent facial erythema associated with rosacea comprises 13 studies. A total of 929 patients with rosacea received at least 1 application of oxymetazoline HCl cream 1.0% daily, per the target indication; 440 of these patients applied oxymetazoline HCl cream 1.0% daily for up to 1 year in a long-term open-label study.

The applicant assessed the long-term safety of their product in a 52 week trial which evaluated subjects in sufficient numbers and with sufficient exposures, consistent with the recommendations in the ICH E1A Guideline for Industry. No new safety concerns were identified in the long-term trial.

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No serious adverse events reported appear to be treatment related. Severe application site reactions (dermatitis, erythema, pain, and pruritus) leading to study discontinuation were reported. Based on dermal tolerability assessments and provocative dermal safety studies, oxymetazoline HCl cream 1.0% appears reasonably tolerated.

The applicant provided substantial evidence of the effectiveness and safety of oxymetazoline HCl cream 1.0% when used once daily in the target population of subjects with facial erythema of rosacea. Approval of the product would represent a second product specific for the treatment with persistent erythema of rosacea, which is a common clinical challenge in rosacea-affected patients who are already using recognized medical therapies, and has been described as an “unmet need” in rosacea therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No Postmarket Risk Evaluation and Mitigation Strategies are recommended. Labeling is adequate to inform prescribers regarding risks and benefits of Rhofade.

1.4 Recommendations for Postmarket Requirements and Commitments

The reviewer had no recommendations for Postmarket Requirements or Commitments, nor were there any such recommendations from other review disciplines.

2 Introduction and Regulatory Background

2.1 Product Information

Oxymetazoline is a synthetic, direct-acting, imidazoline-type sympathomimetic agonist that is highly selective for the α_{1A} -adrenoceptor and is a partially selective α_{2A} -receptor agonist as well. It is a potent vasoconstrictor. Locally applied α_1 -adrenoreceptor agonists such as phenylephrine hydrochloride, naphazoline hydrochloride, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride are well known for their ability to clinically “get the red out” and have been used as vasoconstrictive agents in over-the-counter preparations for decades. These drugs have been used as decongestants on nasal and ocular mucous membranes for the treatment of conditions such as allergic rhinitis and conjunctivitis and decrease erythema and edema of the mucous membranes with safety and excellent efficacy.

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2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, Mirvaso (brimonidine) Gel, 0.33% is the only product approved in the United States exclusively for the treatment of the erythema of rosacea. However, two currently-marketed products address erythema in their indications:

- Noritate ® (metronidazole) Cream, 1% is indicated for “the topical treatment of inflammatory lesions and erythema of rosacea.”
- Finacea ® (azelaic acid) Gel, 15% is indicated for the “topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.”

2.3 Availability of Proposed Active Ingredient in the United States

Oxymetazoline is currently available in the United States as over-the-counter (OTC) treatments for nasal congestion at a concentration of 0.05% (e.g. Afrin, Dristan, Zicam nasal spray) and for temporary relief of ocular redness at a concentration of 0.025%, (e.g. Visine L. R. and Ocular ophthalmic solution). A combination product containing oxymetazoline HCl for its vasoconstrictive properties, KOVANAZE (tetracaine HCl, 3% and oxymetazoline HCl, 0.05%) nasal spray, was approved on June 29, 2016 for use as regional anesthesia in restorative dental procedures.

The 0.025% oxymetazoline ophthalmic solutions were approved for OTC use under NDAs in 1989 and 1986. The 0.05% oxymetazoline nasal sprays were determined to be generally recognized as safe and effective for use under the final OTC Monograph in 21 CFR Part 341: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human. The maximum dose of oxymetazoline in a 10 hour period according to the Monograph is 0.3 mg. To support approval of Kovanaze, the applicant relied in part on the monograph and literature for the safety of oxymetazoline.

2.4 Important Safety Issues With Consideration to Related Drugs

Accidental ingestion of imidazoline derivatives (i.e., oxymetazoline, naphazoline, tetrahydrozoline) in children has resulted in serious adverse events requiring hospitalization (e.g., coma, bradycardia, decreased respiration, sedation, somnolence).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Rhofade (oxymetazoline HCl) Cream, 1% was developed under IND 107983 for the treatment of persistent facial erythema associated with rosacea in adults 18 years or older.

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The original IND application for oxymetazoline HCl cream for the treatment of erythematous rosacea was opened by Vicept Therapeutics, Inc. on March 15, 2010. Under this IND, Vicept Therapeutics, Inc. conducted four Phase 1 dermal tolerability studies in healthy volunteers and four Phase 1 or 2 studies in subjects with moderate to severe erythematous rosacea.

In 2011, Allergan, Inc. acquired Vicept Therapeutics, Inc. and IND ownership was transferred from Vicept Therapeutics, Inc. to Allergan, Inc. on July 25, 2011. On July 27, 2011, the Agency and the applicant met for an End-of-Phase 2 (EOP2) meeting, which was requested by Vicept Therapeutics, Inc. on April 7, 2011. During this meeting, the Agency provided comments on the Phase 3 study design and the statistical analysis plan proposed by Vicept Therapeutics, Inc., the proposed nonclinical and CMC plans, and the scales proposed for the Phase 3 program.

On May 30, 2012, the applicant submitted a protocol for a non-drug study to validate the Clinician Erythema Assessment (CEA) scale with photonic guide. The Agency sent an advice letter regarding this protocol on December 3, 2012.

On December 18, 2013, the Agency and the applicant met for a second EOP2 meeting. The meeting package contained new protocols for two identically-designed Phase 3 trials. The applicant submitted amended protocols for these Phase 3 trials on March 6, 2014, and the Agency sent an advice letter regarding that submission on May 27, 2014. Based on this advice letter, the applicant submitted amended protocols for the Phase 3 trials on July 18, 2014. An advice letter regarding the proposed amendments was sent to the applicant on October 7, 2014.

On March 5, 2014 an advice letter was sent to the sponsor advising them that a TQT study is not needed for (oxymetazoline) cream, 1% for the treatment of erythema in patients with rosacea. On March 7, 2014 an advice letter was sent to the sponsor advising them that a waiver request for conduct of a dermal carcinogenicity study with oxymetazoline HCl cream is granted.

On October 14, 2015, the applicant and the Agency met for a Pre-NDA meeting. The Agency provided general comments on the content and format of the proposed NDA and how the data should be submitted (data tabulation datasets, data definition files, annotated case report forms, and analysis datasets). During the meeting, the Agency and the applicant discussed the container closure and stability data.

On July 18, 2014 an advice letter was sent agreeing to a pediatric plan that recommends a pediatric waiver.

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2.6 Other Relevant Background Information

In case of overdosage or accidental ingestion, oxymetazoline can cause peripheral vasoconstriction and severe central nervous depression including hypertension followed by reflex bradycardia and hypotension, marked reduction in body temperature, sweating, drowsiness and coma, particularly in susceptible adults and children.

On December 10, 2012 (77 FR 73294), the Commission issued a rule requiring special packaging (also called child-resistant or CR packaging) for any over-the-counter or prescription products containing the equivalent of 0.08 milligrams or more of a specified imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package.

After a serious adverse event involving topical brimonidine (another alpha agonist under study for erythema of rosacea) DMEPA recommended a child resistant container closure system designed to not resemble a toothpaste container and additional precautions to avoid inadvertent ingestion by children of subjects to include increased warnings on the label and Patient Use Instructions. These recommendations were conveyed to Allergan in an advice letter dated April 23, 2012. Allergan submitted a proposal to address these concerns on July 31, 2012. The Agency sent an advice letter agreeing to the proposal on Dec 13, 2012.

There do not appear to be occurrences of accidental ingestion by children during the clinical trials.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Four sites were chosen for inspection:

- Site 14006 (Leon Kircik/ Study 004) because of a relatively large number of subjects (23) response rates for both Rhofade and vehicle are much higher than the average, and a large treatment effect. Large number of protocol violations, which included 5 subjects being “randomized into incorrect stratum”. (b) (6)
- Site 14007 (Angela Moore/ Study 004): relatively large number of subjects (32), response rates for both Rhofade and vehicle are much higher than the average, and a large treatment effect.
- Site 15025 (Stephen Schleicher/ Study 005): moderate number of subjects (15), very large response rates for the Rhofade treatment arm, and a large treatment effect. Nine subjects had protocol violations regarding safety assessments (i.e., “study safety assessment not performed as specified per protocol”).

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- Site 15016 (Leslie Baumann/ Study 005): a relatively large number of subjects (24) (b) (6)

Three of the inspections were classified as no action indicated (NAI) and the data generated by these sites appear acceptable in support of the respective indication. The method and results for each investigation are as follows:

- **Leslie Baumann (16001)**
This inspection was performed as a data audit for NDA 208552. At this site for Protocol 199201005, 45 subjects were screened, 21 subjects were screen failures, and 24 subjects were enrolled and completed the study. The study records of all 45 subjects were reviewed for informed consent. Source data was compared with data listings for all 24 enrolled subjects. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
- **Leon Kircik (14006)**
This inspection was performed as a data audit for NDA 208552. At this site for Protocol 199201-004, 29 subjects were screened, six subjects were screen failures, and 23 subjects were enrolled and completed the study. All enrolled subjects signed the informed consent form prior to the start of screening procedures. Source documents and Case Report Forms (CRFS) were compared with data listings. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
- **Angela Moore (14007)**
This inspection was performed as a data audit for NDA 208552. At this site for Protocol 199201-004, 33 subjects were screened, 32 subjects were enrolled, and 30 subjects completed the study. All enrolled subjects signed the informed consent form prior to the start of screening procedures. Source documents and Case Report Forms (CRFS) were compared with data listings. The study records of 16 subjects were reviewed in depth. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

For the fourth site, protocol deviations were noted but did not appear to have a significant impact on safety or efficacy considerations. DSI concluded that “this study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.” A voluntary action indicated (VAI) classification was issued.

- **Joel Schlessinger (16028)**
This inspection was performed as a data audit for NDA 208552. At this site for Protocol 199201-005, 16 subjects were screened, and 15 subjects were randomized and completed the study. The study records of all 16 subjects were

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reviewed. Appropriate informed consent for all subjects was obtained and documented prior to any study-related testing

The inspection found that the investigator failed to adhere to protocol and had inadequate and inaccurate records which included: lost study binder, missing CRFs, and paper prospectively completed for assessments that were never actually conducted or recorded in the CRF database.

3.2 Compliance with Good Clinical Practices

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 certifying that investigators and their spouses/dependents were in compliance with 21 CFR part 54. The following potentially conflicting financial interests were identified:

- [REDACTED] (b) (6) has a presence of grants, consultation and honoraria variable that have a monetary value that can go over \$25,000 and in study **199201-004** served as the study coordinating investigator and enrolled [REDACTED] (b) (6) subjects at [REDACTED] (b) (6) site
- [REDACTED] (b) (6) has approximately 860 shares of the sponsor company and [REDACTED] (b) (6) site in study **199201-006** enrolled [REDACTED] (b) (6) subjects
- [REDACTED] (b) (6) has approximately 2000 shares of the sponsor company and [REDACTED] (b) (6) site in study **199201-006** enrolled [REDACTED] (b) (6) subjects

The above sites were recommended for inspection and DSI found that the data generated by these sites appear acceptable in support of the respective indication. The data from these sites were included in the analysis. Refer to the appended clinical investigator financial disclosure review template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The team Quality Assessment Review finds that the applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

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The facility review team from the Office of Process and Facility (OPF) has issued an "Approval" recommendation for the facilities involved in this application.

However, the issues on labels/labeling are not completely resolved at this time. Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6) until the labeling issues are satisfactorily resolved. Labeling negotiations with the applicant are ongoing as the clinical review was being finalized.

It was determined that the container closure airless pump would be designated a device and the product would be a combination product. Keith Marin in CDRH reviewed the information related to the pump and has requested additional information. An information request was sent to the applicant on January 3, 2017. The adequacy of the response is pending at the time of the closing of the clinical review.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

Dr. Cindy Xinguang Li's review finds that NDA 208552 for RHOFADE (oxymetazoline hydrochloride) Cream, 1.0% is approvable from a Pharmacology/Toxicology perspective provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the RHOFADE label.

The toxicity profile of oxymetazoline HCl topical cream has been well characterized by the nonclinical studies conducted by the sponsor. The overall nonclinical findings are summarized below:

- No evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay); and one in vivo genotoxicity test (mouse micronucleus assay at oral doses \leq 2.5mg/kg/day).
- Repeat-dose dermal toxicity studies were conducted in rats for up to 6 months and in minipigs for up to 9 months with oxymetazoline cream. Tail lesions and local toxicities were observed in rats.
- The oral Tg.ras H2 mouse assay at doses up to 2.5 mg/kg/day oxymetazoline did not reveal any neoplastic changes. A treatment related increased incidence of non-neoplastic lesions was noted in kidney, brain and mesenteric lymph nodes.
- The potential fertility and early embryonic development study toxicity was evaluated after oral administration in rats. Decreased number of corpora lutea and increased post-implantation losses were noted at the high dose of 0.2 mg/kg/day; however, there were no

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effects on the fertility and mating parameters. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for rat early embryonic development was established at the high dose tested of 0.2 mg/kg/day.

- The potential embryo-fetal development toxicity was evaluated after oral administration in rats. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for embryo-fetal development effects was established at the high dose tested of 0.2 mg/kg/day. The C_{max} and AUC_{0-tlast} at 0.2 mg/kg/day were 0.541 ng/mL and 3.43 ng.hr/mL on GD day 17, respectively.
- The potential embryo-fetal development toxicity was evaluated after oral administration in rabbits. The NOAEL for maternal toxicity was established at the mid-dose of 0.5 mg/kg/day. The NOAEL for embryo-fetal development effects was established at the high dose tested of 1.0 mg/kg/day. The C_{max} at 1.0 mg/kg/day was 14.0 ng/mL on GD day 17. The AUC₀₋₂₄ at 1.0 mg/kg/day was 76.2 ng.hr/mL on GD day 17.
- The potential prenatal and postnatal development toxicity was evaluated after oral administration in rats. The NOAEL for maternal toxicity was established at the mid-dose of 0.1 mg/kg/day. The NOAEL for prenatal and postnatal developmental effects was identified at 0.05 mg/kg/day based on increases in pup mortality at 0.2 mg/kg/day and decreased pup weights, observations at necropsy, and delayed sexual maturation at ≥ 0.1 mg/kg/day.

There are no significant safety concerns for oxymetazoline HCl cream at the proposed clinical dose. No nonclinical postmarketing requirement is recommended for this NDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Oxymetazoline is an alpha_{1A} adrenoceptor agonist. Oxymetazoline acts as a vasoconstrictor.

4.4.2 Pharmacodynamics

The pharmacodynamics of Rhofade Cream has not been studied.

4.4.3 Pharmacokinetics

The pharmacokinetics of oxymetazoline was evaluated following topical administration of Rhofade Cream, 1% in a thin layer to cover the entire face in adult subjects with erythema associated with rosacea. The mean weight of cream for each dose administration ranged from 0.33 g to 0.37 g. Plasma oxymetazoline concentrations were measurable in most of the subjects. Following the first dose application, the mean \pm standard deviation (SD) peak concentrations (C_{max}) and area under the concentration-

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time curves from time 0 to 24 hours (AUC_{0-24hr}) were 60.5 ± 53.9 pg/mL and 895 ± 798 pg*hr/mL, respectively. Following once daily applications for 28 days, the mean ± SD C_{max} and AUC_{0-24hr} were 66.4 ± 67.1 pg/mL and 1050 ± 992 pg*hr/mL, respectively. Following twice daily applications for 28 days, the mean ± SD C_{max} and AUC_{0-24hr} were 68.8 ± 61.1 pg/mL and 1530 ± 922 pg*hr/mL, respectively.

The excretion of oxymetazoline has not been characterized in humans. The distribution of oxymetazoline was evaluated by an in vitro study that demonstrated 56.7% to 57.5% of oxymetazoline bound to human plasma proteins. Oxymetazoline was shown to be minimally metabolized by liver microsomes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for oxymetazoline HCL 1% cream included the following clinical trials conducted in support of approval:

Table 1: Tables of Clinical Trials for NDA 208552

Study Number	Study Objectives	Study Design Type of Control	Key Entry Criteria	Number of Subjects	Duration of treatment
<i>Patient Pharmacokinetic (PK) and Initial Tolerability Studies (Module 5.3.3.2)</i>					
V-101- ROSE-202	to evaluate the dose-response relationship of 4 concentrations of Oxy cream and a matching vehicle cream when applied to the face and to evaluate the safety and efficacy of 4 concentrations of Oxy cream and its vehicle when applied to the face for 28 consecutive days	Phase 2, randomized, double-blind, vehicle controlled, parallel-group, dose-response, efficacy/safety study in patients with moderate to severe erythematous rosacea	18 years of age or older with a clinical diagnosis of stable erythematous rosacea, Subject's Self-Assessment and CEA grades of ≥ 3, ≤ 3 inflammatory lesions (papules and/or pustules) and no cysts within the treatment area	183 enrolled 37 Oxy 0.01% QD 37 Oxy 0.06% QD 37 Oxy 0.10% QD 35 Oxy 0.15% QD 37 Vehicle QD	28 days
<i>Controlled Safety and Efficacy Studies Pertinent to the Claimed Indication (Module 5.3.5.1)</i>					
199201-002	to evaluate the safety and efficacy of Oxy cream 0.5%, 1.0%, and 1.5%, once-daily and twice daily	Phase 2, randomized, double-blind, vehicle controlled, parallel-group, dose-ranging, efficacy/safety	18 years of age or older with a grade of ≥ 3 on the CEA scale and either "more redness than I	356 enrolled and included in mITT population 45 Oxy 0.5% QD 44 Oxy 1.0% QD 44 Oxy 1.5% QD 44 Vehicle QD	28 days

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	topical application compared to vehicle for 28 consecutive days for the treatment of patients with moderate to severe facial erythema associated with rosacea	study in patients with moderate to severe persistent facial erythema associated with rosacea	prefer” or “completely unacceptable redness” on the Subject Self-Assessment of erythema scale, and stable facial erythema with minimal variation; no greater than 3 inflammatory lesions on the face	45 Oxy 0.5% BID 45 Oxy 1.0% BID 45 Oxy 1.5% BID 44 Vehicle BID	
199201-004	to evaluate the efficacy and safety of Oxy 1.0% cream compared with vehicle cream, applied topically QD for 29 days to the face of patients with moderate to severe persistent facial erythema associated with rosacea	Phase 3, pivotal, randomized, double-blind, vehicle-controlled, parallel group, efficacy/safety study	18 years of age or older with grades of ≥ 3 on both the CEA and SSA scales and with no greater than 3 inflammatory lesions on the face	440 enrolled 222 Oxy 1.0% QD 218 Vehicle QD	29 days
199201-005	same as Study 199201-004	same as Study 199201-004	same as Study 199201-004	445 enrolled 224 Oxy 1.0% QD 221 Vehicle QD	29 days
<i>Uncontrolled Study Pertinent to the Claimed Indication (Module 5.3.5.2)</i>					
199201-006	to evaluate the long-term safety and efficacy of Oxy 1.0% cream applied topically once daily for 1 year (52 weeks) to the face of patients with moderate to severe persistent facial erythema associated with rosacea	Phase 3, open-label, longterm, efficacy/safety study	18 years of age or older with grades of ≥ 3 on both the CEA and SSA scales	440 enrolled 440 Oxy 1.0% QD	52 weeks
<i>Dermal safety studies</i>					
V-101-HDSS-101	to determine the cumulative irritation potential of the test materials	Phase 1, controlled, 21-day cumulative irritation patch test study in healthy adult volunteers	healthy volunteers 18 years of age or older who were not pregnant or nursing and who had no chronic asthma or atopic	35 enrolled All subjects treated with white petrolatum (negative control), vehicle cream, 0.5% sodium	20 days

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			dermatitis/ eczema or psoriasis that would have confounded results	lauryl sulfate (positive control) and Oxy 0.5% cream	
V-101-HDSS-102	to assess the potential of the test materials to induce contact sensitization by repetitive applications to skin of healthy volunteers	Phase 1, controlled, repeat insult patch test study in healthy adult volunteers	healthy volunteers 18 years of age or older who were not pregnant or nursing and who had no chronic asthma or atopic dermatitis/ eczema or psoriasis that would have confounded results	225 enrolled All subjects treated with white petrolatum (negative control), vehicle cream, 0.5% sodium lauryl sulfate (positive control) and Oxy 0.5%	3-week induction period, 2-week rest period, then a single challenge
V-101-HDSS-103	to evaluate the potential of Oxy 0.5% cream to produce phototoxicity reactions in normal use	Phase 1, controlled, open label (evaluator masked), single-dose phototoxicity test study in healthy adult volunteers	healthy volunteers 18 to 70 years of age who were not pregnant or nursing, who were willing to avoid sun exposure, and who have no history of atopic dermatitis, skin cancer, dysplastic nevi, or other skin pathology	32 enrolled All subjects treated with Oxy 0.5% and vehicle cream with and without UV radiation	24-hour occluded exposure to test materials, then reapplication and irradiation
V-101-HDSS-104	to evaluate the potential of Oxy 0.5% cream to produce photoallergenicity reactions in normal use, and with higher doses than normally used, comparing sites with Oxy 0.5% alone and Oxy 0.5% irradiated versus vehicle alone, vehicle irradiated, untreated control alone and untreated control irradiated	Phase 1, controlled, open label (evaluator masked), repeat-dose photocontact allergenicity test study in healthy adult volunteers	healthy volunteers 18 to 70 years of age who were not pregnant or nursing, who were willing to avoid sun exposure, and who have no history of psoriasis, atopic dermatitis, skin cancer, dysplastic nevi, or other skin pathology	49 enrolled All subjects treated with Oxy 0.5% and vehicle cream with and without UV radiation	≤ 3-week induction period, 9- to 14-day rest period, 2-day challenge period

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5.2 Review Strategy

Discipline chemistry, pharmacology, statistics, clinical outcome assessment and labeling reviews were completed. The clinical review has considered these reviews and synthesized an overall clinical recommendation based on the provided input.

Safety and efficacy was planned to be primarily supported by two identically-designed Phase 3 trials (004 and 005). Additional integrated safety analysis includes subjects once daily with oxymetazoline HCl cream 1.0% or vehicle in the Phase 2 dose-ranging trial 002. The safety review also includes data from 1 open-label, long-term safety study (006) in which all patients were treated with oxymetazoline HCl cream 1.0% for 52 weeks. Dermal safety studies conducted with the 0.5% product (101, 102, 103 and 104) were included in the safety review.

Section 5.3 below discusses the two identically-designed Phase 3 trials (Trials 004 and 005). Efficacy from trials 004 and 005 are reviewed in section 6; safety from integrated analysis of trials 002, 004 and 005 are described throughout section 7; safety from trial 006 7.5.2 and dermal safety studies reviewed in section 7.7

5.3 Discussion of Individual Studies/Clinical Trials

The applicant conducted two identically-designed Phase 3 trials (Trials 004 and 005) as shown in the table below:

Table 2: Overview of Phase 3 Trials to Support Efficacy

Trial	Location	Study Population	Treatment Arms	Number of Subjects	Dates
004	U.S. (20 sites)	Male and female subjects \geq 18 years of age with CEA \geq 3 and SSA \geq 3	RHOFADE Cream, 1.0%	222	5/22/2014 –
			Vehicle Cream	218	12/19/2014
005	U.S. (24 sites)		RHOFADE Cream, 1.0%	224	6/18/2014 –
			Vehicle Cream	221	5/20/2015

Title

Efficacy and Safety of Oxymetazoline HCl Cream 1.0% for the Treatment of Persistent Erythema Associated with Rosacea

Investigators

004 Leon Kircik, MD
005 Leslie Baumann, MD

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All other clinical investigators are listed in the financial disclosure attachment.

Objective

The objective of this study was to evaluate the efficacy and safety of oxymetazoline HCl cream 1.0% compared with vehicle, applied topically once daily (QD) for 29 days to the face of patients with moderate to severe persistent facial erythema associated with rosacea.

Trial Design

Both trials were randomized, double-blind, parallel-group, vehicle-controlled, 57-day trials investigating the safety and efficacy of oxymetazoline cream, 1.0% compared to vehicle cream for the treatment of facial erythema associated with rosacea.

Subjects

Each trial was designed to enroll and randomize approximately 440 subjects in a 1:1 ratio to receive either oxymetazoline cream, 1.0% (N=220) or vehicle cream (N=220). Randomization was stratified by baseline CEA score and center.

For enrollment, the protocol specified the following key inclusion criteria:

- Male or female 18 years of age or older
- Clinical diagnosis of rosacea
- Moderate to severe persistent facial erythema associated with rosacea at baseline, as determined by:
 - Clinician Erythema Assessment (CEA) score ≥ 3
 - Subject Self-Assessment (SSA) score ≥ 3

Excluded comorbid medical conditions included: 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, rosacea conglobate, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin, peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, chronic recurring facial acne

Excluded concomitant medications included: monoamine oxidase (MAO) inhibitors, products containing oxymetazoline, topical glucocorticosteroids applied to the face, systemic or nasal corticosteroids, any prescription or OTC product for the treatment of acne or rosacea, and ANY product to reduce redness to the face, systemic antibiotics that are known to have an effect on rosacea such as erythromycin or doxycycline, isotretinoin laser, light-source (e.g., intense pulsed light [IPL], photodynamic therapy [PDT]) or other energy-based therapy to the face, previous or current use of Mirvaso (brimonidine) topical gel, 0.33%.

Methodology

Subjects were instructed to apply study product in a thin layer topically to the entire face including forehead, nose, each cheek, and chin, once daily in the morning at

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approximately the same time of day for 29 days. On Days 1, 15, and 29, the protocol specified all subjects to apply study product under supervision by the study staff at the site. Subjects were evaluated at the following study visits: screening (Day -45 to -1), baseline (Day 1) and Day 15, Day 29 (end of treatment), post Day 29 visit (4 to 7 days after end of treatment), and Day 57 (end of study).

Efficacy measures

The primary efficacy measures were:

- Investigator's assessment of the patient's overall severity of erythema in the treatment area as measured by the 5-point CEA scale with photonumeric guide
- Patient's self-assessment of the overall severity of rosacea facial redness in the treatment area as measured by the 5-point SSA scale with photoguide

Both instruments (CEA and SSA) used the same set of photos. The grades and descriptions of the rating scales are as follows:

Table 3: Clinician Erythema Assessment (CEA) Scale

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

(1) Normal healthy skin color as seen in individuals without rosacea.

(2) Source: Study Protocol

Table 4: Subject Self-Assessment (SSA) Scale

Grade	Description
0	No signs of unwanted redness
1	Almost clear of unwanted redness
2	Mild redness
3	Moderate redness
4	Severe redness

Source: Study Protocol

The protocol defined secondary endpoints are discussed in Section 6.1.5.

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6 Review of Efficacy

Efficacy Summary

The applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, pivotal Phase 3 trials (Trials 004 and 005). The trials evaluated the safety and efficacy of RHOFADE cream, 1.0% compared to vehicle cream. The trials enrolled subjects aged 18 years or older with a clinician erythema assessment (CEA) score of 3 (moderate erythema) or greater and a Subject Self-Assessment (SSA) score 3 (moderate redness) or greater. The protocol-specified primary efficacy endpoint was the proportion of subjects with composite success (defined as a 2-grade improvement from baseline in both CEA and SSA) measured at hours 3, 6, 9 and 12 on Day 29. The primary endpoint was analyzed using the Generalized Estimating Equation (GEE) method to account for the repeated measures on each subject (i.e., hours 3, 6, 9, and 12).

The table below presents the results for the primary efficacy endpoint on Day 29. In both trials, RHOFADE cream, 1.0% was statistically superior (p-values <0.001) to vehicle cream.

Table 5: Composite Success¹ by Hour on Day 29 (ITT, MI²)

	Trial 004			Trial 005		
	RHOFADE (N=222)	Vehicle (N=218)	P- value ⁽³⁾	RHOFADE (N=224)	Vehicle (N=221)	P- value ⁽³⁾
Hour 3	11.9%	5.5%	<0.001	14.3%	7.4%	0.001
Hour 6	15.5%	8.3%		13.4%	4.8%	
Hour 9	17.7%	6.0%		15.5%	8.5%	
Hour 12	14.8%	6.0%		12.3%	6.1%	

Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

(3) P-value is based on a GEE model with treatment, analysis center and timepoint (hours 3, 6, 9 and 12) as factors in the model.

Gender, racial composition and skin phototype of the study populations reflect what is generally known about the population most often affected by rosacea, i.e. more common in women and in light-skinned Caucasians. Clinical studies of RHOFADE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

There was no evidence of tachyphylaxis observed with short-term, 29 day, use of oxymetazoline cream, 1%.

The Clinical Outcome Assessment (COA) team found that the SSA is not an ideal instrument for a variety of reasons: content validity, test-retest scoring was not optimal, concordance with the CEA is unknown. Some limitations such as reliability (test-retest)

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may be explained by the fluctuating nature of erythema in patients with rosacea.

Subjects did have difficulty distinguishing between the milder categories. However, the

CEA and SSA instruments appear to generally correlate when additional definitions of success were applied and analyzed.

Despite the limitations of the SSA scale identified, it is this reviewer's opinion that the changes seen (and supported by the CEA) are likely to be clinically meaningful to some patients. Approval of the product would represent a second product specific for the treatment with persistent erythema of rosacea, which is a common clinical challenge in rosacea-affected patients who are already using recognized medical therapies, and has been described as an "unmet need" in rosacea therapy.

6.1 Indication

The applicant, Allergan, Inc., is seeking approval of RHOFADE (oxymetazoline) cream, 1.0% for the indication of topical treatment of persistent facial erythema associated with rosacea in adults.

6.1.1 Methods

The statistics and clinical reviewers evaluated the applicant's clinical study reports, datasets, clinical summaries, clinical trial protocols, and proposed labeling. Dr. Matthew Guerra provided analysis of clinical trials 004 and 005.

6.1.2 Demographics

The demographics and baseline disease characteristics are presented in the table below:

Table 6: Subject Demographics

	Trial 004		Trial 005	
	RHOFADE (N=222)	Vehicle (N=218)	RHOFADE (N=224)	Vehicle (N=221)
Age				
Mean (SD)	50.5 (12.9)	48.5 (12.3)	49.3 (12.7)	51.4 (12.2)
Median	50.5	48.0	49.0	52.0
Range	19 – 81	19 – 74	18 – 88	22 – 87
Categories				
18-64	189 (85%)	194 (89%)	198 (88%)	193 (87%)
65+	33 (15%)	24 (11%)	26 (12%)	28 (13%)
Gender				
Male	50 (23%)	43 (20%)	47 (21%)	48 (22%)
Female	172 (77%)	175 (80%)	177 (79%)	173 (78%)
Race				
White	203 (91%)	189 (87%)	201 (90%)	202 (91%)

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Black	3 (1%)	1 (<1%)	0	0
Asian	2 (1%)	3 (1%)	1 (<1%)	3 (1%)
Hispanic	14 (6%)	20 (9%)	22 (10%)	16 (7%)
Other	0	5 (2%)	0	0
CEA				
3 – Moderate	194 (87%)	191 (88%)	187 (83%)	187 (85%)
4 – Severe	28 (13%)	27 (12%)	37 (17%)	34 (15%)
SSA				
2 – Mild	0	0	1 (<1%)	0
3 – Moderate	206 (93%)	194 (89%)	207 (92%)	200 (90%)
4 – Severe	16 (7%)	24 (11%)	16 (7%)	21 (10%)

Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)
 SD: Standard Deviation

The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between each trial. Approximately 88% and 84% of subjects had a CEA score of 3 (moderate) at baseline in Trials 004 and 005, respectively. Approximately 91% and 93% of subjects had a SSA score of 3 (moderate) at baseline in Trials 004 and 005, respectively. In Trial 005, one subject (b) (6) in the RHOFADE arm had a baseline SSA score of 2 (mild) and therefore did not meet the baseline inclusion criterion for SSA.

6.1.3 Subject Disposition

Trial 004 enrolled and randomized a total of 440 subjects (222 to RHOFADE and 218 to vehicle) from 20 sites in the United States. Trial 005 enrolled and randomized a total of 445 subjects (224 to RHOFADE and 221 to vehicle) from 24 sites in the United States. In both trials, the discontinuation rate was higher in the RHOFADE arm compared to the vehicle arm. The discontinuation rates were very similar between the trials. The reasons for discontinuation are presented below:

Table 7: Subject Disposition (ITT)

	Trial 004		Trial 005	
	RHOFADE (N=222)	Vehicle (N=218)	RHOFADE (N=224)	Vehicle (N=221)
Discontinued	12 (5%)	5 (2%)	11 (5%)	5 (2%)
<i>Adverse Event</i>	4 (2%)	1 (<1%)	6 (3%)	1 (<1%)
<i>Lost to Follow-Up</i>	4 (2%)	0	2 (1%)	2 (1%)
<i>Other</i>	0	0	2 (1%)	0
<i>Personal Reasons</i>	4 (2%)	4 (2%)	1 (<1%)	2 (1%)

Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

Differences in the rate appear to be primarily driven by more frequent adverse events. These events were primarily application site reactions and are described in safety section 7.3.3.

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 6.1.4 Analysis of Primary Endpoint(s)

The protocol-specified primary efficacy endpoint was the proportion of subjects with composite success (defined as ≥ 2 -grade reduction in both CEA and SSA) measured at hours 3, 6, 9 and 12 on Day 29. The table below presents the results of the primary efficacy endpoint. In both trials, Rhofade cream, 0.88% was statistically superior (p-values < 0.001) to vehicle cream. The results from the ITT and PP analyses were very similar.

Table 8: Composite Success⁽¹⁾ by Hour on Day 29

	Trial 004			Trial 005		
	RHOFADE	Vehicle	P-value ⁽³⁾	RHOFADE	Vehicle	P-value ⁽³⁾
ITT⁽²⁾	N=222	N=218	<0.001	N=224	N=221	0.001
Hour 3	11.9%	5.5%		14.3%	7.4%	
Hour 6	15.5%	8.3%		13.4%	4.8%	
Hour 9	17.7%	6.0%		15.5%	8.5%	
Hour 12	14.8%	6.0%		12.3%	6.1%	
PP			<0.001			0.001
Hour 3	25/212 (11.8%)	12/215 (5.6%)		30/211 (14.2%)	16/215 (7.4%)	
Hour 6	33/212 (15.6%)	18/215 (8.4%)		28/211 (13.3%)	10/214 (4.7%)	
Hour 9	38/211 (18.0%)	12/215 (5.6%)		33/211 (15.6%)	17/214 (7.9%)	
Hour 12	32/211 (15.2%)	12/215 (5.6%)		26/211 (12.3%)	13/213 (6.1%)	

The proportions of responders in the ITT population for oxymetazoline group at hours 3, 6, 9, and 12 on day 29 were 11.9%, 15.5%, 17.7%, and 14.8%, respectively, compared with the vehicle group at 5.5%, 8.3%, 6.0%, and 6.0%, respectively. The overall treatment effect is modest, although statistically significant.

As an additional analysis on composite success, the applicant separately tested each of the hour timepoints (i.e., hours 3, 6, 9 and 12) and the results of this additional analysis is presented in the table below. For each of the 4 hour timepoints, Rhofade cream, 1.0% was statistically superior (p-values ≤ 0.024) to vehicle cream in both trials.

Table 9: Composite Success⁽¹⁾ Rates by Hours and Days (ITT, MI⁽²⁾)

	Trial 004			Trial 005		
	Rhofade Cream (N=222)	Vehicle Cream (N=218)	P-value ⁽³⁾	Rhofade Cream (N=224)	Vehicle Cream (N=221)	P-value ⁽³⁾
Day 29			<0.001			0.001
Hour 3	12%	6%		14%	7%	
Hour 6	16%	8%		13%	5%	
Hour 9	18%	6%		16%	9%	
Hour 12	15%	6%		12%	6%	

Source: Statistics Reviewer's Analysis

(1) Composite success is defined as ≥ 2 -grade improvement on both CEA and SSA.

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 20 imputed datasets.

(3) P-value is calculated using imputed data and based on a GEE model with treatment, site and timepoint (hours 3, 6, 9 and 12) as factors in the model.

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As sensitivity analyses for the primary efficacy endpoint, the protocol specified using the following alternative definitions of composite success:

1. Averaged Composite Success: achieving at least a 2-grade improvement from baseline to Day 29 on both the average of the CEA scores over hours 3, 6, 9, and 12 and the average of the SSA scores over hours 3, 6, 9, and 12
2. Total Composite Success: achieving at least a 2-grade improvement from baseline to Day 29 on both the CEA and SSA at each hour 3, 6, 9 and 12 (concurrently)

With these sensitivity analyses, oxymetazoline cream, 1% remained superior to vehicle at a level of statistical significance.

Dr. Guerra also conducted two additional sensitivity analyses where missing data was imputed as failures and missing data was imputed under the worst cases scenario (i.e., missing data for the RHOFADE arm is imputed as failures and missing data for the vehicle arm is imputed as successes). The table below presents the results for primary efficacy endpoint in both trials by the various imputation methods.

Table 10: Comparison of Different Approaches for Handling Missing Data for Composite Success⁽¹⁾ by Hour on Day 29 (ITT)

Method	Timepoint	Trial 004			Trial 005		
		RHOFADE (N=222)	Vehicle (N=218)	P-value ⁽⁷⁾	RHOFADE (N=224)	Vehicle (N=221)	P-value ⁽⁷⁾
MI (Primary)⁽²⁾	Hour 3	11.9%	5.5%	<0.001	14.3%	7.4%	0.001
	Hour 6	15.5%	8.3%		13.4%	4.8%	
	Hour 9	17.7%	6.0%		15.5%	8.5%	
	Hour 12	14.8%	6.0%		12.3%	6.1%	
LOCF⁽³⁾	Hour 3	25 (11.3%)	12 (5.5%)	<0.001	31 (13.8%)	18 (8.1%)	0.004
	Hour 6	33 (14.9%)	18 (8.3%)		29 (13.0%)	11 (5.0%)	
	Hour 9	38 (17.1%)	13 (6.0%)		34 (15.2%)	19 (8.6%)	
	Hour 12	32 (14.4%)	13 (6.0%)		27 (12.1%)	14 (6.3%)	
Average Value⁽⁴⁾	Hour 3	26 (11.7%)	12 (5.5%)	<0.001	31 (13.8%)	17 (7.7%)	0.004
	Hour 6	34 (15.3%)	18 (8.3%)		29 (13.0%)	11 (5.0%)	
	Hour 9	39 (17.6%)	13 (6.0%)		34 (15.2%)	19 (8.6%)	
	Hour 12	33 (14.9%)	13 (6.0%)		27 (12.1%)	14 (6.3%)	
Failure⁽⁵⁾	Hour 3	25 (11.3%)	12 (5.5%)	0.003	31 (13.8%)	16 (7.4%)	0.001
	Hour 6	33 (14.9%)	18 (8.3%)		29 (13.0%)	10 (4.5%)	
	Hour 9	38 (17.1%)	13 (6.0%)		34 (15.2%)	18 (8.1%)	
	Hour 12	32 (14.4%)	13 (6.0%)		27 (12.1%)	13 (5.9%)	
Worst Case⁽⁶⁾	Hour 3	25 (11.3%)	14 (6.4%)	0.003	31 (13.8%)	21 (9.5%)	0.066
	Hour 6	33 (14.9%)	20 (9.2%)		29 (13.0%)	16 (7.2%)	
	Hour 9	38 (17.1%)	15 (6.9%)		34 (15.2%)	24 (10.9%)	

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	Hour 12	32 (14.4%)		27 (12.1%)	20 (9.1%)	
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Source: Statistics Reviewer's Analysis and Applicant's Analysis

- (1) Composite success is defined as 2-grade improvement on both CEA and SSA.
- (2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.
- (3) Time-matched last observation carried forward (LOCF) approach (e.g., if a subject is missing CEA data at hour 3 on Day 29, then the missing value will be imputed using the CEA value from hour 3 on Day 15).
- (4) Single-imputation via the average value (e.g., if a subject in the vehicle arm is missing CEA data at hour 3 on Day 29, then the missing value will be imputed using the average of all CEA values for subjects in the vehicle arm who have non-missing CEA data at hour 3 on Day 29).
- (5) Missing data is imputed as failures.
- (6) Missing data for the RHOFADE arm is imputed as failures and missing data for the vehicle arm is imputed as successes.
- (7) P-value is based on a GEE model with treatment, analysis center and timepoint (hours 3, 6, 9 and 12) as factors in the model.

For both trials, the results were generally similar across the various methods; however, under the worst case scenario, the results for Trial 005 became marginally non-significant (p-value = 0.066). This was due to a higher amount of missing data in the vehicle arm for Trial 005 compared to Trial 004.

6.1.5 Analysis of Secondary Endpoints(s)

The protocol specified the following secondary efficacy endpoints:

- Proportion of subjects with at least a 2-grade improvement from baseline on SSA measured at hours 3, 6, 9, and 12 on Day 29
- Percent change from baseline in Rosacea Facial Redness as measured by digital image analysis measured at hours 3, 6, 9, and 12 on Day 29
- Proportion of subjects who report "satisfied" or "very satisfied" on the Satisfaction Assessment for Rosacea Facial Redness (SAT-RFR) Item #9 measured at hours 3, 6, 9, and 12 on Day 29, see Figure 1
- Change from baseline in SAT-RFR Item #4 measured at hours 3, 6, 9, and 12 on Day 29, see Figure 2
- Proportion of subjects with at least a 1-grade improvement from baseline on SSA at hour 1 postdose on Day 1

The table below presents the results of the secondary efficacy endpoints for the ITT population. To control the Type I error rate for testing multiple secondary efficacy endpoints, the protocol specified using a sequential gatekeeping approach. Therefore, although the p-values for the last secondary endpoint (i.e., proportion of subjects with a ≥ 1 -grade Improvement on SSA at on Day 1) are ≤ 0.002 in both trials, they cannot be considered statistically significant since the p-values for the 2nd to last secondary endpoint (i.e., change from baseline on SAT-RFR Item #4 on Day 29) were not less than 0.05 in both trials.

Table 11: Efficacy Results for Secondary Endpoints (ITT population)

	Trial 004			Trial 005		
	RHOFADE (N=222)	Vehicle (N=218)	P-value	RHOFADE (N=224)	Vehicle (N=221)	P-value
≥ 2-grade Improvement on SSA on Day 29⁽¹⁾						

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Hour 3	20.1%	11.1%		24.1%	15.8%	
Hour 6	23.3%	12.9%	<0.001 ⁽⁴⁾	24.8%	14.7%	0.011 ⁽⁴⁾
Hour 9	23.3%	12.0%		22.0%	16.0%	
Hour 12	25.0%	11.5%		23.7%	15.8%	
Percent Change from Baseline in Rosacea Facial Redness⁽²⁾ on Day 29						
Hour 3						
Mean (SD)	-21.4 (94.7)	61.5 (428.9)		-6.7 (144.8)	36.5 (225.5)	
Median	-29.7	3.9		-25.7	0	
Hour 6						
Mean (SD)	-14.2 (97.8)	75.1 (498.8)	<0.001 ⁽⁵⁾	6.7 (170.7)	39.8 (198.1)	<0.001 ⁽⁵⁾
Median	-27.3	-1.3		-16.0	2.3	
Hour 9						
Mean (SD)	-8.0 (92.9)	71.2 (398.1)		6.0 (131.9)	43.7 (200.5)	
Median	-20.1	5.3		-11.0	5.2	
Hour 12						
Mean (SD)	-5.4 (98.5)	74.2 (415.3)		9.2 (145.9)	38.8 (195.3)	
Median	-14.8	1.2		-9.6	1.0	
Success on SAT-RFR Item #9 on Day 29⁽³⁾						
Hour 3	45.9%	27.5%		54.3%	34.1%	
Hour 6	43.7%	24.3%	<0.001 ⁽⁴⁾	49.3%	32.3%	<0.001 ⁽⁴⁾
Hour 9	43.2%	23.4%		49.8%	33.6%	
Hour 12	41.9%	24.8%		47.5%	36.4%	
Change from Baseline on SAT-RFR Item #4 on Day 29⁽³⁾						
Hour 3	-1.5	-1.5		-1.8	-1.6	
Hour 6	-1.5	-1.5	0.906 ⁽⁴⁾	-1.8	-1.6	0.205 ⁽⁴⁾
Hour 9	-1.5	-1.5		-1.8	-1.7	
Hour 12	-1.5	-1.5		-1.8	-1.7	
≥1-grade Improvement on SSA at on Day 1⁽¹⁾						
Hour 1	30.2%	17.4%	0.001 ⁽⁶⁾	29.7%	16.8%	0.002 ⁽⁶⁾

Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

(1) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

(2) Missing data was imputed using the last observation carried forward (LOCF) approach.

(3) Missing data was imputed using the time-matched LOCF approach.

(4) P-value is based on a GEE model with treatment, site (pooled) and timepoint (hours 3, 6, 9 and 12) as factors in the model.

(5) P-value is based on rank data using on a GEE model with treatment, site (pooled) and timepoint (hours 3, 6, 9 and 12) as factors in the model.

(6) P-value is based on the CMH test stratified by site (pooled).

6.1.6 Other Endpoints

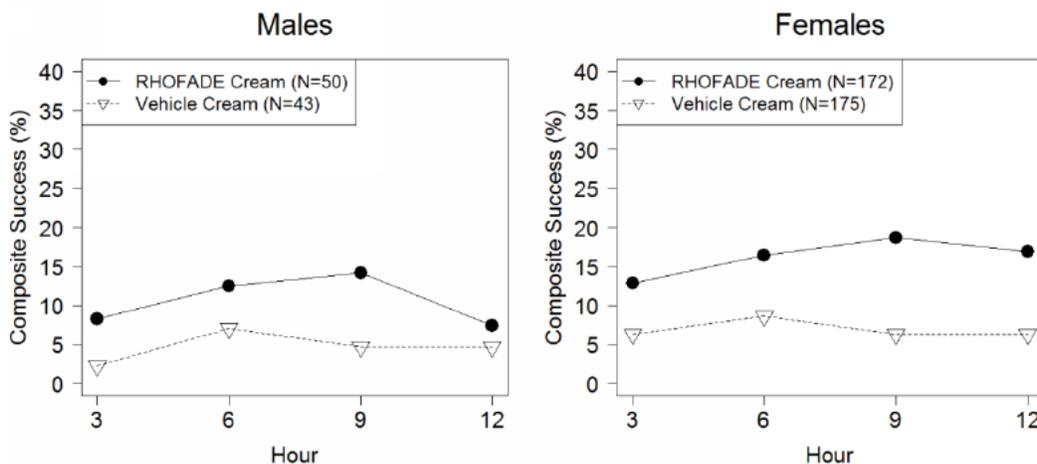
No additional endpoints were analyzed.

6.1.7 Subpopulations

Gender, racial composition and skin phototype of the study populations reflect what is generally known about the population most often affected by rosacea, i.e. more common in women and in light-skinned Caucasians. Clinical studies of RHOFADE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

The figures below display the composite success rates by hour and gender on Day 29 for Trials 004 and 005, respectively. In both trials, the treatment effect was slightly larger in females compared to males.

Figure 1: Composite Success⁽¹⁾ by Hour and Gender on Day 29 for Trial 004 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

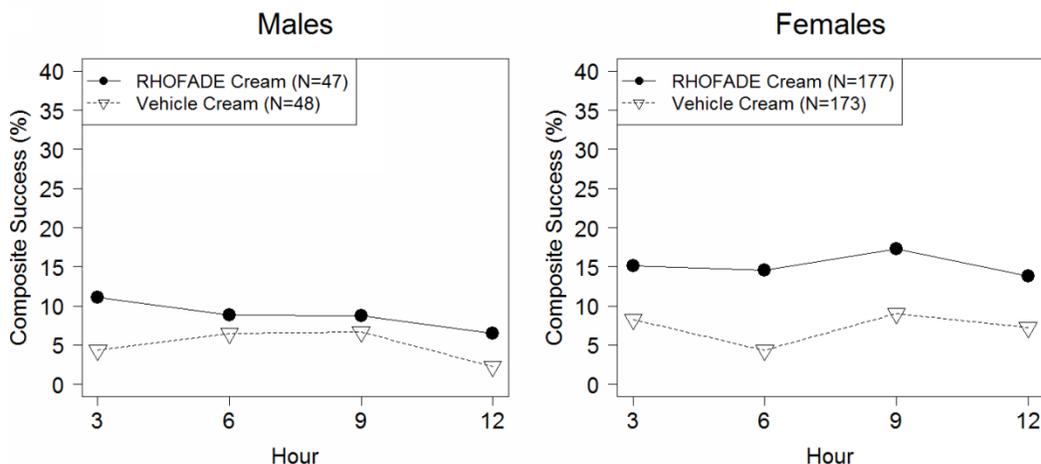
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Figure 2: Composite Success⁽¹⁾ by Hour and Gender on Day 29 for Trial 004 (ITT, MI⁽²⁾)



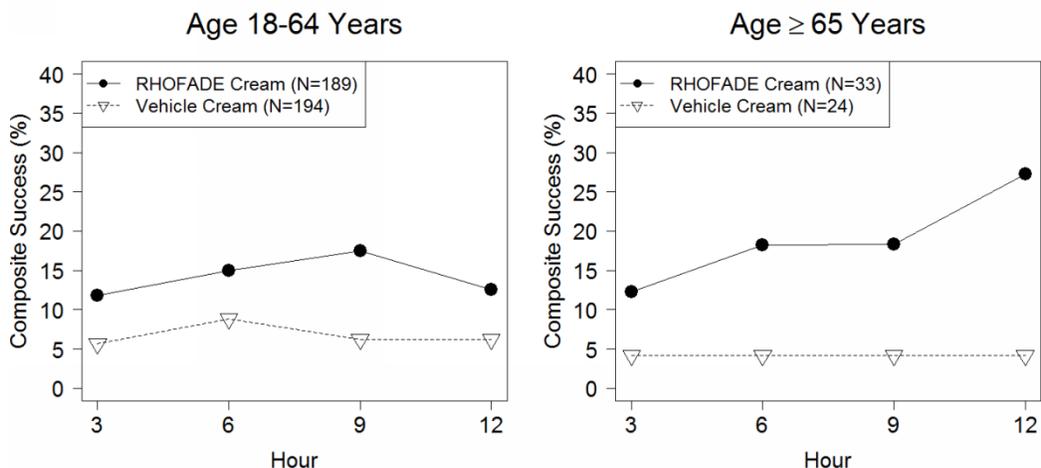
Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

Age was dichotomized by this reviewer into two groups (18-64 and ≥ 65) and the results for these subgroups are displayed in Figures below for Trials 004 and 005, respectively. The treatment effect was slightly larger in subjects aged ≥ 65 years compared to subjects aged 18-64 years in both trials.

Figure 3: Composite Success⁽¹⁾ by Hour and Age on Day 29 for Trial 004 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

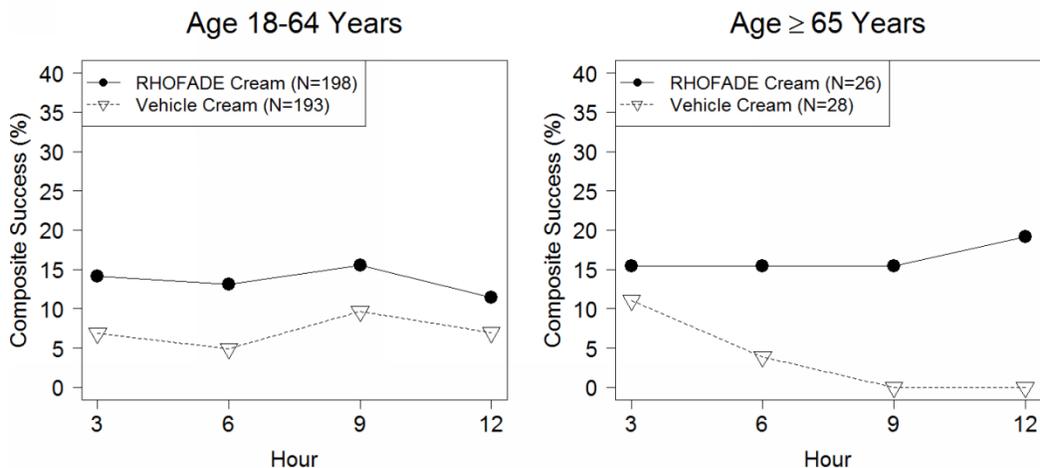
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Figure 4: Composite Success⁽¹⁾ by Hour and Age on Day 29 for Trial 005 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

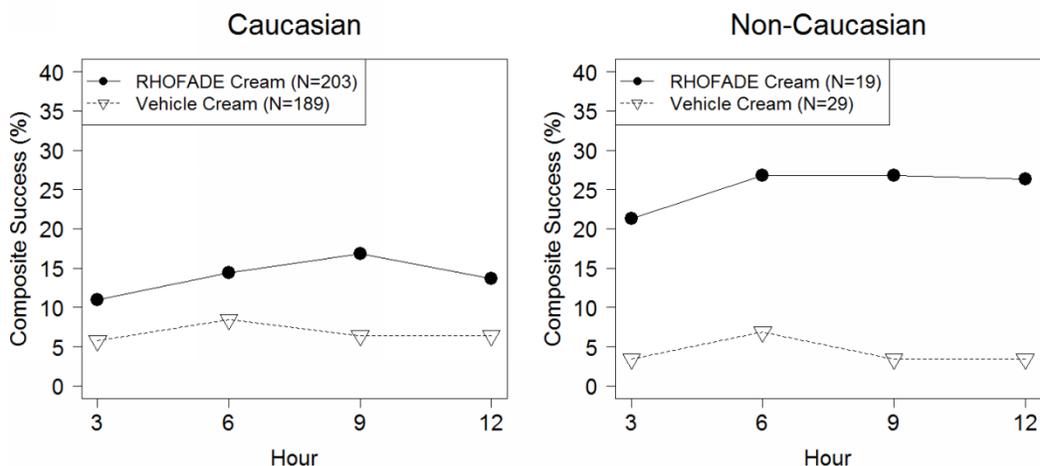
(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

It should be noted that only 13% of subjects in Trial 004 and 12% of subjects in Trial 005 were ≥65 years of age. ICH E7 guidance states that for drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow detection of clinically important differences. The controlled clinical trials did not achieve this number.

Figures 9 and 10 display the results by race (Caucasian vs. non-Caucasian). The treatment effect was larger in non-Caucasians compared to Caucasians in Trial 004. For the non-Caucasians in Trial 005, the response rate at hour 3 was higher in the vehicle arm compared to the RHOFADe arm. It should be noted that only 11% of subjects in Trial 004 and 9% of subjects in Trial 005 were non-Caucasian.

Figure 5: Composite Success⁽¹⁾ by Hour and Race on Day 29 for Trial 004 (ITT, MI⁽²⁾)



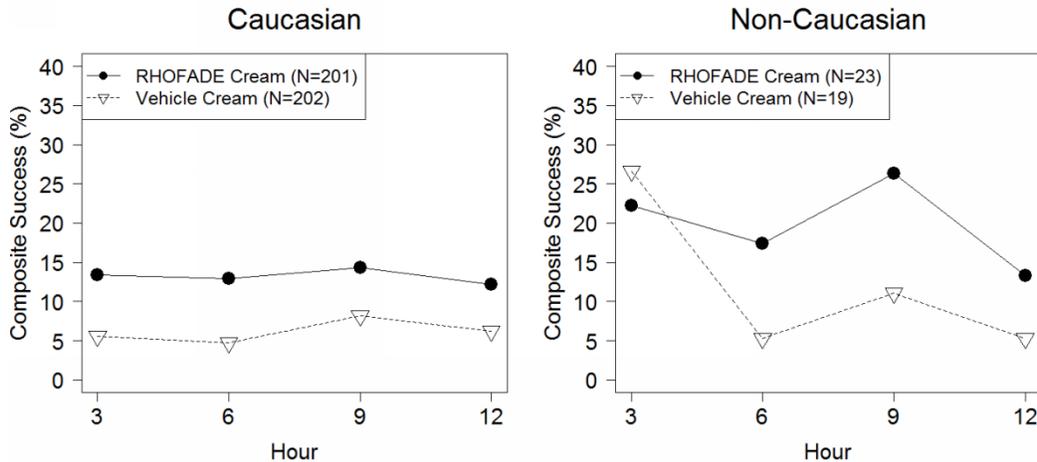
Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

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- (1) Composite success is defined as 2-grade improvement on both CEA and SSA.
- (2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

Figure 6: Composite Success⁽¹⁾ by Hour and Race on Day 29 for Trial 005 (ITT, MI⁽²⁾)

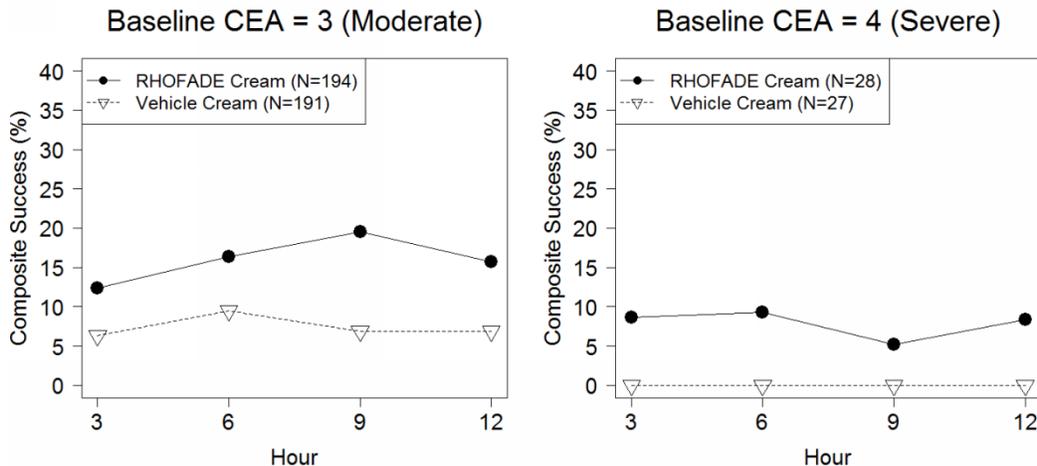


Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

- (1) Composite success is defined as 2-grade improvement on both CEA and SSA.
- (2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

Figures 11, 12, 13 and 14 present the results by baseline disease severity (i.e., baseline CEA and SSA scores) and the treatment effects were generally similar across the severity subgroups.

Figure 7: Composite Success⁽¹⁾ by Hour and Baseline CEA Score on Day 29 for Trial 004 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

- (1) Composite success is defined as 2-grade improvement on both CEA and SSA.
- (2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

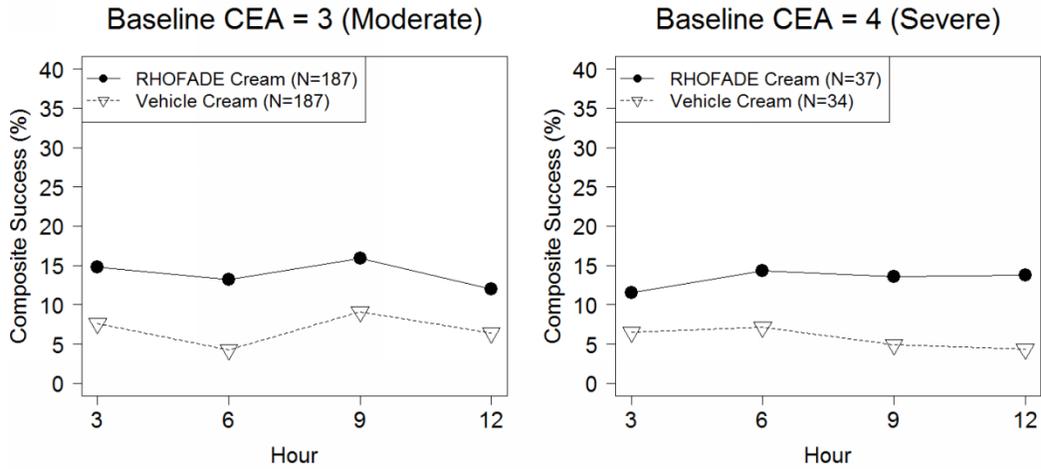
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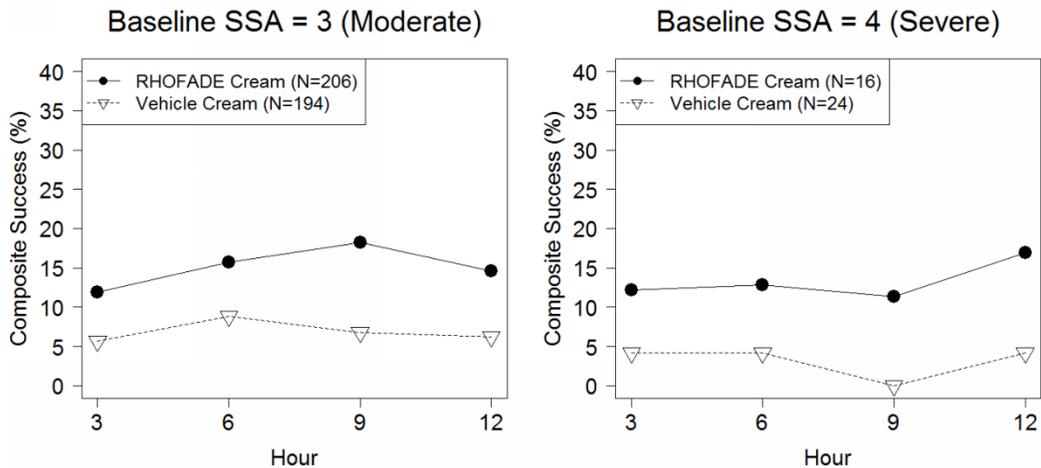
Figure 8: Composite Success⁽¹⁾ by Hour and Baseline CEA Score on Day 29 for Trial 005 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

- (1) Composite success is defined as 2-grade improvement on both CEA and SSA.
- (2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

Figure 9: Composite Success⁽¹⁾ by Hour and Baseline SSA Score on Day 29 for Trial 004 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

- (1) Composite success is defined as 2-grade improvement on both CEA and SSA.
- (2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

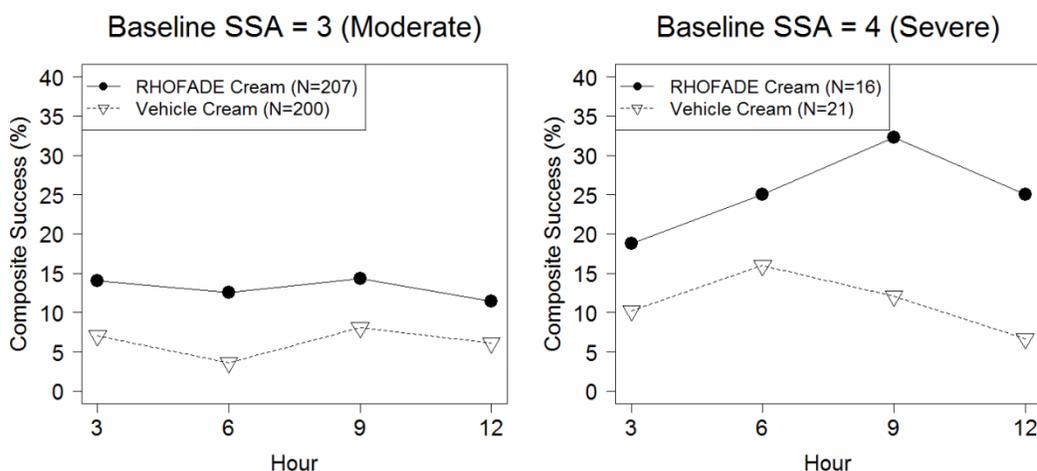
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Figure 10: Composite Success⁽¹⁾ by Hour and Baseline SSA Score on Day 29 for Trial 005 (ITT, MI⁽²⁾)



Source: Statistics Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

(3) One subject (15001-3308) in the RHOFADE arm had a baseline SSA score of 2 (mild) and is not included in the plot.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Phase 2 studies explored several concentrations (from 0.01% to 1.5%) and 2 dosing schedules (BID and QD). A statistically significant reduction in facial erythema was also demonstrated with the 1.5% and 1.0% doses of oxymetazoline cream following twice-daily dosing (with the second dose administered 6 hours after the first dose); however, no additional treatment benefit was observed with twice-daily dosing over once-daily dosing. All concentrations of oxymetazoline were well tolerated.

The primary dose-ranging study exploring efficacy was trial 199201-002 (002). The objective of this study was to evaluate the safety and efficacy of oxymetazoline HCl cream 0.5%, 1.0%, and 1.5%, once-daily and twice-daily topical application compared with vehicle for 28 consecutive days for the treatment of patients with moderate to severe facial erythema associated with rosacea.

The dose regimen included 8 groups:

Group 1 Oxymetazoline 0.5% once-daily (hereafter referred to as Oxy 0.5% QD)

Group 2 Oxymetazoline 1.0% once-daily (hereafter referred to as Oxy 1.0% QD)

Group 3 Oxymetazoline 1.5% once-daily (hereafter referred to as Oxy 1.5% QD)

Group 4 Vehicle once-daily (hereafter referred to as vehicle QD)

Group 5 Oxymetazoline 0.5% twice-daily (hereafter referred to as Oxy 0.5% BID)

Group 6 Oxymetazoline 1.0% twice-daily (hereafter referred to as Oxy 1.0% BID)

Group 7 Oxymetazoline 1.5% twice-daily (hereafter referred to as Oxy 1.5% BID)

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Group 8 Vehicle twice-daily (hereafter referred to as vehicle BID)

A total of 357 patients were enrolled, of which 356 patients were randomized: 45, 45, 45, 44, 44, 44, 45, and 44 patients were randomized to the Oxy 0.5% QD, Oxy 1.0% QD, Oxy 1.5% QD, vehicle QD, Oxy 0.5% BID, Oxy 1.0% BID, Oxy 1.5% BID, and vehicle BID treatment groups, respectively.

Key Inclusion Criteria: Male or female patients 18 years of age or older with moderate to severe facial erythema associated with rosacea defined as a grade of ≥ 3 on the CEA scale and the SSA.

The primary efficacy variable was defined as patients with at least a 2-grade improvement on both CEA and SSA from baseline (predose on day 1) over a 12-hour period measured at hours 2, 4, 6, 8, 10, and 12 on day 28.

A statistically significant reduction in facial erythema as measured by the composite assessment, i.e., the proportions of patients with at least a 2-grade decrease (improvement) from baseline over a 12-hour period for both the CEA and SSA on day 28, was demonstrated with the 1.5% and 1.0% doses of oxymetazoline cream following twice-daily dosing ($p = 0.006$ and $p = 0.021$, respectively), and with all 3 doses of oxymetazoline cream (1.5%, 1.0%, and 0.5%) following once-daily dosing ($p = 0.012$, $p = 0.006$, and $p = 0.049$, respectively).

Based on this study outcome, Oxymetazoline cream, 1.0%, once daily was selected as the dose for further study in Phase 3.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Adrenergic-mediated vasoconstriction is associated with unwanted pharmacological and clinical phenomena, such as tachyphylaxis, tolerance, and rebound vasodilation. Tachyphylaxis occurs in the presence of alpha-adrenergic agonists by reducing the availability of receptors in an effort to maintain homeostasis within the affected cells.

The tables below demonstrate the composite success by hour and day for Trials 004 and 005, respectively.

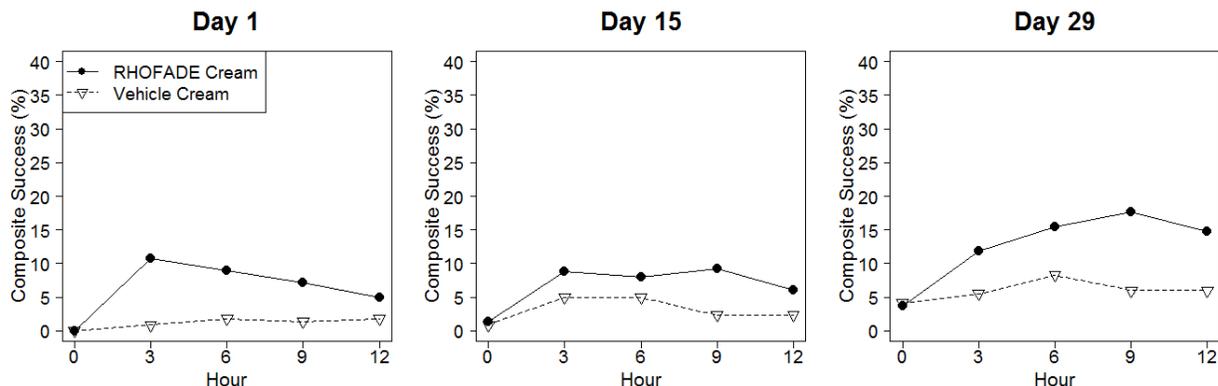
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Table 12: Composite Success⁽¹⁾ by Hour and Day for Trial 004 (ITT, MI⁽²⁾)

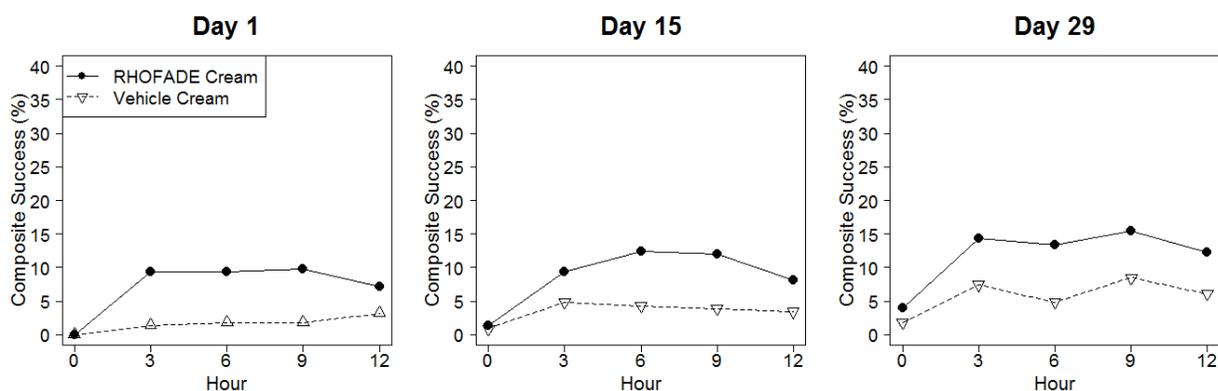


Source: Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

Table 13: Composite Success⁽¹⁾ by Hour and Day for Trial 005 (ITT, MI⁽²⁾)



Source: Reviewer's Analysis (same results as Applicant's Analysis)

(1) Composite success is defined as 2-grade improvement on both CEA and SSA.

(2) Missing data was imputed using the multiple imputation (MI) approach. The rates displayed are the averages over the 20 imputed datasets.

There is no apparent decrease in efficacy effect during the treatment period. However, an assessment period of 29 days may not be sufficiently long enough to assess for tachyphylaxis. Therefore, the reviewer concludes that the data allows only for a conclusion that no evidence of tachyphylaxis was observed with short-term use of oxymetazoline cream, 1%.

Also, it should be noted that the evaluation of composite success on Day 1 and Day 15 was designated as exploratory endpoints and not included in the multiplicity testing strategy (b) (4)

6.1.10 Additional Efficacy Issues/Analyses

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Both, the CEA and the SSA are single item instruments assessing severity of facial erythema (redness) from the clinician's perspective and the patient's perspective respectively. The protocol-specified primary efficacy endpoint (presented in section 6.1.4) was the proportion of subjects with composite success (defined as a 2-grade improvement from baseline in both CEA and SSA) measured at hours 3, 6, 9 and 12 on Day 29. The protocol also specified the proportion of subjects with at least a 2-grade improvement from baseline on SSA measured at hours 3, 6, 9, and 12 on Day 29 as a secondary endpoint. The CEA component was specified as an "other" efficacy endpoint and was not included in the multiplicity testing strategy. Of note, a nearly identical scale (PSA) was used as the patient assessment in a composite primary endpoint for the approval of Mirvaso (brimonidine) gel, 0.33% for the same indication.

The applicant submitted the PRO dossier for the SSA. The sponsor did not provide an evidence dossier for the CEA. The Clinical Outcome Assessment (COA) team was consulted to review the dossier.

The CEA is a single-item ClinRO with 5 response options (i.e., 0=Clear skin with no signs of erythema to 4=Severe erythema/fiery redness, and a photo guide (with 20 photos, 4 photos represent each of the five facial redness severity categories). The SSA is a self-administered electronic tablet device with a single item rated on a 5-point categorical scale (i.e., 0=No signs of unwanted redness to 4=Severe redness). The recall period is 'right now'. Both instruments used in the primary analysis (CEA and SSA) used the same set of photos. The photonumeric guide is presented in Appendix 9.4.

COA found that the SSA is not an ideal instrument for a variety of reasons:

- content validity
- test-retest scoring was not optimal
- concordance with the CEA is unknown

See COA reviewer Yasmin Choudhry's consult response for full details on the SSA instrument for which a PRO dossier was submitted.

When subjects were asked to rank each of 20 photographs of individuals with rosacea into one of five categories by severity, they had difficulty sorting photographs and matched up response options with more than one category of photographs. The most common problem among patients completing the photograph-sorting exercise was difficulty distinguishing between the milder categories. The COA reviewer found the photographs to be overlapping in grades 2/3 and 3/4 as well.

Reviewer comment: This reviewer finds that while grades 0 and 1 appear to overlap, they are reasonably distinct from grades 3 and 4. Grade 2 appears to be less distinct.

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COA also found that the instrument may be unreliable due to a low test-retest score.

This test determines the reproducibility of scores and refers to an instrument’s ability to reproduce identical measurements between testing when no change has occurred in the underlying concept. Placebo treated subjects were used as the testing population.

However, the ability to measure this concept may be difficult to measure in rosacea.

The disease itself flares and patients with rosacea experience fluctuating degrees of erythema based on many other factors, undermining the premise that no change has occurred in the underlying concept.

Given the limitations of the SSA instrument Dr. Guerra conducted analyses of additional definitions of success based on CEA and SSA and how the scores match up (i.e., concordant and discordant). The table below presents the baseline CEA and SSA scores for the pivotal Phase 3 trials (Trials 004 and 005). In Trial 005, one subject (b) (6) in the Rhofade arm had a baseline SSA score of 2 (mild); however, this subject continued in the trial and was treated. The majority of subjects appear to be considered moderated on both scales.

Table 14: Baseline CEA and SSA Scores for Trials 004 and 005 (ITT)

		Trial 004 (N=440)			Trial 005 (N=445)				
		Baseline CEA			Baseline CEA				
		3 - Moderate	4 - Severe	Total	3 - Moderate		4 - Severe	Total	
Baseline SSA	2 - Mild	0	0	0	Baseline SSA	2 - Mild	1 (0.2%)	0	1 (0.2%)
	3 - Moderate	365 (83.0%)	35 (8.0%)	400 (91.0%)		3 - Moderate	350 (78.7%)	57 (12.8%)	407 (91.5%)
	4 - Severe	20 (4.5%)	20 (4.5%)	40 (9.0%)		4 - Severe	23 (5.2%)	14 (3.1%)	37 (8.3%)
	Total	385 (87.5%)	55 (12.5%)	440		Total	374 (84.0%)	71 (16.0%)	445

CEA and SSA scores on Day 29 are shown individually for comparison. The table below presents the CEA and SSA scores on Day 29 by hours (3, 6, 9 and 12) for Trials 004 and 005.

Table 15: CEA and SSA Scores on Day 29 by Hours for Trials 004 and 005 (ITT, MI)

	Trial 004				Trial 005			
	CEA		SSA		CEA		SSA	
	Rhofade (N=222)	Vehicle (N=218)	Rhofade (N=222)	Vehicle (N=218)	Rhofade (N=224)	Vehicle (N=221)	Rhofade (N=224)	Vehicle (N=221)
Hour 3								
0 - Clear	8%	1%	0.5%	0%	6%	1%	1%	1%
1 - Almost Clear	27%	19%	17%	9%	30%	19%	21%	12%
2 - Mild	31%	33%	45%	35%	38%	40%	46%	40%
3 - Moderate	30%	40%	37%	51%	23%	37%	30%	43%

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4 - Severe	4%	7%	0.5%	5%	3%	3%	2%	4%
Hour 6								
0 - Clear	4%	1%	2%	1%	3%	1%	2%	1%
1 - Almost Clear	28%	16%	19%	11%	28%	16%	20%	11%
2 - Mild	32%	33%	42%	34%	40%	41%	43%	41%
3 - Moderate	31%	41%	36%	48%	25%	40%	33%	43%
4 - Severe	5%	8%	1%	6%	4%	2%	2%	5%
Hour 9								
0 - Clear	6%	2%	2%	1%	2%	1%	2%	2%
1 - Almost Clear	25%	15%	19%	9%	30%	17%	17%	12%
2 - Mild	29%	31%	44%	36%	37%	50%	48%	40%
3 - Moderate	34%	45%	34%	49%	28%	38%	30%	43%
4 - Severe	6%	7%	1%	5%	3%	2%	3%	3%
Hour 12								
0 - Clear	6%	2%	2%	1%	2%	2%	2%	2%
1 - Almost Clear	17%	13%	21%	8%	22%	16%	19%	11%
2 - Mild	32%	32%	39%	35%	34%	36%	39%	35%
3 - Moderate	37%	45%	38%	50%	37%	42%	36%	48%
4 - Severe	9%	8%	1%	7%	5%	5%	3%	4%

Source: Statistical Reviewer's Analysis

(4) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 20 imputed datasets.

Looking at the scales separately, the CEA reported a slightly higher treatment effect SSA. The clinicians generally categorized subjects into the extremes (e.g. clear and severe) more frequently than the subject's themselves.

The table below presents the results using various definitions of success based on CEA and SSA on Day 29 for Trials 004 and 005. The protocol-specified primary efficacy endpoint was the proportion of subjects with composite success (2-grade improvement from baseline on both CEA and SSA) measured at hours 3, 6, 9, and 12 on Day 29. It should be noted that none of the additional success criteria presented in this table were included in the multiplicity testing strategy; therefore, the p-values should be viewed as nominal.

Table 16: Results using Various Definitions of Success Based on CEA and SSA on Day 29 for Trials 004 and 005 (ITT, MI⁽¹⁾)

Success Criteria	Time	Trial 004			Trial 005		
		Rhofade Cream (N=222)	Vehicle Cream (N=218)	P-value ⁽¹⁾	Rhofade Cream (N=224)	Vehicle Cream (N=221)	P-value ⁽¹⁾
≥2-grade improvement on both CEA and SSA (Primary Endpoint)	Hour 3	12%	6%	<0.001	14%	7%	0.001
	Hour 6	16%	8%		13%	5%	
	Hour 9	18%	6%		16%	9%	
	Hour 12	15%	6%		12%	6%	

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≥2-grade improvement on CEA and SSA score of 0 or 1	Hour 3	11%	5%	0.001	13%	6%	0.002
	Hour 6	15%	8%		12%	3%	
	Hour 9	17%	6%		14%	7%	
	Hour 12	14%	6%		11%	6%	
≥2-grade improvement on CEA and SSA score of 0	Hour 3	0.5%	0%	0.425*	0.5%	0.5%	0.399*
	Hour 6	1.4%	0.5%		1.8%	0%	
	Hour 9	1.8%	0.9%		2.3%	1.8%	
	Hour 12	0.9%	0.5%		0.9%	0.9%	
Score of 0 or 1 on both CEA and SSA	Hour 3	11%	5%	0.002	13%	6%	0.002
	Hour 6	14%	8%		12%	3%	
	Hour 9	17%	6%		13%	7%	
	Hour 12	14%	6%		11%	6%	
CEA score of 0	Hour 3	8%	0.5%	0.004*	6%	0.5%	0.003*
	Hour 6	4%	1%		3%	1%	
	Hour 9	6%	2%		2%	1%	
	Hour 12	6%	2%		2%	2%	
SSA score of 0	Hour 3	0.5%	0%	0.211*	1%	1%	0.959*
	Hour 6	2%	0.5%		2%	1%	
	Hour 9	2%	1%		2%	1%	
	Hour 12	2%	1%		2%	2%	

Source: Statistical Reviewer's Analysis

- (1) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 20 imputed datasets.
- (2) P-value is calculated using imputed data and based on a GEE model with treatment, site and timepoint (hours 3, 6, 9 and 12) as factors in the model. For p-values marked with *, the site covariate had to be removed for the model to converge.

Few subjects achieved a score of clear and even a fewer number of subjects rated themselves a 0 on the SSA; the deltas are small. The overall treatment effect is modest, although statistically significant. The results from the primary endpoint (2-grade improvement from baseline in both CEA and SSA) appear to be driven by ≥2-grade improvement on CEA and SSA score of 1.

Despite the limitations of the SSA scale identified, it is this reviewer's opinion that the changes seen (and supported by the CEA) are likely to be clinically meaningful to some patients. Approval of the product would represent a second product specific for the treatment with persistent erythema of rosacea, which is a common clinical challenge in rosacea-affected patients who are already using recognized medical therapies, and has been described as an "unmet need" in rosacea therapy.

7 Review of Safety

Safety Summary

The applicant provided substantial evidence to support the safety of once daily use of oxymetazoline HCl cream 1.0%. The applicant assessed the short-term safety of oxymetazoline HCl cream 1.0% in trials with treatment periods of 28/ 29 days that evaluated subjects with facial erythema of rosacea. Adverse events in the integrated safety database that were most commonly reported were application site reactions.

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The applicant assessed the long-term safety of their product in a 52 week trial which evaluated subjects in sufficient numbers and with sufficient exposures, consistent with the recommendations in the ICH E1A Guideline for Industry. No new safety concerns were identified in the long-term trial.

No serious adverse events reported appear to be treatment related. Severe application site reactions (dermatitis, erythema, pain, and pruritus) leading to study discontinuation were reported. Based on dermal tolerability assessments and provocative dermal safety studies, oxymetazoline HCl cream 1.0% appears reasonably tolerated.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The proposed dosage for Rhofade is oxymetazoline HCl cream 1.0% daily (QD). Specifically: apply a pea-sized amount once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin, avoiding the eyes and lips. Phase 3 Trails 004 and 005 included 2 treatment groups: oxymetazoline HCl cream 1.0% and vehicle to be applied as in the proposed labeled dose. Phase 2 study 002 included 8 treatment groups, with doses above and below the dosage studied in Phase 3: oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% QD; oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% BID; and vehicle QD and BID. Additional safety from some of the treatment arms was provided from this Phase 2 study as well as from data from an open-label, long-term safety study in which all patients were treated with oxymetazoline HCl cream 1.0% (Study 006).

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAE) were defined as a postbaseline adverse event in which

- the onset date was on or after the date of the first study treatment or
- the onset date was prior to the date of the first study treatment and
 - the severity worsened on or after the date of the first study treatment or
 - the event became serious on or after the date of the first study treatment

TEAEs were coded using the following MedDRA versions:

- version 16.0 for Study 002
- version 17.1 for Study 004
- version 18.0 for Studies 005 and 006

For the ISS, the applicant coded TEAE data from the integrated studies using MedDRA version 18.0.

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7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary evidence of safety to support oxymetazoline HCl cream 1.0% for the treatment of persistent facial erythema associated with rosacea in adults 18 years of age or older, is based on:

- integrated data for the safety populations from the 2 pivotal studies with oxymetazoline HCl cream 1.0% (pivotal phase 3 Studies 004 and 005)
- integrated data for the safety populations from 3 randomized, vehicle-controlled studies with oxymetazoline HCl cream 1.0% that included a 28- or 29-day treatment period in adult patients with moderate to severe erythema associated with rosacea (Studies 004 and 005 and phase 2 Study 002)
- data from 1 open-label, long-term safety study in which all patients were treated with oxymetazoline HCl cream 1.0% (Study 006)

Phase 3 Studies 004 and 005 included 2 treatment groups: oxymetazoline HCl cream 1.0% QD and vehicle QD. Study 002 included 8 treatment groups: oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% QD; oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% BID; and vehicle QD and BID. For the purpose of the integrated analyses, the applicant only included the treatment arms of once daily with oxymetazoline HCl cream 1.0% or vehicle. The safety populations include all patients who received at least 1 application of oxymetazoline HCl cream 1.0%. This reviewer also evaluated the 1.5% QD and 1.0% and 1.5% BID groups for safety signals.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Oxymetazoline HCl solution has been marketed in the United States (US) as an over-the-counter treatment for nasal congestion (0.05% nasal spray) for more than 40 years, and for temporary relief of ocular redness (0.025% ophthalmic solution) for 30 years.

The clinical development program of oxymetazoline for the treatment of persistent facial erythema associated with rosacea comprises 13 studies in which oxymetazoline HCl cream was administered. Across these 13 studies, 2404 study subjects were enrolled. Of these, 2062 patients with rosacea were included in the safety populations of 9 studies in which oxymetazoline HCl cream of any concentration (from 0.05% to 1.5%) or vehicle was applied topically to the face. In total, 929 patients with rosacea received at least 1 application of oxymetazoline HCl cream 1.0% QD, per the target indication; 440 of these patients applied oxymetazoline HCl cream 1.0% QD for up to 1 year in a long-term open-label study. In addition, 182 patients with rosacea received at least 1

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application of oxymetazoline HCl cream at a higher dosage (1.0% applied twice daily [BID] or 1.5% applied QD or BID).

Reviewer comment: Rosacea is a chronic indication, and the applicant evaluated the long-term safety of their product by conducting the long-term trial 006, which provided exposures in accordance with ICH Guideline E1A. Given the extensive history of use as an over-the-counter product, the numbers of subjects and durations of exposure are sufficient to address the recommendations in the ICH E1A Guideline.

7.2.2 Explorations for Dose Response

Phase 2 studies explored several concentrations (from 0.01% to 1.5%) and 2 dosing schedules (BID and QD). A statistically significant reduction in facial erythema was also demonstrated with the 1.5% and 1.0% doses of oxymetazoline cream following twice-daily dosing (with the second dose administered 6 hours after the first dose); however, no additional treatment benefit was observed with twice-daily dosing over once-daily dosing. All concentrations of oxymetazoline were well tolerated.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate to explore potential adverse reactions. There was no special animal and/or in vitro testing for this product.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate in methodology and scheduling. Safety data presentation included:

- Adverse events for all trials
- Vital signs summaries for all trials
- Dermal tolerability and focused adverse event assessments for all trials
- Laboratory assessments for trial 002
- ECG assessments for trial 002
- Post-treatment CEA/ SSA assessments to evaluate rebound

The adequacy of protocols 004, 005, 006 were discussed at the End-of-Phase-2 meeting on 12/18/2013 and were found to be acceptable. Additionally, Dr. Jane Liedtka reviewed the protocols (5/19/2014) not under a SPA and no additional safety monitoring was recommended. The applicant conducted four dermal safety studies. A waiver for thorough QT study was granted after consult with the QT-IRT team.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant conducted in vitro studies to evaluate the metabolism and explore the drug interaction potential of oxymetazoline.

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The following is a summary of oxymetazoline metabolism and drug interaction findings from Dr. Yanhui Lu's clinical pharmacology review:

- The results of in vitro studies using human liver microsomes showed that oxymetazoline could be metabolized into mono-oxygenated and dehydrogenated products of oxymetazoline. The extent of metabolism is limited; and approximately 96% of oxymetazoline remained not metabolized after 120 minute incubation with human liver microsomes.
- The results of in vitro studies using human liver microsomes showed that oxymetazoline at concentrations up to 100 nM did not inhibit enzyme activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.
- The results of in vitro studies using primary cultures of cryopreserved human hepatocytes showed that oxymetazoline at concentrations up to 100 nM did not induce mRNA expression of CYP1A2, CYP2B6, or CYP3A4.
- An exploratory analysis indicated that oxymetazoline exposure was not increased in subjects who had concomitant use of oral moderate CYP2C19 inhibitors in Study 199201-002.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant incorporated assessments directed at capturing potential cardiac adverse events for similar drugs in the class. Clinical assessments in the development program included vital signs in studies 002, 004, and 005. Electrocardiograms assessments were conducted in trial 002.

7.3 Major Safety Results

7.3.1 Deaths

In controlled trials, one death occurred in a vehicle-treated subject (b) (6) in study 004. A 66-year-old, Caucasian male with a history of myocardial infarction, diabetes type 2, hyperlipidemia, experienced sudden cardiac death. The cause of death was atherosclerotic cardiovascular disease. There were no deaths reported in the open-labelled, long-term safety study.

Reviewer comment: Due to this being a single event in the development program and the subject's comorbid diseases, causality cannot be determined.

7.3.2 Nonfatal Serious Adverse Events

Few SAEs occurred in the controlled core studies (002, 004, and 005). During the entire study periods of the Core Studies (inclusive of the treatment and posttreatment periods combined), serious TEAEs were reported by 1.0% (5/489) and 1.2% (6/483) of patients in the Oxy 1.0% and vehicle groups, respectively. Across all Core Studies, over

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the entire study periods, no serious TEAE was reported by more than 1 patient in either treatment group. Across all studies, no serious TEAE was considered by the investigator to be treatment related. There is one additional SAE reported for the oxymetazoline 1.0% twice daily dose. The cases are described below:

Oxy 1.0% BID

- Patient (b) (6) a 50-year-old Caucasian female randomized to the Oxy 1.0% BID retreatment group, experienced a serious adverse event of cerebrovascular accident on day 29 of study drug administration. The patient was hospitalized and discharged after 1 day with sequelae of memory changes. This event was not considered to be related to study medication by the investigator and did not result in study discontinuation.

Oxy 1.0% QD

- Patient (b) (6), a 63-year-old Caucasian male with a medical history of left anterior cruciate ligament (ACL) injury and ACL surgery, was randomized to the Oxy 1.0% QD group. The patient experienced a serious adverse event of chondrocalcinosis pyrophosphate (pseudogout) in the left knee on posttreatment day 42. The subject had surgery on his left knee 2 days later, and was administered methylprednisolone sodium succinate for swelling, and further treatment with oral prednisone. The patient was discharged the next day with resolution without sequelae of the chondrocalcinosis pyrophosphate. This SAE does not appear to be related to the study treatment.
- Patient (b) (6) had a fall which occurred during the treatment 62 year old Hispanic male with a history of hypertension and was taking lisinopril concomitantly period on day 14, was of moderate severity, and was serious because it resulted in hospitalization. The investigator considered the fall to be not related to study treatment. However, no details regarding the nature of the fall are provided in order for this reviewer to concur. It is not clear of dizziness/ hypotension/ hypertension or cardiac causes were involved. The patient discontinued from the study on (b) (6) due to personal reasons.
- Patient (b) (6), 45 year old Caucasian female road traffic accident occurred during the treatment period on day 27, and was serious because it resulted in hospitalization for observation. Subject experienced a skin abrasion according to the report investigator considered both events to be not related to study. However, no details regarding the nature of the MVA are provided in order for this reviewer to concur. It is not clear if dizziness/ hypotension/ hypertension or cardiac causes were involved.

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- Patient [REDACTED] ^{(b) (6)}, 46-year-old Caucasian female with a history for osteoarthritis for approximately greater than 1-5 years. Osteoarthritis was reported on day 33 in the post-treatment period. The subject was hospitalized for an elective right total knee arthroplasty after completion of treatment. The investigator considered the osteoarthritis to be not related to study treatment and this reviewer concurs.
- Patient [REDACTED] ^{(b) (6)}, 49-year-old Caucasian female had a suspicious lesion of the left ala of her nose that was present prior to the screening visit for approximately 6-12 months. Basal cell carcinoma was reported on day 18 of the treatment period after a biopsy confirmed the diagnosis. The basal cell was removed and the subject completed the study. The investigator considered the basal cell carcinoma to be not related to study treatment and this reviewer concurs.

Reports of SAEs associated with treatment with Vehicle are as follows:

- Pneumonia
- atrial fibrillation with CHF
- goiter and hyperparathyroidism
- motor vehicle accident resulted in hospitalization for multiple fractures
- rotator cuff repair with surgical complications

There were 3.4% (15/440) subjects reporting SAEs in open-labelled study (006) which included

- basal cell carcinoma (6)
- squamous cell carcinoma (1)
- cholangiocarcinoma (1)
- chest pain/ angina (2)
- Parkinson's disease (1)
- Chronic sinusitis (1)
- sepsis (1)
- cholecystitis (1)
- appendicitis (1)

Reviewer comment: A review of the patient narratives for non-melanoma skin cancers was not suggestive of a relationship between the drug and the adverse event. Although some appeared on the face/ears as would be expected, the lesions occurred outside of the recommended area of application. A review of the chest pain cases found confounding medical conditions and subjects completed the study. The remainder of the cases do not appear to be related to the study drug.

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7.3.3 Dropouts and/or Discontinuations

During the treatment period of the Core Studies (002, 004 and 005), study discontinuations due to TEAEs were reported by 2.2% (11/489) and 0.4% (2/483) of patients in the Oxy 1.0% and vehicle groups, respectively. The TEAEs leading to the discontinuation of patients in the Oxy 1.0% group were: application site dermatitis (1.2% [6/489] of patients); application site erythema (0.4% [2/489] of patients); and application site pruritus, hypersensitivity, and headache (1 patient [0.2%] each). The 2 TEAEs leading to the discontinuation of vehicle-treated patients were angioedema and rotator cuff syndrome. Rotator cuff syndrome was the only serious TEAE that led to study discontinuation through day 28/29 of treatment. During the posttreatment period, discontinuations due to TEAEs were reported by no patients in the Oxy 1.0% group

In Study 006, 1.4% (6/440) of patients discontinued the study due to TEAEs during the first 29 days. All of these TEAEs were application-site TEAEs and were considered by the investigator to be treatment related. No TEAE leading to study discontinuation was a serious TEAE. A summary of discontinuations for the first month of therapy from the core studies and trial 006 are shown in the table below.

Table 17: Subjects Who Discontinued Study due to TEAEs through Day 28/29 of Treatment

System Organ Class Preferred Term	Pooled Core Studies ^a		Study 199201-006
	Oxy 1.0% (N = 489)	Veh (N = 483)	Oxy 1.0% (N = 440)
Overall	11 (2.2)	2 (0.4)	6 (1.4)

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General disorders and administration site conditions			6 (1.4)
Overall	9 (1.8)	0 (0.0)	3 (0.7)
Application site dermatitis	6 (1.2)	0 (0.0)	2 (0.5)
Application site erythema	2 (0.4)	0 (0.0)	0 (0.0)
Application site pruritus	1 (0.2)	0 (0.0)	2 (0.5)
Application site pain	0 (0.0)	0 (0.0)	1 (0.2)
Application site hypoaesthesia	0 (0.0)	0 (0.0)	1 (0.2)
Application site paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders			0 (0.0)
Overall	1 (0.2)	0 (0.0)	0 (0.0)
Hypersensitivity	1 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders			0 (0.0)
Overall	0 (0.0)	1 (0.2)	0 (0.0)
Rotator cuff syndrome	0 (0.0)	1 (0.2)	0 (0.0)
Nervous system disorders			0 (0.0)
Overall	1 (0.2)	0 (0.0)	0 (0.0)
Headache	1 (0.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders			0 (0.0)
Overall	0 (0.0)	1 (0.2)	0 (0.0)
Angioedema	0 (0.0)	1 (0.2)	0 (0.0)

Oxy 1.0% = oxymetazoline HCl cream 1.0% group; TEAEs = treatment-emergent adverse events; Veh = vehicle group

Note: Treatment period for Study 199201-002 was through day 28. Treatment period for Studies 199201-004 and 199201-005 was through day 29. Data reported from Study 199201-006 are through day 29. All TEAEs are represented, regardless of relationship to treatment. Within each preferred term, a patient is counted at most once. a Studies 199201-002, 199201-004, and 199201-005

Source: Module 5.3.5.3, ISS Table 3-7 and Module 5.3.5.2, CSR 199201-006, Table 14.6-12

Reviewer comment: Application site reactions, some severe, were reported to lead to study discontinuation for a small percentage of subjects. Additional application site reactions leading to discontinuation occurred throughout the duration of long-term trial 006. Section 7.5.2 describes the total number of drop outs over the 52 weeks for trial 006. Of the total number of subjects (in trials 002, 004, 005 and 006) who discontinued treatment with oxymetazoline 1% due to an application site reaction, approximately 66% of the reactions occurred within the first 2 weeks of treatment and the remainder after 1 month of treatment. There does not appear to be an increase in severity of application site reactions with a longer time-to-onset/ duration of treatment. The majority of reactions resolved without sequelae. Labeling for application site reactions may be considered. However, there does not appear to be a way to predict which patients will have reactions. Also, it is highly likely that patients will discontinue therapy should an application site reaction occur.

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7.3.4 Significant Adverse Events

During the entire study periods of the Core Studies (inclusive of the treatment and posttreatment periods combined), 7 severe TEAEs were reported by 5 subjects in the Oxy 1.0%. Severe TEAEs reported in the Oxy 1.0% group were migraine (2), application site dermatitis(1), osteoarthritis (1); application site erythema, application site pain, and application site pruritus by 1 subject. Sixteen severe TEAEs reported in 7 subjects in the vehicle group and were goiter and hyperparathyroidism by 1 patient; rotator cuff syndrome, procedural pain, CHF, HTN by 1 subject; vomiting, peri-arthritis, joint dislocation, injection site laceration, atherosclerosis by 1 subject each; and one subject with multiple AEs related to traumatic injury.

Additional severe TEAEs were reported in open-labelled study 006 (see section 7.5.2). There were additional reports of application site reactions: dermatitis (4), erythema (2), rosacea (3), pain (1), and pruritus (1). There were also reports of basal cell carcinoma (2) and photosensitivity reaction/ sunburn (2).

7.3.5 Submission Specific Primary Safety Concerns

Alpha-adrenergic agonists may cause systemic and ocular hypertension. Both of these safety concerns are discussed here. This class of products may also potentiate vascular insufficiency.

Hypertension

In pivotal studies 004 and 005 the preferred term of hypertension was reported for a similar number of subjects in both treatment arms, 2/445 (0.4%) and 3/439 (0.7%) for oxymetazoline HCl cream 1% and vehicle, respectively.

In long-term study 006, 2.5% (11/440) of patients reported adverse events of hypertension over the entire study; 1 was a pretreatment adverse event that was ongoing for the entire study and the other 10 were TEAEs reported during the 52-week treatment period. Of these 11 patients, 3 had a medical history of hypertension as reported in their medical history. Of the remaining 8 patients who did not report a medical history of hypertension, 7 patients had elevated systolic and/or diastolic blood pressure measurements at the screening or baseline (predose on day 1) visit that were not reported as pretreatment adverse events. The remaining 1 patient reporting hypertension as a TEAE had blood pressure measurements at screening within the normal reference range (120/79 mm Hg) that were subsequently elevated at the visit most closely corresponding to the TEAE onset date (148/96 mm Hg at the week 12 visit), at which point treatment with losartan was initiated.

Hypertension is a common disease and it is difficult to assess causality to any of the reported cases. The data to date, do not support an increased risk for hypertension related to treatment with oxymetazoline HCl cream 1%.

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Intraocular hypertension

Intraocular pressure (IOP) was not measured in studies evaluating the safety of oxymetazoline HCl cream 1%. Two early Phase one trials evaluating a single dose of either 0.15% or 0.5 %oxymetazoline HCl cream evaluated IOP.

Study V-101-ROSE-201 was a phase 1, single-center, 2-way crossover, relative bioavailability study comparing oxymetazoline HCl cream 0.15% and oxymetazoline HCl solution 0.05% (referred to by its trade name, Afrin, and administered as a nasal spray) in patients with moderate to severe erythematous rosacea. A total of 22 patients received (in double blind, random order) either one 0.5-g topical facial application of oxymetazoline HCl cream 0.15% or 3 sprays (0.1 mL/spray) of oxymetazoline HCl solution 0.05% (Afrin) in each nostril (total of 0.3 mg oxymetazoline). After a washout period the actives were crossed. Intraocular pressure (IOP) was measured at each treatment visit. There were no notable changes in IOP.

Study V-101-ROSE-205 was a phase 1, single-center, 2-way crossover, relative bioavailability study comparing oxymetazoline HCl cream 0.5% and oxymetazoline HCl solution 0.05% (referred to by its trade name, Afrin, and administered as a nasal spray) in patients with moderate to severe erythematous rosacea. A total of 28 patients received (in double blind, random order) either one 0.5-g topical facial application of oxymetazoline HCl cream 0.15% or 3 sprays (0.1 mL/spray) of oxymetazoline HCl solution 0.05% (Afrin) in each nostril (total of 0.3 mg oxymetazoline). After a washout period the actives were crossed. Intraocular pressure (IOP) was measured at each treatment visit. There were no notable changes in IOP with the exception of one subject who recorded an elevated IOP (> 21 mm Hg) following treatment with oxymetazoline HCl cream 0.5% and control nasal spray. However, it was determined that the patient's predose IOP values at treatment visit 1 were 26 and 25 mm Hg in the right and left eyes, respectively. At all subsequent timepoints, the IOP measurements were the same or lower in the respective eyes.

Although IOP was not measured in studies evaluating the safety of oxymetazoline HCl cream 1%, the applicant has some cross-study comparison data that suggests systemic levels for C_{max} after dermal application of oxymetazoline HCl cream 1% may approach that of nasal application of oxymetazoline HCl solution 0.05%. The applicant reports that cross comparison PK data demonstrate that following dermal administration of oxymetazoline HCl cream 1.0% QD (the to-be-marketed dose and regimen) for 28 days in the phase 2 study 199201-002, the mean steady-state plasma C_{max} was 27% of the C_{max} observed after single-dose treatment (3 sprays in each nostril) with Afrin, in previous studies.

It is recommended that labeling include class warning information on potential risks of systemic and intraocular hypertension.

Vascular Insufficiency

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The studies in support of approval were conducted to exclude subjects with syndromes of vascular insufficiency (as was done for Mirvaso). Subjects were excluded if they had a 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. However in trials 004 and 005, there were 18 subjects with a history of coronary insufficiency (based on preferred terms of MI, CAD, or angina), one subject with a history of vasculitis and one subject with a history of Bachel's disease. There does not appear to be any cases of vascular insufficiency in the treatment group based on AE reporting. There was one case of atherosclerosis reported in the vehicle group.

Because the susceptible population was not well studied, this reviewer recommends class labeling similar to that in the Mirvaso label: Rhofade should be used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thrombangiitis obliterans, scleroderma, or Sjögren's syndrome.

Although there is a tendency to move away from terms such as "use with caution" in product labeling, it is this reviewer's opinion that prescribers would likely understand the meaning of the precaution based on mechanism of action. Also, strengthening the language would imply that there is additional data, specific to this product, regarding these adverse events. At this time, there is no additional data to suggest an increased risk for class warning events with oxymetazoline cream, 1%.

Labeling should reflect the population studied as it was not studied in diseases of vascular insufficiency, narrow angle glaucoma, severe or unstable cardiovascular disease, or with concomitant treatment of MAOIs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

TEAEs were reported by 16.8% (82/489) and 12.6% (61/483) of patients in the Oxy 1.0% and vehicle group. No TEAE was reported by $\geq 2\%$ of patients in either treatment group. The most frequently reported TEAEs (reported by $\geq 1\%$ of patients in any treatment group) were headache, application site dermatitis, applications site pruritus, rosacea, and application site erythema as shown in the table below:

Table 18: Subjects Reporting Treatment-emergent Adverse Events $\geq 1\%$ in Pooled Trials 002, 004, 005 and Long-term Trial 006

System Organ Class Preferred Term	Pooled Core Studies ^a	Study 199201-006
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	Oxy 1.0% (N = 489)	Veh (N = 483)	Oxy 1.0% (N = 440)
Overall ^b	82 (16.8)	61 (12.6)	66 (15.0)
General Disorders and Administration Site Conditions			28 (6.4)
Overall	31 (6.3)	10 (2.1)	4 (0.9)
Application site dermatitis	9 (1.8)	0 (0.0)	8 (1.8)
Application site pruritus	5 (1.0)	4 (0.8)	2 (0.5)
Application site erythema	5 (1.0)	2 (0.4)	8 (1.8)
Application site pain	4 (0.8)	1 (0.2)	7 (1.6)
Application site paraesthesia	1 (0.2)	1 (0.2)	
Skin and Subcutaneous Tissue Disorders			12 (2.7)
Overall	14 (2.9)	5 (1.0)	7 (1.6)
Rosacea	7 (1.4)	1 (0.2)	8 (1.8)
Nervous System Disorders			7 (1.6)
Overall	11 (2.2)	13 (2.7)	
Headache	7 (1.4)	11 (2.3)	

Oxy 1.0% = oxymetazoline HCl cream 1.0% group; TEAEs = treatment-emergent adverse events; Veh = vehicle group
 Note: Treatment period for Study 199201-002 was through day 28. Treatment period for Studies 199201-004 and 199201-005 was through day 29. Data reported from Study 199201-006 are through day 29. All TEAEs are represented, regardless of relationship to treatment. Within each preferred term, a patient is counted at most once.

a Studies 199201-002, 199201-004, and 199201-005

b Overall number (%) of patients reporting all TEAEs

Source: Module 5.3.5.3, ISS Tables 3-1.1 and 3-2.1 and Module 5.3.5.2, CSR 199201-006, Tables 14.6-6 and 14.6-7

7.4.2 Laboratory Findings

Laboratory evaluations (i.e., hematology, chemistry, and urinalysis) were conducted in Study 199201-002. Laboratory assessments were not deemed necessary in the Pivotal Studies and Study 006 because, in Study 002, changes from baseline were small across each evaluated parameter and were not considered to be clinically relevant.

The adequacy of protocols 004, 005, 006 were discussed at the End-of-Phase-2 meeting on 12/18/2013 and were found to be acceptable. Additionally, Dr. Jane Liedtka reviewed the protocols (5/19/2014) and no additional laboratory monitoring was recommended.

Laboratory data for Phase 2 study 002 was submitted with this application. This reviewer also noted that for subjects in this trial, the mean changes from baseline at days 29 and 56/exit were small and not likely to be clinically relevant.

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7.4.3 Vital Signs

Vital sign assessments included blood pressure (systolic and diastolic blood pressure [mm Hg]), pulse rate (beats/minute), and body temperature (°C). For each of these variables, changes from baseline data were summarized for the Core Studies (002, 004, 005).

Vital sign measurements were similar across the oxymetazoline-treated patients and vehicle-treated patients and were within acceptable ranges for each timepoint. No clinically meaningful differences between treatment groups were observed with regard to vital signs measurements, in terms of raw values or changes from baseline during the treatment period (days 1, 15, and 29) or following treatment (follow-up visit and day 57/exit visit).

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were performed in Study 002. ECGs were not deemed necessary as part of the safety evaluation in the Pivotal Studies (004 and 005) and Study 006, because the results from ECG evaluations in Study 002 concluded that topical oxymetazoline HCl cream 1.5%, 1.0%, and 0.5% administered QD or BID for 28 consecutive days did not cause clinically significant ECG changes.

The adequacy of protocols 004, 005, 006 were discussed at the End-of-Phase-2 meeting on 12/18/2013. QT-IRT was consulted regarding a QT waiver/End of Phase 2 Meeting Package. The QT-IRT response was that "A TQT study is not required for this compound. ECG monitoring should be conducted as clinically indicated." Dr. Jane Liedtka reviewed the protocols (5/19/2014) and no additional ECG monitoring was recommended.

ECG summary data for Phase 2 study 002 was submitted with this application. Changes in heart rate and PR interval were consistent with the expected circadian variation. No consistent change was observed for QRS interval, QTcF interval, or diagnostic abnormalities. The analysis appears to show no clinically relevant ECG effect of 1.5%, 1.0% and 0.5% oxymetazoline topical creams, administered once or twice daily for 28 consecutive days, on ECG intervals and diagnostic abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

In studies 004 and 005, facial dermal tolerability assessments included evaluations of dryness and scaling by the investigator and evaluations of stinging/burning and itching (pruritus) by the patient. Skin blanching and disease progression involving telangiectasia and inflammatory lesions was also assessed.

Dryness/ scaling

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In each study, investigators assessed dryness and scaling in the treatment area using the same 4-point scales (0 to 3) shown in the table below:

Table 19: Scales for Investigator-assessed Dryness and Scaling

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

Source: Applicant's Table 6 SCS

Stinging/burning

In each study, the investigator asked the patient if he/she was experiencing stinging/burning and itching using the 4-point scales (0 to 3) shown in the table below:

Table 20: Patient-assessed Stinging/Burning and Pruritus Scales

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 that is 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

Source: Applicant's Table 7 SCS

In Trials 004 and 005 assessments were performed on days 1, 15, and 29 predose and at 6 and 12 hours post-dose, and once at each of the follow-up and exit visits.

Across all postbaseline timepoints for all 4 assessments (dryness, scaling, stinging/burning, and itching), the majority of subjects in both treatment groups had a

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severity rating of “none.” Similar proportions of patients in each treatment group reported at least a 1-severity grade worsening from their baseline dermal tolerability assessment, at any timepoint during the 29-day treatment periods as shown in the table below:

Table 21: Dermal Tolerability Based on the Number of Subjects with at Least a 1-Severity-Grade Worsening From Baseline at Any Timepoint through Day 29

Dermal Tolerability Assessment	Pooled Pivotal Studies ^a		
	Oxy 1.0% (N = 445)	Veh (N = 439)	P-value ^b
Investigator assessments			
Dryness	114/445 (25.6)	96/437 (22.0)	0.203
Scaling	91/445 (20.4)	76/437 (17.4)	0.246
Patient assessments			
Stinging/burning	82/445 (18.4)	88/437 (20.1)	0.520
Itching (pruritus)	86/445 (19.3)	66/437 (15.1)	0.097

Oxy 1.0% = oxymetazoline HCl cream 1.0% group; Veh = vehicle group

Note: For all assessments, the scale was: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Analysis was based on observed cases. Evaluations were conducted on days 1, 15, and 29 predose and at 6 and 12 hours postdose.

^a Studies 199201-004 and 199201-005

^b P-values were based on Pearson's chi-square test.

Source: Module 5.3.5.3, ISS Table 4.2

Based on this assessment, tolerability of the treatment arm appears similar to vehicle. However, adverse event profiles report an imbalance for application site reactions. Based on the totality of the evidence (AEs, dermal tolerability assessment, and provocative dermal safety studies), it appears that the majority of subjects were able to tolerate treatment.

Skin blanching

Skin blanching was evaluated in studies 004 and 00 using the 5-point (NA, 0 to 3) scale shown in the table below:

Table 22: Application Site Skin Blanching Scale

Score	Grade	Description
NA	NA None	Redness still present
0	Mild	Normal, healthy, skin color in the application area
1	Moderate	Slightly paler than normal in the application area
2	Severe	Much paler than normal in the application area; with or without moderate streaking
3		Unacceptable paleness leading to unnatural skin color in the application area; with or without severe streaking

Source: Applicant's Table 10 SCS

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In the Pivotal Studies 004 and 005, skin blanching evaluations were performed at predose and hours 6 and 12 postdose on days 1, 15, and 29, and once at each of the follow-up and exit visits.

The majority of subjects in both groups had skin blanching ratings of NA (redness still present) or 0 (none), indicating that most patients did not experience skin blanching with either treatment. Based on shift tables, the most common shift from baseline at postdose timepoints during the 29-day treatment period was from NA (redness still present) at baseline to 0 (none). One subject experienced severe blanching on Day 1, 6 hours post-treatment. No other subjects reported severe blanching at any timepoint.

Rosacea can progress and involve telangiectasia and inflammatory lesions. The applicant assessed both of these symptoms in their studies.

Inflammatory lesions

For Trials 004 and 005, patients were excluded if they had greater than 3 inflammatory lesions on the face. In studies 004, 005 the investigator recorded the number of inflammatory lesions (papules and/or pustules) on the patient's face as part of the safety evaluation at screening and predose on days 1, 15, and 29, and once at each of the follow-up and exit visits.

Mean inflammatory lesion counts at baseline were the same (0.6) in the Oxy 1.0% and vehicle groups in the Pivotal Studies Population. Change from baseline is shown in the table below:

Table 23: Inflammatory lesion Count: Change from Baseline

Visit ^a	Pooled Pivotal Studies ^b			
	Statistic	Oxy 1.0% (N = 445)	Veh (N = 439)	P-value ^c
Day 1 (baseline)		n = 445	n = 439	
Mean		0.6	0.6	0.909
SD		0.85	0.89	
Median		0.0	0.0	
Min, max		0, 3	0, 3	
Day 15		n = 432	n = 428	
Mean		0.2	0.0	0.243
SD		1.53	1.25	
Median		0.0	0.0	
Min, max		-3, 12	-3, 10	
Day 29		n = 426	n = 432	

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Mean	0.1	0.1	0.781
SD	1.31	1.34	
Median	0.0	0.0	
Min, max	-3, 12	-3, 12	

max = maximum; Min = minimum; Oxy 1.0% = oxymetazoline HCl cream 1.0% group; SD = standard deviation; Veh = vehicle group

Note: Analysis was based on observed cases. Evaluations during the treatment period were conducted predose on days 1, 15, and 29.

a Visit was based on visit window.

b Studies 199201-004 and 199201-005

c P-value was based on a Wilcoxon rank-sum test.

Source: : Module 5.3.5.3, ISS Table 4-7

On average, both treatment groups experienced similar changes from baseline in inflammatory lesion counts at any postbaseline timepoint during the treatment period. Between-group differences in change from baseline were not statistically significant at any postbaseline timepoint. While the majority of subjects have either maintained or improved in their lesion count, the maximum number of lesions increased to 12 for some subjects. A similar increase is noted for some subjects in the vehicle arm.

Telangiectasia

In studies 004 and 005, the investigator used an inflammatory lesion count and the Clinician's Telangiectasia Assessment (CTA) to evaluate the average overall severity of telangiectasia on the patient's face and to ensure that treatment of erythema with oxymetazoline HCl cream 1.0% does not cause worsening of telangiectasia, another manifestation of the disease condition. The CTA comprises the 5-point scale (0 to 4) as shown in the table below:

Table 24: Clinician's Telangiectasia Assessment Scale

Score	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 the presence of clearly visible telangiectasia
4	Severe, with the presence of many visible telangiectasia

Source: applicants table 9, SCS

Assessments in trials 004 and 005 were performed as part of the safety evaluation at screening and predose on days 1, 15, and 29, and once at each of the follow-up and exit visits.

Based on frequency distributions, the proportions of patients at each severity grade were similar between the Oxy 1.0% and vehicle groups in both trials. A similar proportion of patients in both treatment groups experienced any worsening from baseline in terms of CTA during the 29-day treatment period. Few patients (in either

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treatment group in each study) had severe assessments of telangiectasia at any post-baseline timepoint.

7.4.6 Immunogenicity

Not applicable for this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The occurrence of adverse events did not appear to suggest a correlation with cumulative dose.

7.5.2 Time Dependency for Adverse Events

This section will discuss the safety findings from the open-label, long-term trial.

Study 006 was a phase 3, multicenter, open-label, long-term study to evaluate the efficacy and safety of oxymetazoline HCl cream 1.0% applied topically once daily to the faces of patients with moderate to severe persistent facial erythema associated with rosacea. A total of 440 patients were enrolled. All patients received at least 1 application of study medication and were included in the safety population. Study medication was applied once daily for 52 consecutive weeks followed by a 14-day posttreatment period. Patients were permitted to use concomitant treatments for inflammatory lesions of rosacea.

Study Centers: A total of 25 sites in the United States (US) participated in the study.

Study Initiation Date (First Patient Enrolled): 09 April 2014

Study Completion Date (Last Patient Completed): 24 August 2015

Key Inclusion Criteria:

Male or female patients, 18 years of age or older with moderate to severe persistent facial erythema associated with rosacea as determined by a grade of ≥ 3 on both the Clinician Erythema Assessment (CEA) Scale with photonic numeric guide and Subject Self-Assessment for Rosacea Facial Redness (SSA) Scale with photoguide

Key Exclusion Criteria:

Any uncontrolled systemic disease; 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, and severe or unstable or uncontrolled cardiovascular disease; current treatment with monoamine

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oxidase inhibitors; females who were pregnant, nursing, or planning a pregnancy during the study or who were of childbearing potential not using a reliable method of contraception; previous participation in clinical trials associated with oxymetazoline cream for facial rosacea in the 6 months prior to enrolling into the study; previous or current use of marketed Mirvaso® (brimonidine) topical gel, 0.33%

Safety:

Safety assessments included adverse events, urine pregnancy tests for women of childbearing potential, physical examinations, vital signs, Investigator's Global Assessment of Disease Severity (IGA), Clinician's Telangiectasia Assessment (CTA), inflammatory lesion counts, dermal tolerability assessment, and skin blanching assessment.

Efficacy, Pregnancy and rebound are described in sections 6 and 7.6.2, and 7.6.4, respectively.

Discontinuations

Fourteen patients in the oxymetazoline group (3.2%) discontinued from the study due to TEAEs. The most commonly reported TEAE that led to study discontinuation was application site dermatitis, reported by 6 patients (1.4%). TEAEs that led to study discontinuation that were reported by 2 patients (0.5%) each were application site erythema and application site pain; all other events were reported by 1 patient (0.2%) each. Most of the TEAEs that led to discontinuation were deemed by the investigator as related to treatment. There was no TEAE leading to study discontinuation was reported during the 2-week posttreatment period.

Deaths and SAEs

No patient died during the study. Serious TEAEs were reported by 3.4% (15/440) of patients over the entire study period. None was considered to be treatment-related by the investigator and none resulted in study discontinuation. The most commonly reported serious TEAE was basal cell carcinoma, reported by 6 patients (1.4%). All other serious TEAEs were reported by 1 patient (0.2%) each (acute kidney injury, angina pectoris, appendicitis, cellulitis, chest pain, cholangiocarcinoma, cholecystitis, chronic sinusitis, coronary artery disease, Parkinson's disease, sepsis, and squamous cell carcinoma).

Common AEs

During the 52-week treatment period, TEAEs were reported by 43.2% (190/440) of patients. The highest incidence of TEAEs (24.8%) occurred during the first quarter (day 1 through day 90); the incidence was lower in quarters 2, 3 and 4, i.e., 14.1%, 15.7%, and 13.6%, respectively

The most frequently reported TEAEs (by $\geq 2\%$ of patients) were upper respiratory tract infection (3.4%, 15/440); rosacea (3.2%, 14/440); application site dermatitis and

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nasopharyngitis (3.0% each, 13/440); hypertension (2.5%, 11/440); headache (2.3%, 10/440); and application site pain, application site pruritus, and sinusitis (2.0% each, 9/440).

The most commonly reported TEAEs determined by the investigator to be treatment-related were application site dermatitis (1.8%), application site paresthesia (1.6%), application site pain (1.1%), and application site pruritus (1.1%).

The most frequently reported treatment-related TEAEs (i.e., by $\geq 1\%$ of subjects) were: application site dermatitis (1.8%, 8/440), application site paraesthesia (1.6%, 7/440), and application site pain and application site pruritus (1.1% each, 5/440).

Severe TEAEs

3 cases of application site dermatitis and 1 case each of application site pain, application site erythema, and photosensitivity reaction were reported as severe. The subject who reported photosensitivity reaction discontinued from the study.

Dermal tolerability

Across all postbaseline timepoints for patient assessments of itching and stinging/burning, the majority ($> 85\%$) of patients had a severity rating of "none." Across all postbaseline timepoints for investigator assessments of dryness and scaling, the majority ($> 71\%$ for dryness and $> 81\%$ for scaling) of patients had a severity rating of "none."

Most subjects did not experience skin blanching during the 52-week treatment period. No subject experienced severe blanching and 1 subject experienced moderate blanching at a single timepoint over the entire study period.

Assessments of disease progression

Mean inflammatory lesion count was 3.5 at baseline and decreased to mean counts in the range of 1.5 to 2.9 at all postbaseline timepoints. At all timepoints, the median number of inflammatory lesions was 0 and the median change from baseline was also 0.

A total of 44.8% of subjects had worsening from baseline in telangiectasia (CTA) at any timepoint during the 52-week treatment period. Based on frequency distributions, the severity of telangiectasia assessments based on the CTA was unchanged by the end of the 52-week treatment period, compared with that of baseline.

Reviewer comment: The long-term trial identified no new safety concerns. The numbers of subjects exposed sufficient to address the recommendations in the ICH E1A Guideline.

Study product was generally well-tolerated. Application site reactions, some severe, were reported to lead to study discontinuation for a small percentage of subjects. There

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does not appear to be an increase in severity of application site reactions with a longer time-to-onset/ duration of treatment. The majority of reactions resolved without sequelae. Labeling for application site reactions may be considered. However, there does not appear to be a way to predict which patients will have reactions. Also, it is highly likely that patients will discontinue therapy should an application site reaction occur.

Labeling should also reflect the population studied as it was not studied in diseases of vascular insufficiency, narrow angle glaucoma, severe or unstable cardiovascular disease, or with concomitant treatment of MAOIs.

7.5.3 Drug-Demographic Interactions

The applicant conducted subgroup analyses for all TEAEs regardless of causality that were reported through day 29 by age group (age 18 to 64 years, ≥ 65 years), race (Caucasian, non-Caucasian), and gender (male, female) in the Core Studies Population. The results are shown in the table below:

Table 25: TEAEs Through Day 28/29 by Subgroup

	Pooled Core Studies ^a	
	Oxy 1.0% (N = 489)	Veh (N = 483)
Overall	82 (16.8)	61 (12.6)
Age subgroup		
18 to 64 years	74/424 (17.5)	50/425 (11.8)
≥ 65 years	8/65 (12.3)	11/58 (19.0)
Race subgroup		
Caucasian	74/443 (16.7)	50/432 (11.6)
Non-Caucasian	8/46 (17.4)	11/51 (21.6)
Gender subgroup		
Male	19/106 (17.9)	6/97 (6.2)
Female	63/383 (16.4)	55/386 (14.2)

Oxy 1.0% = oxymetazoline HCl cream 1.0% group;

TEAEs = treatment-emergent adverse events; Veh = vehicle group

Note: Within each preferred term, a patient is counted at most once.

^a Studies 199201-002, 199201-004, and 199201-005

Source: Module 5.3.5.3, ISS Tables 3-1.1, 3-12.1, 3-12.2, 3-13.1, 3-13.2, 3-14.1 and 3-14.2

It appears that there is no notable difference in overall incidence of TEAEs based on age group, race group, or gender. Analysis also showed that a greater proportion of Caucasian subjects and subjects 18 to 64 years in the Oxy 1.0% group compared with their respective vehicle group, reported AEs in the general disorders and administration site conditions SOC. However, the small number of subjects in each of these subgroups makes it difficult to draw meaningful conclusions based on these data.

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7.5.4 Drug-Disease Interactions

Drug-disease interaction analyses were not done. Oxymetazoline cream has not been evaluated in subjects with renal or hepatic impairment.

7.5.5 Drug-Drug Interactions

Available in vitro study results did not suggest that Rhofade has an inhibitory effect or causes induction of CYP enzyme activity (see section 7.25).

Reviewer comment: This reviewer recommends class labeling for drug-drug interactions similar to Kovanaze and include MAOIs, nonselective beta adrenergic antagonists, and tricyclic antidepressants. Also, due to the cardiac effects caused by alpha-1 antagonists, drugs that cause additive effects such as anti-hypertensives and/or cardiac glycosides should also be addressed in labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

A single report of a thyroid malignancy were reported the long-term, open-label trial. Additionally, there were reports of non-melanoma skin cancer [basal cell (6) and squamous cell (1)].

Mechanistically, there is no reason to suspect that exposure to oxymetazoline cream contributed to development to any of these malignancies. The applicant was granted a waiver request for conduct of a dermal carcinogenicity study with oxymetazoline HCl cream is granted based on:

- no genotoxicity noted in standard battery of genotoxicity tests
- no hyperplasia noted in a 6 month dermal toxicity study in rats or in a 9 month dermal toxicity study in minipigs, and
- no carcinogenic signal noted in the oral Tg.rasH2 mouse assay.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women with erythema of rosacea were excluded from participation in the clinical trials. Across all 13 clinical studies of oxymetazoline HCl cream submitted with this NDA, 2 pregnancies were reported:

- One subject in the long-term open-label study (006) had a positive pregnancy test on day 175 of treatment and was discontinued from the study as a result. No

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adverse events were reported for this patient, and the pregnancy resulted in the delivery of a healthy child.

- Subject (b) (6) (0.10% oxymetazoline) had a positive pregnancy test at Day 35 in the dose-response study, V-101-ROSE-202. The subject experienced a spontaneous abortion.

No adequate and well-controlled studies of oxymetazoline HCl cream 1.0% have been conducted in pregnant women. Published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations. These data are limited by the small number of cases exposed, multiple comparisons which may have resulted in chance findings, and analyses based on decongestants as a group.

Reviewer comment: The pregnancy outcomes from the trial are not sufficient to inform pregnancy risk but may be conveyed in labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

Rosacea is a condition that primarily affects adult patients. The agreed upon pediatric study plan concluded that pediatric study requirements for this application may be waived because necessary studies are impossible or highly impracticable because there are too few children with this condition to study.

Additionally, the most recent approval for the same indication [NDA 204708 for Mirvaso (brimonidine) topical gel, 0.33% on 23 August 2013], was granted a full waiver of the pediatric study requirement because the Agency determined “necessary studies are impossible or highly impracticable because there are too few children with this condition to study.”

Based on Allergan’s own analysis of data from the U.S. Claims database (MarketScan) between 01 January 2010 and 31 December 2011 that combined all forms of rosacea, the prevalence rate in children 0 to 17 years of age was determined to be (b) (4) %. A pediatric waiver is recommended as per the agreed upon PSP. The pediatric population affected by this disease condition is so small that clinical studies are impossible or highly impracticable and a pediatric waiver is recommended as per the agreed upon PSP. The application will be presented to PeRC on January 11, 2016.

The language proposed for Section 8.4 of the label is as follows:

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

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7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Oxymetazoline HCl cream 1.0% is not expected to have any potential for abuse or dependence.

Adrenergic-mediated vasoconstriction is associated with unwanted pharmacological and clinical phenomena, such as tachyphylaxis, tolerance, and rebound vasodilation. Most of the studies describing rebound relate to the use of nasal vasoconstrictors. The picture is not as well-defined in the eye. One study shows that use of tetrahydrozoline was associated with tachyphylaxis, but not rebound.

The applicant attempted to assess rebound effect by in clinical trials by using the primary efficacy measures, the CEA and SSA to evaluate worsening of erythema compared with baseline following cessation of treatment. For all studies, subjects with a baseline CEA and/or SSA grades of 3 (moderate) were included in the analyses.

For trials 004 and 005, worsening of erythema compared with baseline was analyzed based upon CEA and SSA scores at day 29 predose, at the follow-up visit, at the day 57/exit visit. For the entire posttreatment period (from after day 29 through day 57/exit), for the Oxy 1.0% and vehicle groups, respectively, 1.7% (6/355) and 0.6% (2/349) of patients experienced worsening of erythema compared with baseline based on the CEA and SSA considered together; 8.3% (31/372) and 5.6% (21/374) of patients experienced worsening based on the CEA alone; and 3.9% (16/406) and 3.1% (12/390) of patients experienced worsening based on the SSA alone. The results are shown in the table below:

Table 26: Subjects with Worsened Erythema from Baseline Based on CEA, SSA and Composite (CEA/SSA) Endpoint Measurements in Trials 004 and 005

Variable Visit/Period ^a	Pooled Pivotal Studies ^b		
	Oxy 1.0% (N = 445)	Veh (N = 439)	P-value ^c

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CEA & SSA	n = 362	n = 353	
Day 29 predose ^d	0/345 (0.0)	1/346 (0.3)	> 0.999 ^h
Follow-up visit ^e	2/343 (0.6)	0/346 (0.0)	0.247 ^h
14-day posttreatment period ^f	2/342 (0.6)	0/345 (0.0)	NC
Day 57/exit	4/353 (1.1)	2/346 (0.6)	0.686 ^h
Entire posttreatment period ^g	6/355 (1.7)	2/349 (0.6)	0.286 ^h
CEA	n = 380	n = 378	
Day 29 predose ^d	23/361 (6.4)	9/371 (2.4)	0.009
Follow-up visit ^e	17/359 (4.7)	10/371 (2.7)	0.144
14-day posttreatment period ^f	17/358 (4.7)	10/370 (2.7)	NC
Day 57/exit	21/370 (5.7)	15/371 (4.0)	0.301
Entire posttreatment period ^g	31/372 (8.3)	21/374 (5.6)	0.145
SSA	n = 413	n = 394	
Day 29 predose ^d	4/397 (1.0)	6/388 (1.5)	0.542 ^h
Follow-up visit ^e	11/393 (2.8)	7/386 (1.8)	0.360
14-day posttreatment period ^f	11/391 (2.8)	7/384 (1.8)	NC
Day 57/exit	10/404 (2.5)	9/387 (2.3)	0.891
Entire posttreatment period ^g	16/406 (3.9)	12/390 (3.1)	0.508

CEA = Clinician's Erythema Assessment; NA = not applicable; NC = not calculated;
 Oxy 1.0% = oxymetazoline HCl cream 1.0% group; QD = once daily; SSA = Subject Self-Assessment for
 Rosacea Facial Redness; Veh = vehicle group

Note: Only patients with baseline grades of 3 (moderate) on the CEA and SSA were included in the analysis of the primary variable. Only patients with baseline grades of 3 (moderate) on the CEA were included in the analysis of the CEA. Only patients with baseline grades of 3 (moderate) on the SSA were included in the analysis of the SSA. Analysis was based on observed cases. Evaluations were performed

predose on day 29, at the follow-up visit and all scheduled and unscheduled visits that occurred during a 14-day period following day 29, and on day 57/exit.

a Visit was based on case report form visit.

b Studies 199201-004 and 199201-005

c P-value was based on a Pearson's chi-square test. If 25% or more of the cells had expected counts less than 5, then Fisher's exact test was used instead.

d Represents the 24-hour timepoint after 28 consecutive days of QD treatment.

e Includes data from the scheduled follow-up visit.

f Includes data from scheduled and unscheduled visits for 14 days after the day 29 visit. Patients with more than 1 occasion of worsened erythema compared with baseline were counted only once.

g Includes all visits after day 29/early exit. Patients with more than 1 occasion of worsened erythema compared with baseline were counted only once.

h A Fisher's exact test was performed.

Source: Module 5.3.5.3, ISS Tables 4-3.1 to 4-3.6

The number of subjects who discontinued the study early with worsening erythema was 2. Both oxymetazoline-treated subjects discontinued due to TEAEs of application site dermatitis had CEA and SSA scores of 3 at baseline and 4 at the early exit visit.

For the Study 006 Safety, the timepoints evaluated were predose at the week 52 visit (i.e. immediately before the last treatment application) and week 54 (end of study/posttreatment period).

A small proportion of patients experienced worsening of erythema compared with baseline following discontinuation of long-term oxymetazoline treatment based on CEA

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and SSA scores; at week 54/exit (approximately 13 days after treatment cessation), 0.7% (2/270), 4.5% (14/314), and 0.9% (3/323) of patients, respectively, had worsening of erythema based on the CEA and SSA considered together, the CEA considered alone, and the SSA considered alone.

These rates of worsening of erythema compared with baseline, assessed over a similar time period (at the week 54 visit, approximately 2 weeks after treatment cessation) in the long-term study, were similar to those observed in the vehicle-controlled Pivotal Studies, for the oxymetazoline HCl cream 1.0% and vehicle treatment groups.

Reviewer comment: While after discontinuation of treatment, there was worsening of erythema for some subjects in both the active and vehicle arms of the controlled trials, this reviewer finds it reassuring that the subject assessment yielded a smaller percent of subjects concluding (SSA) worsening erythema and that the delta for all measurements (approximately $\leq 2\%$) is small.

The disease itself flares and patients with rosacea experience fluctuating degrees of erythema based on many other factors, making the interpretation of this outcome measure difficult. That the percentage of subjects who experienced worsening erythema following discontinuation of long-term oxymetazoline treatment was similar to short term use supports the conclusion that there was no apparent rebound effect following cessation of oxymetazoline treatment.

7.7 Additional Submissions / Safety Issues

At the time of the 120 day safety update the applicant submitted the following:

At the time of the NDA submission, the phase 3 clinical trials had been completed. No trials have been on-going and no additional trials have been initiated since the NDA submission, therefore, no new data is available. In addition, no new data relating to safety for oxymetazoline for the treatment of persistent facial erythema associated with rosacea was retrieved from the literature.

The remainder of this section will describe the 4 provocative dermal safety studies conducted with 0.5% oxymetazoline HCL and submitted in support of this application.

Vicept (former sponsor) conducted a 21 day cumulative irritancy trial, a RIPT trial, a phototoxicity trial and a photocontact allergy trial with the 0.5% oxymetazoline HCL cream (V-101). Because a dermal tolerability assessment has been incorporated into phase 3 trials (see section 7.4.5), the Agency agreed that it was reasonable not to conduct further dermal safety trials with the 1% formulation. This comment was conveyed to Allergan at the December 18, 2013 EOP2 meeting.

The cumulative irritation and RIPT studies were conducted by the following:

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The Education & Research Foundation, Inc.
2095 Langhorne Road
Lynchburg, Virginia 24501

The principal investigator was Kappa P. Meadows, M.D.

The phototoxicity and photoallergy studies were conducted by the following:

Suncare Research Laboratories, LLC
2518-8 Reynolda Road
Winston Salem, NC 27106
(336) 725-6501

The principal investigator was Steven R. Feldman, M.D., Ph.D.

1. 21-Day Cumulative Irritation Test: V-101-HDSS-104

OBJECTIVE: The purpose of this study was to determine the cumulative irritation potential of the products listed below.

PRODUCTS:

21-Day Cumulative Irritation Test
Product A: White Petrolatum (Negative Control)
Product B: V-101 Cream Vehicle
Product C: 0.5% Sodium Lauryl Sulfate (SLS) (Positive Control)
Product D: V-101 Cream 0.5%

SUBJECTS: A panel of thirty-five (35) healthy male and female volunteers was recruited from the Lynchburg, Virginia area.

Inclusion Criteria:

Subjects met all of the following criteria for inclusion in the study:

1. Healthy, volunteer subjects of either sex, at least 18 years of age.
2. All females of childbearing potential submitted to a urine pregnancy test and had negative results at Day 1 and at the final study visit and also were using an effective method of birth control (e.g. abstinence, implants, injectables, oral contraceptives, intrauterine contraceptive devices or double barrier) or agreed to use an effective method of birth control prior to becoming sexually active.
3. Any skin type or race providing their degree of skin pigmentation did not interfere with making readings of skin reactions.
4. Willingness to follow the study procedures and complete the study.
5. Written informed consent obtained.

Exclusion Criteria:

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1. Any skin disease such as atopic dermatitis/eczema or psoriasis that would in any way confound interpretation of the study results.
2. Chronic asthma sufferers.
3. Pregnancy or nursing mothers.
4. A history of sensitivity to any component of any of the formulations.
5. Use of chronic medications (such as antihistamines, corticosteroids, analgesics, and anti-inflammatories) for one week before and during the study. Daily use of 81 mg of aspirin was allowed.

STUDY DESIGN: Test product (0.2 grams) was applied to the absorbent area of the occlusive patches and placed on the subject's back. The patches remained in place for 24 hours, except on Saturdays when they remained in place for 48 hours. At least 5 minutes after patch removal the site was evaluated using a 5-point scale.

0 = No sign of irritation

1 = Slight erythema

2 = Noticeable erythema with slight infiltration

3 = Erythema with marked edema

4 = Erythema with edema and blistering

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc., were noted as comments.

Patching and grading was repeated for a total of 18 applications in a twenty-two day period, applying the same test product to the same site. If severe irritation (Grade 3 or 4) was observed at any site, no further applications were made to that site, and the maximum score was assigned to that site for the duration of the study.

The test product irritation index was calculated as follows:

35 subjects - 0 drops = 35 completed subjects x 18 applications x 3 (grade at which product is dropped) = 1890.

The applicant used the following adjusted classification system from Berger and Bowman to interpret the results:

Scor	%of	Indications from Test	Description of Observed
0 to 147	0% to 7.78%	Mild material- no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e.,
>147to 597	>7.78% to 31.59%	Probably mild in normal use	Evidence of slight potential for very mild cumulative irritation under conditions

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>597 to 1347	>31.59% to 71.27%	Possibly mild in normal use	Evidence of moderate potential for mild cumulative irritation under
>1347 to 1740	>71.27% to 92.06%	Experimental cumulative irritant	Evidence of strong potential for mild- to-moderate cumulative irritation under
>1740 to 1890	>92.06% to 100%	Experimental primary irritant	Evidence of potential for primary irritation under

DISPOSITION: Thirty-five (35) subjects were enrolled on the study. No subjects discontinued.

RESULTS: The negative and positive controls performed as expected with the irritation indices of 262 and 1675 respectively. The negative control did not exceed a score of 1 in any subject. The positive control performed as a cumulative irritant with thirty-three out of thirty-five subjects stopping application due to severe irritation. Twenty-one subjects reached grade 3, twelve subjects reached grade 4, one subject reached grade 2 and one subject reached grade 1.

The vehicle cream performed similarly to the negative control with an irritation index of 191. The application was not discontinued due to a severe reaction; the vehicle control did not exceed a score of 1 in any subject.

The irritation score for the test product was 357, higher than its vehicle and the negative control. Also unlike vehicle and the negative control, three subjects achieved severe irritation (one grade 4, two grade 3), with 2 of them discontinuing the application. Seven subjects reached a grade 2, twenty-four subjects reached a grade 1 and three subjects remained grade 0.

Reviewer comment: The applicant concludes that irritation for the test cream probably mild in normal use. After reviewing the data, this reviewer agrees with this assessment. Adverse dermal reactions which occurred in the clinical trials will be described in section 6 of product labeling.

2. Repeat Insult Patch Test (RIPT): V-101-HDSS-102

OBJECTIVE: The purpose of this study was to assess the potential of the test materials to induce contact sensitization by repetitive applications to skin of healthy.

PRODUCTS:

Product A: White Petrolatum (Negative Control)
 Product B: V-101 Cream Vehicle
 Product C: 0.5% Sodium Lauryl Sulfate (Control)
 Product D: V-101 Cream 0.5%

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SUBJECTS: A panel of two hundred twenty-five (225) healthy adult male and female volunteers was recruited from the [REDACTED] (b) (6) area.

Inclusion Criteria:

Subjects met all of the following criteria for inclusion in the study:

6. Healthy, volunteer subjects of either sex, at least 18 years of age.
7. All females of childbearing potential submitted to a urine pregnancy test and had negative results at Day 1 and at the final study visit and also were using an effective method of birth control (e.g. abstinence, implants, injectables, oral contraceptives, intrauterine contraceptive devices or double barrier) or agreed to use an effective method of birth control prior to becoming sexually active.
8. Any skin type or race providing their degree of skin pigmentation did not interfere with making readings of skin reactions.
9. Willingness to follow the study procedures and complete the study.
10. Written informed consent obtained.

Exclusion Criteria:

6. Any skin disease such as atopic dermatitis/eczema or psoriasis that would in any way confound interpretation of the study results.
7. Chronic asthma sufferers.
8. Pregnancy or nursing mothers.
9. A history of sensitivity to any component of any of the formulations.
10. Use of chronic medications (such as antihistamines, corticosteroids, analgesics, and anti-inflammatories) for one week before and during the study. Daily use of 81 mg of aspirin was allowed.

STUDY DESIGN:

Induction phase: Test product (0.2 grams) was applied to the absorbent area of the occlusive patches and placed on the subject's back. For the three-week induction period, three applications per week (Monday, Wednesday and Friday) were made. Monday and Wednesday patches were removed after 48 hours of wear and Friday patches were removed after 72 hours of wear. At least 5 minutes after patch removal the site was evaluated using a 5-point scale.

- 0 = No sign of irritation
- 1 = Slight erythema
- 2 = Noticeable erythema with slight infiltration
- 3 = Erythema with marked edema
- 4 = Erythema with edema and blistering

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc., were noted as comments.

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Challenge Phase: After approximately a two-week rest period, a single challenge application was made. Evaluations were made at 5 minutes, 24 hours and 48 hours after patch removal using the same scale.

DISPOSITION:

Two-hundred three (203) subjects completed the study. Twenty-two (22) subjects dropped prior to completion of study. The majority of subjects discontinued due to subject request or missing 2 visits. One subject discontinued due to a serious adverse event (hospitalized for a hemicolectomy for a non-malignant adenomatous polyp). Two subjects discontinued due to concomitant medications.

Two serious AEs occurred in 2 subjects: hemicolectomy and appendectomy. A total of 25 adverse events were reported. The majority are injuries and musculoskeletal and connective tissue disorders. In this reviewer's opinion, none of the AEs appear to be related to the study procedure and none appear to be related to a known side effect of oxymetazoline.

RESULTS:

The negative and positive irritant controls performed as expected in regard to irritation in the with the induction phase. The majority of scores for the negative control were 0 or 1 (one subject had a score of 2). The positive control had 123 subjects with a grade 3 or higher.

The vehicle cream performed similarly to the test product in regard to irritation in the induction phase, with the vehicle slightly less irritating. The vehicle had more subjects reporting with a grade of 0 (83 vs. 31 with test product). The number of subjects with a severe score of 3/4 was similar for vehicle and test products, 2 subjects with grade 3 (vehicle) vs. 1 subject with grade 3 and 1 subject with grade 4 (test). In the challenge phase subject grades either decreased or remained unchanged for all products.

Reviewer comment: The applicant concludes that there was no evidence of sensitization for any of the test products. After reviewing the data, this reviewer agrees with this assessment. Adverse dermal reactions which occurred in the clinical trials will be described in section 6 of product labeling.

3. Phototoxicity Test: V-101-HDSS-103

OBJECTIVE: The objective was to evaluate the potential of V-10I Cream 0.50% to produce phototoxicity reactions in normal use by the population.

PRODUCTS: V-101 Cream 0.50% and vehicle

STUDY DESIGN:

Six progressive full-spectrum UV doses were administered in 25% intervals for determination of the minimal erythema dose (MED), which was the lowest dose that produced erythema with defined borders (Grade 2).

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A single, duplicate, occluded 24 hour duplicate application of the test article, vehicle and untreated control sites, in Finn Chambers (occlusive), followed by removal of the chambers and irradiation of one of each of the duplicative sites with UVR (10 J/cm² of UVA only then 0.5 MED of full-spectrum UV).

Responses of all sites were scored prior to, immediately following, 24 ± 2 hours and 48 ± 4 hours after UVR doses. Grading Scale for Erythema Responses to UV Doses is as follows:

- 0 = No sign of irritation
- 1 = Slight erythema
- 2 = Noticeable erythema with slight infiltration
- 3 = Erythema with marked edema
- 4 = Erythema with edema and blistering

SUBJECTS: Thirty-two subjects were enrolled who met the inclusion/exclusion criteria described below.

Inclusion

- Written informed consent
- Review of the list of prohibited medications
- Review of a list of test product ingredients
- At least 18 and no more than 70 years old
- Fitzpatrick Skin Type I, II or III
- Good general health
- Willing to avoid sun exposure, tanning lamps and use of any topical products on the test areas
- Willing and able to complete all study visits
- Female subjects must fulfill the following:
 - Post-menopausal for at least one year, or
 - Have had a hysterectomy or tubal ligation, or
 - If of child-bearing potential must undergo a urine pregnancy test with a negative result, and agree to use an approved method of birth control throughout the study (i.e., oral/systemic contraceptives, intrauterine device (IUD), or spermicide in combination with a barrier method of contraception), Or must be abstinent, or in a monogamous relationship with a partner who has had a vasectomy

Exclusion

- Use of topical corticosteroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) applied in the test area within less than 2 weeks prior to study enrollment
- Use of systemic corticosteroids within less than one month prior to study enrollment
- Intent to use any of the above during the study

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- Use of any other systemic or topical drugs that might affect responses to UVR or interfere with responses to test product, including thiazides, tetracyclines and NSAIDs
- Intent to use any of the above during the study
- History of photosensitivity disease or sensitivity to cosmetics or topical products
- Currently pregnant or nursing
- Significant systemic disease, infection, cataracts, glaucoma, diabetes or lupus
- History of psoriasis, atopic dermatitis, skin cancer, dysplastic nevi or other skin pathology
- Sunburn, excessive tan, uneven skin tones or blemishes of the midback or use of a tanning lamp within past 3 months
- Intent to tan or expose the test area to sunlight during the study
- Participation in any clinical study within the past 30 days
- Any other condition which might increase the risk of study participation or compromise study results
- Severe physical, neurological or mental disease
- Employee or direct relative of an employee of Suncare Research Laboratories or Vicept Therapeutics, Inc.
- Due to equipment limitations the subject's weight did not exceed 300lbs.

DISPOSITION: Thirty-two subjects were enrolled. All of the subjects completed the study. Subjects included 18 females and 14 males, ranging in age from 26 to 62 years. The mean age was 44.8. Two subjects were categorized as Fitzpatrick skin type of I. Types II and III were equally represented.

RESULTS: There were no irritation grades above 2, and relatively few instances of grade 2.

Reviewer comment: The applicant concludes that there was no evidence of phototoxicity. After reviewing the data, this reviewer agrees with this assessment. No labeling for photo-protection is recommended at this time.

4. Photocontact Allergy Test: V-101-HDSS-104

OBJECTIVE: To evaluate the potential of V-101 Cream 0.50% to produce photo-contact allergenicity reactions in normal use by the population by applying higher doses of V-101 Cream 0.50%.

PRODUCTS: V-101 Cream 0.50% and vehicle

STUDY DESIGN: This is an open-label, evaluator-blind, controlled study in 50 healthy volunteer subjects. The induction phase consisted of six duplicate, 24 hour exposures to V-101 Cream 0.50% and V-101 Vehicle in separate, occlusive chambers, one site received UV and one site receiving no UV. Duplicate, untreated control sites were also covered with chambers. UVR doses of 3 MEDs (Minimal Erythema Doses) of UVA and UVB (full-spectrum simulated solar UVR) were then administered to these sites and one control site that received an empty chamber. Responses of all sites were graded

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immediately by a blinded evaluator, using the Irritation Response Grading Scale as shown below:

Irritation Response Grading Scale

0 = No sign of irritation

1 = Slight erythema

2 = Noticeable erythema with slight infiltration

3 = Erythema with marked edema

4 = Erythema with edema and blistering

The entire procedure was repeated five more times over a 3 week period.

SUBJECTS: Fifty (50) subjects were screened and of these 49 subjects with Fitzpatrick Skin Types I, II and III were enrolled based on the study criteria described below.

Inclusion Criteria

- Subjects are capable of understanding and willing to sign a statement of Informed Consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization
- Male and Female subjects 18-70 years of age.
- Subjects with Fitzpatrick skin types I-III
- Subjects in good general health
- Subjects willing to avoid sun exposure, tanning lamps and use of any topical products on the test areas.
- Subjects willing and able to complete all study visits.
- Female subjects must be post-menopausal for at least one year; or have had a hysterectomy; or have had a tubal ligation; or if of childbearing potential, must agree to use an approved method of birth control throughout the study (i.e., oral/systemic contraceptives, intrauterine device (IUD), or spermicide in combination with a barrier method of contraception), or must be abstinent, or in a monogamous relationship with a partner who has had a vasectomy and have a negative urine pregnancy test at Screening.

Exclusion Criteria

- Use of topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) applied in the area for 2 weeks prior to Visit 1 and for the duration of the study. Use of any other systemic or topical drugs that might affect responses to UVR or interfere with responses to test product including thiazides, tetracyclines and NSAIDs.
- History of photosensitivity disease or sensitivity to cosmetics or topical products
- Pregnant or breastfeeding
- Significant systemic disease, infection, cataracts, glaucoma, diabetes or lupus
- History of psoriasis, atopic dermatitis, cancerous or precancerous lesions, dysplastic nevi, or other skin pathology
- Sunburn, excessive tan, uneven skin tones or blemishes of the mid-back or use of tanning lamps or beds within 3 months before enrollment

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- Use of systemic or topical drugs that might affect responses to UVR or interfere with responses to test product including: corticosteroids, thiazides, tetracyclines and NSAIDs
- Subjects who have participated in a study 30 days prior to enrollment
- Any other condition that might increase the risk of study participation or compromise study results, or subjects with severe physical, neurological or mental disease.
- Employees or direct relatives of an employee of the Study Center or Vicept Therapeutics.

DISPOSITION: Of the 49 subjects enrolled, 2 subjects dropped out within Week 1 of the study. Forty-seven (47) subjects completed the study: Subject 07 was unable to complete after Visit 1 procedures due to work schedule conflict and Subject 38 was unable to complete after Visit 2 procedures due to family obligation. Of the subjects who completed the study, thirty-six (36) were females (76.6%) and eleven (11) males (23.4%). Ages for the subjects ranged from 19 to 68 years (mean=44.7,SD=12.2). Four subjects were categorized as Fitzpatrick skin type of I. Types II and III were equally represented. The MED of the subjects ranged from 10 to 20 (mean = 16.7).

RESULTS:

No serious adverse events were reported, and no subjects dropped out due to adverse events. A total of 21 non-serious adverse events were reported for 14 subjects, and included Tape Irritation (7), Itching at UVR exposure sites with erythema and edema (3), Sore Throat (1), Headache (1), Ear Ache (1), Heartburn (1), Sprained thumb (1), Eye Itching due to seasonal allergies (1), Diarrhea (1), Thumb Weakening due to soft tissue damage (1), Back Pain (1), Congestion (1) and Cold Symptoms (1). Thumb weakness was ongoing at the conclusion of the study. All of the other AEs were resolved before the conclusion of the study.

For all sites, there were no irritation grades above grade 3. Irradiated sites had higher scores than non-irradiated sites. However, the scores for the test product were similar to those of the vehicle cream and untreated control. Scores for the challenge stages were mainly 2 and below.

Reviewer comment: The applicant concludes that there was no evidence of photoallergenicity. After reviewing the data, this reviewer agrees with this assessment. No labeling for photo-protection is recommended at this time.

8 Postmarket Experience

The product is not marketed.

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9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The Medical Officer has reviewed all labeling (that was available as the review was closing) in its entirety; labeling negotiations with the applicant were pending as the clinical review was being finalized.

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NDA 208552

Rhofade (oxymetazoline) Cream, 1.0%

Regarding the proprietary name “Rhofade”, it is this clinical reviewer’s opinion that the name may be misleading. The “fade” part of the name seems to imply a disappearance. The implications of the preceding term “Rho” is less clear. While Rho is a Greek letter, Rhodamine is a red-florescent dye used in the area of science. Additionally, Rhodamine Red is a pantone color. The product is seeking a claim essentially for the disappearance of redness. Including “fade” in the name may set up an expectation that all patients will experience fading of their redness. Very few subjects achieved a clear appearance and the name itself seems to overstate efficacy from a clinical perspective. The clinical team’s concern was expressed to the team at the Office of Prescription Drug Promotion. The comments were taken into consideration and the team maintains their non-objection to the proprietary name “Rhofade”.

9.3 Advisory Committee Meeting

Not applicable.

Clinical Review
Amy Sakulich Voitach, D.O., M.S.
NDA 208552
Rhofade (oxymetazoline) Cream, 1.0%
9.4 Photonumeric Guide

APPEARS THIS WAY ON ORIGINAL

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.

Clinical Review
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NDA 208552
Rhofade (oxymetazoline) Cream, 1.0%

CEA Scale Grade 0
Clear skin with no signs of erythema



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CEA Scale Grade 1
Almost clear of erythema, slight redness



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Rhofade (oxymetazoline) Cream, 1.0%

CEA Scale Grade 2
Mild erythema, definite redness



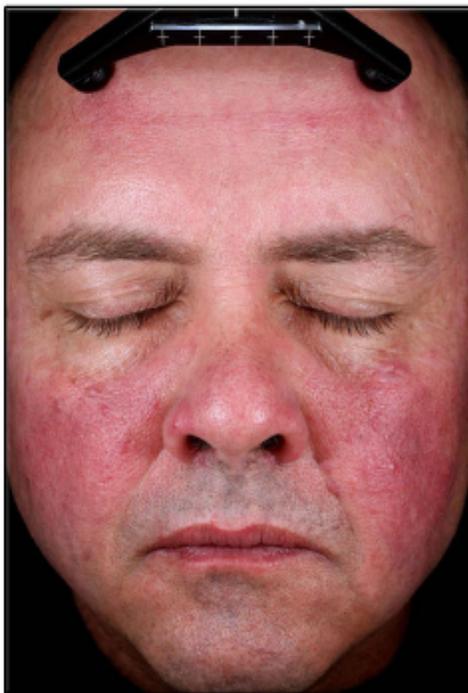
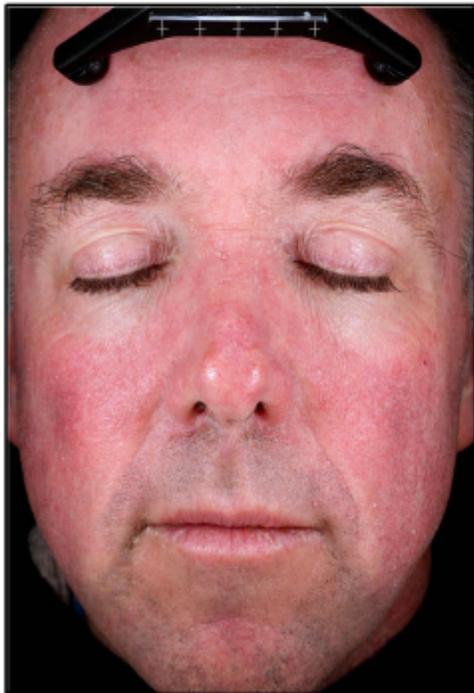
Clinical Review
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NDA 208552
Rhofade (oxymetazoline) Cream, 1.0%

CEA Scale Grade 3
Moderate erythema, marked redness



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Rhofade (oxymetazoline) Cream, 1.0%

CEA Scale Grade 4
Severe erythema, fiery redness



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/s/

AMY S WOITACH
01/09/2017

DAVID L KETTL
01/10/2017