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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s) Brenda Carr, M.D.
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Established Name brimonidine
(Proposed) Trade Name Mirvaso
Therapeutic Class alpha adrenergic agonist
Applicant Galderma Research and
Development

Formulation(s) gel, 0.33%
Dosing Regimen once daily
Indication(s) topical treatment of facial
erythema of rosacea
Intended Population(s) adults 18 years of age or older

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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

Brimonidine topical gel, 0.33% 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.¹⁻⁵ 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.^{1,6} The disease is reported to be rare in children,^{3,4} although it may be underreported.⁵

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 277 subjects were randomized to the brimonidine group, and 276 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 Days 29, Day 15 and Day 1. The testing on Day 29 was performed first as the primary analysis. If the result was statistically significant, the testing was to continue to Day 15 and then to Day 1. Brimonidine gel, 0.33% was superior to vehicle at each time point on each day in both trials, and the results were statistically significant for each assessment. The applicant established that once daily use of brimonidine gel, 0.33% was effective for the topical treatment of the facial erythema of rosacea.

A total of 1210 subjects were exposed to the to-be-marketed formulation across the clinical development program. The applicant pooled the data from three trials for the integrated safety analyses (a Phase 2b dose-finding trial and the two pivotal trials) which made for 330 subjects in the brimonidine gel, 0.33% group and 331 in the vehicle group. All subjects in the pooled database applied study product once daily. Adverse events in the integrated database were most commonly reported in the Skin and subcutaneous tissue disorders system organ class (SOC). “Erythema,” “skin burning

sensation,” and “skin warm” were the events in this SOC that were reported by $\geq 1\%$ of brimonidine-treated subjects and at higher frequency relative to the vehicle group. “Flushing” was reported only by brimonidine-treated subjects and was reported by 2.7% of subjects by the reviewer’s assessment. No serious adverse events were reported in the pooled database from use of the product as intended. The applicant conducted a long-term trial, which evaluated a sufficient number of subjects at appropriate drug exposures to address the recommendations in the ICH E1A Guideline for Industry.⁷ No new safety concerns were identified in the long-term trial. Brimonidine gel, 0.33% was generally well-tolerated. The applicant established that the safety profile for once daily use of brimonidine gel, 0.33% for the topical treatment of the facial erythema of rosacea is acceptable.

The applicant submitted the application via the 505(b)(2) pathway, and they conducted a comparative bioavailability, maximal use trial to support the 505(b)(2) application. The applicant demonstrated that the systemic exposure to brimonidine gel, 0.33% under maximal use conditions was less than that of the listed comparator Alphagan (brimonidine tartrate ophthalmic solution) 0.2%. Thus, the applicant adequately established a “clinical bridge” to the listed drug. This allowed the applicant to rely on the agency’s findings of safety for the 0.2% solution to support aspects of the nonclinical portion of the marketing application.

The applicant provided substantial evidence of the effectiveness and safety of brimonidine gel, 0.33% when used once daily in the target population of subjects with facial erythema of rosacea. However, the reviewer recommends that the indication specify that the product is intended for “the topical treatment of the *persistent* erythema of rosacea in adults 18 years of age or older” (Note: The emphasis is for purposes of this review and not recommended for the label). Refining the wording would better define the intended target population for the applicant’s product, as brimonidine gel, 0.33% is not intended for treatment of transient erythema or the perilesional erythema which may be associated with inflammatory lesions of rosacea.

Approval of the product would represent a new and specific treatment for patients with persistent erythema of rosacea, providing for the first product exclusively indicated for this particular manifestation of the disease. The development program was designed around this specific indication. Brimonidine gel, 0.33% would introduce an important new therapy to the armamentarium of treatment for patients with rosacea.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

During the review cycle for this application (on May 28, 2013), the division requested that the applicant submit a Patient Package Insert (PPI). The division requested the PPI as an additional safeguard that would supplement the label and the child-resistant container closure system to manage the risk of unintended exposure to brimonidine gel,

0.33%. The specific risk of concern was of ingestion of the product by children. Accidental ingestion of practically any product (e.g. household product) may be a generic concern pertaining to young children. However, there were two occurrences of this event during the clinical trials with brimonidine gel, 0.33%. Both of the occurrences involved the young children of a single study subject, and both children experienced serious adverse events (see Section 7.3.2 for details).

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

The established name of the product is brimonidine, and the proposed trade name is Mirvaso. Brimonidine is an alpha adrenergic receptor agonist. The applicant proposed their 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. The applicant considered that brimonidine may diminish the erythema of rosacea via “direct cutaneous vasoconstriction.” The applicant proposed marketing of a gel formulation, which represents a new dosage form.

Per MAPP 5021.1 (Office of Pharmaceutical Science “Naming of Drug Products Containing Salt Drug Substances”), “The USP Salt Policy is a naming and labeling policy applicable to drug products that contain an active ingredient that is a salt. The policy stipulates that USP will use the name of the active moiety, instead of the name of the salt, for such a drug product when creating drug product monograph titles. The USP Salt Policy stipulates that USP will base the strength of the product on the active moiety” (p.1). The USP salt policy became official on May 1, 2013, which was during the review cycle for this application, i.e. after submission of the application.

In their submission (including in draft labeling), the applicant referenced the product and strength as the salt, i.e. brimonidine tartrate, 0.5%. The product contains 0.5% brimonidine tartrate (salt) which is equivalent to 0.33% brimonidine (active moiety). In accordance with the USP salt policy, the drug product strength in the label should be revised to be expressed in terms of the active moiety, rather than the salt strength equivalent. That is, the product should be (and will be) described in the label as “Mirvaso (brimonidine) gel, 0.33%”, rather than “Mirvaso (brimonidine tartrate) gel, 0.5%”. However, as the policy became official after submission of the marketing application, this review may, at times, reference the product as the salt (brimonidine tartrate gel, 0.5%), consistent with its description in the application. This may particularly

be the case in the discussion of the various clinical trials, as several trials evaluated other brimonidine tartrate concentrations, and those comparators were referenced by the salt strength, e.g. brimonidine tartrate gel, (b) (4) %.

Initial development of the product was by CollaGenex, and the code name for the drug substance in their program was “COL-118.” Galderma acquired CollaGenex in 2008 and renamed the drug substance “CD07805/47.” Therefore, “COL-118” and “CD07805/47” in this review both refer to brimonidine tartrate.

Also see Sections 2.3 and 2.4.

2.2 Tables of Currently Available Treatments for Proposed Indications

If approved, brimonidine gel, 0.33% would become the first 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.”

The reviewer notes that, unlike Noritate, several other metronidazole products are indicated only for “topical application in the treatment of inflammatory papules and pustules of rosacea.” These products are available at 0.75% strength in cream, gel and lotion formulations. Additionally, a metronidazole 1% gel is marketed that is indicated only for treatment of inflammatory lesions.

2.3 Availability of Proposed Active Ingredient in the United States

Brimonidine tartrate is available in solution formulations for treatment of ophthalmic indications, e.g. reduction of elevated intraocular pressure open-angle glaucoma or ocular hypertension. For these indications, it is currently available as single-active-ingredient products at 0.1% and 0.15% concentrations. The 0.5% and 0.2% ophthalmic solutions were discontinued (not for reasons of safety or efficacy). Brimonidine tartrate is also available as a fixed combination product with timolol maleate (for reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP). A fixed combination suspension with active ingredients brimonidine tartrate and brinzolamide was approved on April 19, 2013 for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2.4 Important Safety Issues With Consideration to Related Drugs

Alpha-2 adrenergic agonists are most commonly used in the treatment of systemic hypertension.⁸ These agents are also used to reduce intraocular pressure (as discussed above). Clonidine is described as the prototypic agent in this class, and bromindine is a derivative of clonidine.⁸ Brimonidine is reported to reduce intraocular pressure without the impact on systemic blood pressure of clonidine (even when clonidine is applied topically to the eye). However, because it can cross the blood-brain barrier, brominidine may cause hypotension and sedation, although to a lesser extent than clonidine.⁸ Labels for brimonidine ophthalmic solutions describe a study conducted in pediatric glaucoma patients (ages 2 to 7 years) who were treated with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily, and the most commonly observed adverse reactions were somnolence and decreased alertness (also see Section 7.6.3).

The clonidine label lists the most frequent “adverse effects” for clonidine as dry mouth, drowsiness, dizziness, constipation, and sedation.⁹ The label describes clinical reactions that may be observed with abrupt withdrawal of clonidine, including agitation, headache, and tremor with a rapid rise in blood pressure. Rarely, “hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal” (“Warnings” section of clonidine label).

The labels for brimonidine tartrate ophthalmic products carry warnings about the possible potentiation of syndromes associated with vascular insufficiency and use in patients with severe cardiovascular disease. Those labels also describe the potential for drug interactions with antihypertensives/cardiac glycosides, CNS depressants, tricyclic antidepressants, and monoamine oxidase inhibitors. The label for the applicant’s product will be labeled similarly.

The applicant described that tachyphylaxis and rebound nasal airway congestion have been described with oxymetazoline, an alpha-adrenergic receptor agonist used for nasal airway congestion.¹ The applicant included evaluations for the potential for tachyphylaxis and rebound in the clinical development program. See Sections 6.1.9 and 7.6.4, respectively.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Brimonidine gel was developed under commercial IND 74,841. The agency had several communications with Galderma (and CollaGenex before them) during the development program, as listed below:

August 9, 2006: Pre-IND Meeting
October 31, 2007: Guidance Meeting

March 10, 2008: End of Phase 2 Meeting
December 3, 2008: Guidance (first meeting with Galderma)
March 5, 2009: Carcinogenicity Special Protocol Assessment Agreement Letter
April 27, 2010: Guidance Meeting
March 30, 2011: Clinical Special Protocol Assessment Agreement Letter
March 2, 2012: Teleconference
April 3, 2012: Advice letter regarding March 2 teleconference
May 16, 2012: Pre-NDA Meeting
June 27, 2012: Guidance Meeting - Child-resistant container closure system
September 10, 2012: Proprietary Name Granted ("Mirvaso")

Major milestone meetings and select discussions from certain other meetings are summarized below. Some advice was given at more than one meeting, i.e. the same advice was dispensed more than once. However, this review generally will not repeat the mention of advice that was given on more than one occasion.

October 31, 2007: guidance

- The agency advised CollaGenex that, [REDACTED] (b) (4)
[REDACTED] may be too broad of an indication; [REDACTED] (b) (4)

March 10, 2008 - End of Phase 2 Meeting (with CollaGenex)

- Pertaining to the "clinical bridge" for the proposed 505 (b)(2) application, discussion included conduct of a cross-over study with the proposed topical gel versus an approved 0.2% ocular solution under maximal usage conditions in the target population.
- For demonstration of efficacy, the applicant would need a co-primary endpoint composed of an investigator assessment and a subject self assessment of erythema. Ideally, the scales for these assessments would be validated and have clearly defined, mutually exclusive and clinically meaningful category descriptors. The two scales should be used simultaneously to define success, as the scales would be highly correlated. The results should be concordant for success to be clinically meaningful.
- Ensure that treatment of erythema does not worsen other manifestations of rosacea.
- Because of the product's transient (non-durable) effect on erythema, the agency recommended that the primary endpoint reflect the assessment of treatment effects over the whole course of the trial. A repeated measurement approach might be used to capture a clinically relevant treatment effect over the course of the trial.

December 3, 2008 guidance (first meeting with Galderma)

- Because the product contained titanium dioxide, the Chemistry, Manufacturing, and Controls (CMC) reviewer told the applicant that the SPF value should be determined as per 21 CFR 352 Subpart D). CMC would agree with the applicant that titanium dioxide is not acting as an active sunscreen ingredient if the applicant demonstrated that the SPF value of the proposed product is below 2. (See Section 7.4.5 for discussion of the study results.)
- The applicant was advised to assess the potential for tachyphylaxis and rebound effect.

April 27, 2010 (guidance)

- The applicant's proposal for the "clinical bridge" for the planned 505(b)(2) application was discussed. The agency recommended possible approaches for construct of an appropriate "clinical bridge" between the ophthalmic solution and the topical gel. One option was for a trial in which subjects would be administered a single ophthalmic dose of brimonidine solution to each eye on Day 1 with associated PK sampling. After a one-day washout, subjects would cross-over to treatment with brimonidine tartrate topical gel. The applicant elected to follow this approach. The comparative bioavailability and maximal use trial, RD.06.SRE.18143, is discussed in Section 4.4.3 of this review.
- The applicant should provide the rationale for the proposed "2 week no-treatment follow-up" time point for assessment of a "rebound effect." The applicant was told that they may need additional earlier time points for assessment.

March 30, 2011 - Clinical Special Protocol Assessment Agreement

The applicant requested Special Protocol Assessment of their Phase 3 protocol on February 11, 2011 ("RD.06.SPR.18140: A Multicenter, Randomized Double-Blind, Vehicle-Controlled, Parallel Group Study to Demonstrate the Efficacy and Assess the Safety of CD07805/47 Gel 0.5% Applied Topically Once Daily in Subjects with Moderate to Severe Facial Erythema Associated with Rosacea"). The letter included agreement on:

- the general study design, including schedule for follow-up visits
- the proposed dose regimen of once daily
- the proposed population with regard to disease severity
- proposed definition of a primary endpoint
- proposal to not monitor routinely for electrocardiogram abnormalities (obtain as clinically indicated)
- proposal to use the Intent to Treat (ITT) population, defined as all randomized subjects to whom study drug was administered as the primary analysis population
- proposal to sequentially test the composite success at Hours 3, 6, 9 and 12 at Day 29 first, and if statistically significant, to test responses at Day 15 and at Day 1 was acceptable

Areas of non-agreement included:

- The Statistical Analysis Plan (SAP). The applicant stated that the SAP would be developed during the study, and finalized prior to database lock and unblinding. The agency's position was that a SAP for a Phase 3 trial should be part of, or developed separately during the development of the study protocol.
- Requiring exclusion of patients on tricyclic anti-depressants, beta blockers, cardiac glycosides and antihypertensive agents (the agency advised against this).
- Secondary endpoints intended for a labeling claim, should be clinically meaningful. A secondary endpoint where success is defined as a 1-grade improvement on the CEA or on the PSA scale might not be (clinically meaningful).

April 3, 2012 Advice/Information Request Letter

- The agency sent this letter in follow-up to a March 2, 2012 teleconference, in which the need for additional safeguards (labeling and container/closure changes), to decrease the risk of accidental ingestion of brimonidine topical gel were discussed. The agency had received reports of serious adverse events in two children who had ingested brimonidine topical gel (they were children of a study subject); see Section 7.3.2.

May 16, 2012: Pre-NDA Meeting

- The applicant proposed a full waiver from the requirement for pediatric studies because of the rarity of cases of rosacea reported in pediatric patients. The agency considered the applicant's proposal reasonable.
- The agency agreed with the applicant's proposed pooling strategies for the safety analyses, and concluded that the applicant's plan to not pool data for the efficacy analyses was "reasonable."

2.6 Other Relevant Background Information

505(b)(2)

The applicant submitted the marketing application via the 505(b)(2) pathway. They relied on agency's findings of safety and effectiveness for the approved listed drug, Alphagan (brimonidine tartrate ophthalmic solution 0.2%; NDA 20613) to support some of the nonclinical portions of the application. Alphagan is no longer marketed, but was not discontinued for reasons of safety or effectiveness. Therefore, per the cover letter to the submission, the applicant performed a "comparative clinical pharmacokinetic study to bridge to the listed drug, using the ANDA product designated as the reference listed drug in the Orange Book as the comparator." That product was Bausch & Lomb's brimonidine tartrate ophthalmic solution 0.2%. This approach was acceptable.

Proprietary name

The Division of Medication Error Prevention and Analysis determined that, “The proposed proprietary name (Mirvaso) was acceptable from both a promotional and safety perspective” (final review March 5, 2012).

Development of the Patient Self Assessment (PSA) scale

Primary efficacy was assessed by a composite endpoint which measured improvement on a Clinician Erythema Assessment (CEA) scale and a Patient Self Assessment (PSA) scale.

The Study Endpoints and Labeling Development (SEALD) provided pre-submission consult on development of the applicant’s subject self-assessment instruments. The applicant stated that the PSA scale used in the Phase 2b and Phase 3 trials was developed and validated consistent with the FDA Guidance entitled “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” (December 2009).

The applicant worked with experts in Patient Reported Outcomes in development of the PSA (and other self-assessment scales that explored “other aspects of facial erythema”). (b)(4) conducted a study on behalf of the applicant, and the applicant stated that the study was conducted to address agency concerns about the content validity of the PSA scales. (b)(4) conducted the study in two phases:

- Phase 1 was a qualitative study in subjects with facial erythema of rosacea and was intended to refine and evaluate the content validity of the PSA.
- Phase 2 evaluated the “reliability, validity, and responsiveness” of the PSA using data from the Phase 2b trial RD.06.SRE.18161 (18161), which evaluated efficacy and safety of brimonidine gel in subjects with facial erythema of rosacea. The applicant stated that the analyses of the PSA data from the Phase 2b trial demonstrated that the PSA scales were “reliable and robust, and...appropriately validated.”

The applicant used the same five-category PSA (evaluated in 18161) in the two Phase 3 pivotal trials, RD.06.SRE.18140 (18140) and RD.06.SRE.18141 (18141), and the long-term trial, RD.06.SRE.18142 (18142).

Thus, the applicant relied on a five-category PSA scale that aligned with the five-category Clinician Erythema Assessment (CEA) scale for the Phase 3 composite primary endpoint. (The agency had informed the applicant that it would be difficult to interpret study results from a composite endpoint if the scales had different numbers of categories.) The final version of the scale was also comparable to the CEA in content.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On submission, the application was sufficiently complete and organized, such that necessary data could be accessed and reviewed without difficulty.

3.2 Compliance with Good Clinical Practices

The applicant attested in the cover letter that all clinical trials submitted in the application were conducted in compliance with good clinical practices.

Two sites were from each pivotal trial, 18140 and 18141, were selected for inspection, for a total of four sites. The sites were selected based on the large number of subjects enrolled and the size of the treatment effect. The Clinical Inspection Summary was provided by Janice Pohlman, M.D., M.P.H. in the Good Clinical Practice Assessment Branch of the Division of Good Clinical Practice Compliance in the Office of Scientific Investigations. The following table from Dr. Pohlman’s summary includes site information and investigation outcomes.

Table 1 Inspection Summary (Source: Clinical Inspection Summary by Dr. Pohlman)

Site #/Name of CI/Location	Protocol # and # of Subjects	Inspection Date	Final Classification
Site #8017 Kimberly Grand, M.D. 10215 Kingston Pike, Suite 200 Knoxville, TN 37922	Protocol RD.06.SPR18140 28 subjects	January 28 - 31, 2013	No deviation from regulations.
Site #8076 Michael Jarratt, M.D. 8140 North Mopac Blvd. Building 3, Suite 120	Protocol RD.06.SPR18140 27 subjects	January 29 - February 4, 2013	Deviation(s) from regulations
Site #8283 Leslie Baumann, M.D. 4500 Biscayne Blvd., Suite 105 Miami, FL 33137	Protocol RD.06.SPR18141 33 subjects	January 28 – February 21, 2013	No deviation from regulations
Site #8198 Michael Heffernan, M.D. 7401 Maryland Ave. St. Louis, MO 63130	Protocol RD.06.SPR18141 34 subjects	January 14 - 16, 2013	No deviation from regulations

Dr. Jarratt’s was the only site (#8076) issued a Form FDA 483, Inspectional Observations citing two items:

1. “An investigation was not conducted in accordance with the investigational plan.”

- A subject was enrolled without having had a screening chemistry panel analysis.
 - A sub-investigator conducted clinical erythema assessments on 18 subjects prior to completing (Clinician’s Erythema Assessment) harmonization training.
2. “Failure to prepare or maintain adequate case histories with respect to informed consent.”
- The person conducting the consent discussion signed and dated the form approximately 5 and a half weeks after the subject signed the form.

Dr Pohlman (OSI reviewer) stated that “In Dr. Jarratt’s February 21, 2013 written response, he notes that the sub-investigator has participated in other clinical studies which utilize the CEA assessment performed by the same Sponsor. When it was discovered that the sub-investigator had not completed training for this particular study, the training was performed.”

The research coordinator at Dr. Baumann’s (#8382) site fabricated one reading of one subject’s blood pressure. The fabrication was initially detected by routine study monitoring, and the research coordinator was ultimately fired. No other issues were identified as this site, and the site was not issued a Form 483. To address this discovery, the applicant defined a modified intent-to-treat population which excluded all subjects from Dr. Baumann’s site (see Section 6.1.4).

In the assessment of data integrity, the conclusions of OSI for all four sites inspected was, “The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.”

3.3 Financial Disclosures

The applicant disclosed financial arrangements with six investigators, five of whom were investigators (b) (6). The sixth was an investigator (b) (6). The applicant appears to have adequately disclosed financial arrangements with clinical investigators. The applicant had a reasonable mitigation plan (b) (6). (b) (6) The six investigators and the nature of the disclosure for each are described below.

Dr. (b) (6)

- Consulting Fees: totaling \$26,938 (\$24,438 (b) (6) (b) (6); \$20,838 of the above payments occurred during (b) (6) (b) (6))
- Trial participation: (b) (6); Dr. (b) (6) enrolled (b) (6) (b) (6) respectively
- (b) (6) (b) (6)

Dr. (b) (6)

- Research Fees (including trial costs) totaling \$51,718
- Trial participation: (b) (6); Dr. (b) (6) enrolled (b) (6)
- Minimization of Potential Bias: (b) (6)

Dr. (b) (6)

- Consulting and Research Fees (including trial costs) totaling \$25,560
- Trial participation: (b) (6) Dr. (b) (6) enrolled (b) (6)
- Minimization of Potential Bias: (b) (6)

Dr. (b) (6)

- Research Fees (including trial costs) totaling \$51,425
- Trial participation: (b) (6); Dr. (b) (6) enrolled (b) (6)
- Minimization of Potential Bias: (b) (6)

Dr. (b) (6)

- Consulting Fees and Research Grant (including trials) (b) (6) totaling \$361,405 (\$291,405 of the above payments occurred during the (b) (6); the full amount of \$361,405 occurred during the (b) (6)).
- Trial participation: (b) (6); Dr. (b) (6) enrolled (b) (6) (b) (6) respectively
- Minimization of Potential Bias: (b) (6)

Dr. (b) (6)

- Consulting and Research Fees (including trial costs) totaling \$64,165
- Trial participation: (b) (6) Dr. (b) (6) enrolled (b) (6)
- Minimization of Potential Bias: (b) (6)

Matthew Guerra, Ph.D., the statistical reviewer for this application, performed a sensitivity analysis which excluded the five (b) (6) trial sites for investigators who had filed financial disclosures:

- Three sites from trial (b) (6) (Dr. (b) (6)), (b) (6) (Dr. (b) (6)), and (b) (6) (Dr. (b) (6)) and
- Two sites from trial (b) (6): (b) (6) (Dr. (b) (6)) and (b) (6) (Dr. (b) (6))

Dr. Guerra concluded that, the exclusion of the five sites that had financial disclosures from the analyses had “little impact” on the efficacy results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Note: See Section 2.1 of this review for discussion regarding USP Salt Policy.

The CMC reviewer for this application was Hitesh Shroff, Ph.D. The following summary information includes the Medical Officer’s understanding of certain CMC findings, as described in Dr. Shroff’s review. The reader is referred to Dr. Shroff’s review for details and discussions pertaining to these investigations.

Brimonidine topical gel is a white to light yellow, opaque gel, and it contains no novel ingredients. Table 2 lists the composition of the product and includes the function of each ingredient.

Table 2 Composition of brimonidine topical gel (Section P.2.1 of Dr. Shroff’s review)

Components	Percent (w/w)	mg/g	Function
Brimonidine tartrate	0.5	5	Active ingredient
(b) (4)			(b) (4)
(Carbomer Homopolymer Type B)			
Methylparaben			
Phenoxyethanol			
Glycerin			
Titanium dioxide			
Propylene glycol			
Sodium hydroxide			
Purified water			

Qs=Quantum satis (as much needed to achieve target); NF=National Formulary; USP=United States Pharmacopoeia.

^a No monograph for brimonidine tartrate exists in the USP or European Pharmacopoeia (Ph. Eur.).

The applicant conducted a clinical study to evaluate the ability of titanium dioxide (b) (4). See Section 7.4.5 of this review for a discussion of that study.

Per Section P.2.5 of the review, Dr. Shroff found that the long-term and accelerated stability testing “demonstrated that the amounts of the preservatives are sufficient to maintain the overall purity of the brimonidine topical gel.”

Per the Clinical Overview (Section 2), the applicant (b) (4) methylparaben (b) (4) in 2010, having determined that (b) (4)% methylparaben was the optimal concentration in the formulation. The brimonidine tartrate gel, 0.5% with the (b) (4)% methylparaben concentration was evaluated in three trials (Per Table 7 in Section 3.2.P.2.2 of the submission):

- RD.06.SRE.18123 (contact sensitization study)
- RD.06.SRE.18125 (cumulative irritancy study)
- RD.06.SRE.18144 (single-application PK study)

The applicant considered that (b) (4) methylparaben did not impact the safety evaluation of the formulation. The Medical Officer agreed with this assessment and concluded that data from studies which evaluated the formulation containing (b) (4)% methylparaben were relevant to the assessment of safety of the final formulation.

Container Closure System (from Section P.7 of Dr. Shroff’s review)

The agency requested a child-resistant closure system late in the applicant’s development program. The request followed receipt of reports of serious adverse events that resulted from two children ingesting brimonidine gel, 0.33% (see Section 7.3.2 of this review for discussion of those cases).

The clinical trials were conducted with product packaged in tubes with a non child-resistant closure system. The laminated tubes ((b) (4) 30g and 45g sizes) were fitted with (b) (4) screw caps. The laminated tubes and non child-resistant closure systems were supplied by (b) (4).

The commercial product will be supplied in 30g and 45g laminated tubes with child-resistant (b) (4) “push-and-turn” caps from (b) (4) (Section P.7 of the review).
(b) (4)

From Section P.7 (p. 58 of the CMC review), the child-resistant and non-child resistant container closure systems were reported by the applicant to be “very similar” because a) they are both supplied by (b) (4), b) the tubes are made from the same laminate, c) head and shoulders of the tubes are made from the same (b) (4), d) the tubes are the same size, and e) the caps are made from (b) (4). The

components of the container closure systems meet USP, 21 CFR and requirements for food contact applications.

The applicant supplied sufficient information “to establish that the container closure system is adequate to protect the drug product from light and moisture during the expiration dating period.”

Stability (from Section P.8 of Dr. Shroff's review)

The applicant performed the long term and accelerated stability studies of commercial scale brimonidine topical gel in the to-be marketed container closure. The drug product was manufactured at (b) (4)

The drug substance was from (b) (4). The tubes were from (b) (4). The applicant performed stability studies to confirm that the drug product from (b) (4) is “stable on storage during the stability studies.” The stability studies also demonstrated that drug product packaged in tubes from (b) (4) is stable.

The applicant performed stability studies on the drug product packaged in non-child resistant container closure from at least 9 large scale batches and in (b) (4) 30g, 45g (b) (4) tubes. The following long term stability studies are ongoing: 25°C/60% RH up to 36 months, intermediate stability at 30°C/65% RH up to 36 months and accelerated stability at 40°C/75% RH up to 6 months.

The applicant had initiated stability studies on 1 batch of drug product packaged in child resistant container closure and provided stability data up to 3 months with submission of the application. In response to an agency request, the applicant later submitted 6-month stability study data for the child resistant container closure. The applicant also provided weight loss and package integrity data for the child resistant container closure up to 6 months and weight loss and package integrity data up to 18 months for the stability registration batches. Dr. Shroff concluded (p. 63) that:

“The stability study, weight loss and package integrity test results showed that there is no significant change in the strength, purity and quality of the drug product during the course of these studies. The comparative stability studies of child resistant and non-child resistant container closures demonstrated that both container closure systems are equivalent and capable of protecting the drug product during the proposed shelf life. These studies also showed that the drug product manufactured using the drug substance obtained from either (b) (4) is equivalent. The weight loss data of the drug product packaged in non-child resistant and child resistant container closure demonstrated that both container closure systems are equivalent.”

With submission of this additional information, Dr. Shroff concluded that, “The stability data provided is adequate and support the proposed 24-month expiration dating period for the drug product.”

Post-approval Stability Protocol and Stability Commitment

In a communication on May 16, 2013 (and in response to an agency request), the applicant agreed to the following regarding the post-approval stability protocol and stability commitment:

- Submit the results as NDA annual reports.
- Conduct an investigation if a batch fails to meet the specification. The investigation may extend to batches manufactured before and after (the failed batch), as appropriate. If the investigation reveals that the deviation is a single occurrence that does not impact safety or efficacy of the drug product, the applicant will discuss this with the agency and provide justification to continue distribution of the batch.
- Report any change or deterioration in the distributed drug product will be reported in accordance with 21 CFR 314.81.

The applicant also committed to

- “Continue long-term and accelerated stability studies of 3 production scale batches of drug product packaged in *child resistant container closure*.”
- Continue long-term and accelerated stability studies of 9 production scale batches of drug product packaged in *non child resistant container closure*.”

Recommendation and Conclusion on Approvability (p.6)

Dr. Shroff’s “Recommendation and Conclusion on Approvability” was:

- “The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.
- The Office of Compliance has issued an “Acceptable” recommendation for the facilities involved in this application.”

However, from the ONDQA perspective, the application was not ready for an approval recommendation, as labeling issues were outstanding. Note: Labeling negotiations with the applicant had not begun at the time of closing of the CMC review (or any other discipline review).

4.2 Clinical Microbiology

The product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

Jianyong Wang, Ph.D. was the pharmacology/toxicology reviewer for this application.

The applicant submitted a 505(b)(2) application and relied on the agency's findings of safety for the listed drug Alphagan® (brimonidine tartrate ophthalmic solution), 0.2% to complete the nonclinical section of the application. Specifically, the applicant relied on published data for the pharmacology, safety pharmacology, ADME, general toxicity, genotoxicity, carcinogenicity after systemic administration, fertility and early development toxicity, teratogenicity, pre- and post-natal toxicity to provide a complete nonclinical section (per Section 1.2 of the Nonclinical Overview).

The applicant performed the following studies to evaluate the safety of dermally-administered brimonidine 0.33% gel:

- Repeat-dose dermal toxicity studies up to 13 weeks in hairless mice, 57 weeks in rats and 39 weeks in minipigs.
- A dermal carcinogenicity study in rats and a photo(co)carcinogenicity study in hairless mice.
- Investigations of acute dermal tolerance with and without UV exposure in hairless mice
- A primary eye irritation study in rabbits (acute ocular tolerance) and
- An evaluation of contact sensitization potential in guinea pig.

The following summary information represents the Medical Officer's understanding of the certain findings from the applicant's nonclinical studies, as described in Dr. Wang's review. The reader is referred to Dr. Wang's review for details and discussions pertaining to these investigations and the applicant's nonclinical program.

The applicant conducted two chronic dermal toxicology studies:

- A 39-week dermal toxicity study was done in minipigs that received once daily topical doses of water, vehicle and up to 20 mg/kg/day brimonidine tartrate gel (1%, 2 ml/kg/day). No mortality was noted. Additionally, no significant treatment-related effects were noted on body weight, ophthalmology, cardiovascular parameters, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology. The NOAEL was identified as the 20 mg/kg/day dose (1% gel, 2 ml/kg/day).
- A 57-week dermal toxicity study was done in rats that received once daily topical doses of water, vehicle and up to 60 mg/kg/day brimonidine tartrate (2% gel, 3 ml/kg). Animals received a dosing holiday (approximately) three weeks due to decreases in weight gain. Dosing was resumed with decreases in the doses administered to males. Treatment-related mortality was noted in high dose groups (both sexes), with undetermined cause of death in most cases. Lymphoid depletion (minimal to severe generalized) in the thymus at high dose was the only significant histopathological finding. A NOAEL was not identified in this study.

No drug-related neoplasms were observed in a two-year dermal carcinogenicity study conducted in rats. In the analysis of tumor incidence data, schwannoma in the

abdominal cavities in high dose females (2/60) were concluded to be “biologically insignificant” because a) the incidence was not statistically significant compared to vehicle control, b) schwannoma was found in the abdominal cavity in one (of 60) in the vehicle control group in males, c) schwannoma was also seen in one low dose female in the 57-week dermal toxicity study in rats, and d) no compound-related carcinogenic effects were observed in the two dietary carcinogenicity studies conducted with brimonidine tartrate (also see below regarding the dietary carcinogenicity studies). There were no significant test article-related non-neoplastic findings. Per Dr. Wang’s review, the carcinogenicity study was adequately conducted, and the test model was appropriate for this study. The Executive Carcinogenicity Assessment Committee (CAC) discussed this study and provided concurrence with the evaluation of this study on March 26, 2013.

A 12-month dermal photo-carcinogenicity study was conducted in hairless albino mice. Animals received vehicle and up to 2% brimonidine tartrate gel once daily five days per week. Animals were exposed to UVR (simulated sunlight) either one hour before or after study product application (depending on the day of the week). Topical treatment with brimonidine tartrate gel formulations did not enhance UV-induced photocarcinogenesis compared to the vehicle (control) group. “On the contrary, treatment with brimonidine tartrate gel formulations showed a dose-dependent protection effect against the UV-induced photocarcinogenic response; the onset of skin tumors was delayed and the tumor yield was reduced in a dose-dependent manner, as compared to the vehicle control group” (p. 20).

Note: Dr. Wang stated (p.18) that photocarcinogenicity studies are no longer recommended for topical drug products, per the ICH M3(R2) guidance document. However, the recommendation to the applicant for a photocarcinogenicity study was “made prior to implementation of the ICH M3(R2) guidance document.”

Other nonclinical information pertaining to brimonidine tartrate:

- Genetic toxicology tests signaled no genotoxic potential with brimonidine tartrate.
- No drug-related carcinogenic effects were observed at oral doses up to 2.5 mg/kg/day in mice (21-month oral mouse carcinogenicity study) or up to 1 mg/kg/day in rats (a 24-month oral rat carcinogenicity study).
- “Brimonidine tartrate was not teratogenic when administered during gestation at oral doses up to 2.5 mg/kg/day in pregnant rats and up to 5 mg/kg/day in pregnant rabbits. Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effects on male or female fertility at oral doses up to 1 mg/kg/day.”
- Brimonidine tartrate gel (up to 2%) did not show irritancy or phototoxicity in hairless mice.
- MIRVASO Gel is a nonirritant to rabbit eye.
- Brimonidine tartrate gel 2.0% did not show skin sensitization potential in guinea pigs.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Brimonidine tartrate is described as a “relatively selective alpha-2 adrenergic agonist” in the Alphagan P label. The applicant states, in Section 1 of the Summary of Clinical Efficacy, that brimonidine tartrate has, “potent vasoconstrictive activity. As such, brimonidine tartrate is expected to offer a positive effect on inhibiting and reversing cutaneous erythema caused by vasomotor instability through direct cutaneous vasoconstriction.”

4.4.2 Pharmacodynamics

In the clinical development program, four trials (three preliminary) were conducted in subjects with rosacea to determine an optimal formulation, concentration, and dose regimen. These trials were intended to evaluate the clinical effect of brimonidine tartrate on the erythema of rosacea. CollaGenex conducted the three preliminary trials: COL-118-ROSE-101, COL-118-ROSE-102 and COL-118-ROSE-201. The CollaGenex trials did not evaluate the commercial formulation, nor any brimonidine formulations of 0.5% strength. Galaderma conducted trial RD.06.SRE.18144 (18144), a single-application trial (see Section 6.1.8). The primary intent of these trials was dose-finding or formulation selection. The CollaGenex trials are briefly described below.

COL-118-ROSE-101: “A Dose-Response Study of Brimonidine Tartrate in the Reduction of Rosacea-Related Erythema”

Objective: To evaluate the dose-response relationship, tolerability, and duration of effect of brimonidine tartrate (COL-118) applied to a 1 cm² area on the malar region of the face.

Methodology: This was a single-center, single-blind, vehicle-controlled trial in subjects with rosacea. Subjects were evaluated at Screening, before treatment (time 0), and at 15, 30, 45, and 60 minutes after application of study medication and at hourly intervals thereafter until the effect was lost for up to eight hours after treatment. Twenty-one subjects were enrolled and analyzed. The primary efficacy measure was change in Minolta chromameter measurement from pre-dose to two hours post-dose. Commercially available brimonidine tartrate ophthalmic solution 0.2% (Bausch & Lomb) was serially diluted to prepare the study treatments.

Main Inclusion Criteria: Males and females age ≥ 18 years diagnosed with rosacea with moderate to severe erythema on the malar area of the face (a score of ≥ 3 on the Clinician’s Erythema Assessment Scale).

Each concentration of brimonidine tartrate (COL-118) – 0.0125%, 0.025%, 0.05%, 0.1%, and 0.2% – was applied topically as 50 µL on a 1 cm² area on the malar region of the face. Subjects received one application of study product.

Applicant's Conclusions: COL-118 at concentrations of 0.0125% to 0.2% reversed facial erythema in subjects with rosacea in a dose-dependent manner. No adverse events were reported.

COL-118-ROSE-102: “A Study of the Pharmacodynamic Profile of Six Topical Formulations of Brimonidine Tartrate in Rosacea-Related Erythema”

Objective: To evaluate the impact of different formulations on the pharmacodynamic profile of brimonidine tartrate (COL-118) applied to a 1 cm² area on the malar region of the face.

Methodology: This was a single-center, single-blind trial in subjects with rosacea. Formulations were applied topically as 0.02 mL on a 1 cm² area on the malar region of the face. Subjects received one treatment with study product. Subjects were evaluated at Screening, before treatment (time 0), and 15, 30, 45, and 60 minutes after application of study medication and at hourly intervals thereafter until the effect was lost for up to 8 hours after treatment. Twenty subjects were enrolled and analyzed for efficacy and safety. This study evaluated three gel and three cream brimonidine formulations; all were 0.10%. The primary efficacy measures were area under the curve (AUC) relating mean change from baseline (pre-dose) in Minolta chromameter measurements to sampling time and peak efficacy defined as mean maximum change (C_{max}) from baseline in Minolta chromameter measurement.

Applicant's conclusions: All COL-118 gel and cream formulations were reported to have reversed facial erythema in subjects with rosacea. One adverse event of nausea was reported. There were no notable changes in vital signs during the study. The formulations were well-tolerated.

COL-118-ROSE-201: “A Phase II Study of the Dose-Effect and Pharmacodynamic Profile of COL-118 (Brimonidine Tartrate) Gel in Rosacea-Related Erythema”

Objective: To evaluate the dose-response relationship and pharmacodynamic profile of three concentrations of brimonidine tartrate gel (COL-118) applied to the face.

Methodology: This was a randomized, double-blind, vehicle-controlled, parallel-group, multicenter trial in subjects with rosacea. Subjects applied study treatment (0.2%, 0.07% or 0.02% brimonidine tartrate gel, or vehicle) topically to the affected area each morning and as needed thereafter but no more often than every 4 hours and no more than 3 times per day. Treatment duration was 28 days. Study visits were on Days 0, 14, and 28. Blood samples were collected two hours after study drug application on Day 28

for determination of plasma concentrations of COL-118. Subjects at one center returned for a follow-up visit on Day 56 to evaluate a potential rebound effect of the drug. One hundred and ten subjects were randomized: 27 to brimonidine 0.2%, 29 to brimonidine 0.07%, 26 to brimonidine 0.02%, and 28 to vehicle.

Efficacy was evaluated using 5-point scales for Clinician's Erythema Assessment (CEA), Investigator's Global Assessment (IGA), and Clinician's Telangiectasia Grading (CTG), and by patient self-assessment (PSA, including 7 possible responses). Chromameter readings were taken at one center. The primary endpoint was the combined magnitude of the clinical effect measured by the CEA score and the duration of the effect over time evaluated using a composite CEA area under the curve (AUC) score for each of the Day 0, Day 14, and Day 28 visits.

Efficacy Results: The primary endpoint, reduction in erythema (CEA) across all timepoints (0-8 hour) and all visits (Day 0, Day 14, and Day 28), showed a dose-response relationship. Both the 0.2% and 0.07% groups had significantly greater changes from Baseline than the vehicle group ($p < 0.001$ and $p < 0.05$, respectively). A dose-response relationship was also apparent using the dataset for the 0-4 hour observation period. Correlations of dose and reduction in CEA were statistically significant ($p < 0.001$) for both 0-4 and 0-8 hour AUCs. The efficacy was consistent and reproducible over the 3 study visits (Days 0, 14, and 28; $p < 0.001$).

Total inflammatory lesion count did not improve or worsen with study treatment.

Peak efficacy was significantly higher in the 0.2% group than in the vehicle group on Days 0, 14, and 28 when represented by the greatest change from Baseline in CEA and on Day 28 when represented by the greatest change from Baseline in IGA. Peak efficacy was consistent and reproducible across the 3 study visits.

Chromameter data were available for 40 subjects and showed a significant correlation with the CEA results for both the 0-4 hour and 0-8 hour evaluations on Days 0 and 14 ($p < 0.01$).

Safety Results:

The most frequently reported adverse events were pruritus and erythema. All adverse events were mild or moderate. No serious adverse events occurred during the trial. Two subjects discontinued the trial due to adverse events: a subject in the 0.2% group due to a nodule on the left cheek and a subject in the 0.07% group due to a tooth infection. There were no notable changes in vital signs or laboratory results during the study.

Among the 44 subjects in the brimonidine groups for whom blood samples were available, no detectable blood levels of brimonidine were observed (lower limit of quantitation for the assay was 25 pg/mL).

Applicant's Conclusions: Brimonidine tartrate gel 0.2% showed a statistically and clinically significant reduction in rosacea-related erythema as measured by the CEA and IGA scores. The applicant found that the pharmacodynamic profile was consistent and reproducible over the 3 study visits. Topical application did not lead to any significant systemic exposure. All three concentrations of brimonidine gel were well tolerated.

4.4.3 Pharmacokinetics

The clinical pharmacology reviewer for this application was An-Chi Lu, M.S., Pharm.D. The reader is referred to her review for detailed discussion of the Clinical Pharmacology section of the application.

The applicant submitted data from three trials conducted to evaluate the relative bioavailability of CD07805/47 (brimonidine tartrate) 0.5% gel. These trials compared brimonidine plasma levels following ocular and dermal routes of administration and used the listed drug brimonidine tartrate 0.2% ophthalmic solution (Bausch & Lomb) as a reference product. The applicant did not conduct any trial to specifically evaluate the absolute bioavailability of brimonidine tartrate 0.5% gel.

The three pharmacokinetic trials were:

- COL-118-BAPK-101: single-day crossover study in healthy subjects; evaluated brimonidine tartrate 0.2% gel
- RD.06.SRE.18126: single-day crossover study in subjects with rosacea; evaluated brimonidine tartrate 0.18% gel
- RD.06.SRE.18143: multiple-dose study under maximal use conditions in subjects with rosacea (“the clinical bridge”)

All three trials evaluated the pharmacokinetic parameters for one-day ophthalmic instillation of Bausch & Lomb brimonidine tartrate 0.2% ophthalmic solution and for facial application of brimonidine tartrate gel. Trial 18143 evaluated the to-be-marketed concentration and proposed dose regimen, i.e. brimonidine tartrate 0.5% gel once daily. Study 18143 also used the more sensitive analytical method with the limit of quantification (LOQ)=10 pg/mL. The applicant concluded that the PK parameters for brimonidine tartrate 0.2% ophthalmic solution were consistent across the three studies. This section of the review will focus on the comparative bioavailability, maximal-use pharmacokinetic (PK) trial, 18143.

RD.06.SPR.18143 (18143): *“Comparative bioavailability and pharmacokinetics study to assess the systemic exposure of both CD07805/47 topical gel applied across different concentrations and dose regimens under maximal use conditions [0.07 % twice daily (BID), 0.18 % once daily (QD) or twice daily (BID) and 0.5% once daily (QD)] and Brimonidine tartrate ophthalmic solution 0.2% administered as three single doses over 24 hours in subjects with moderate to severe facial erythema associated with rosacea.”*

Study objectives:

- To evaluate the safety of CD07805/47 gel (0.07%, 0.18%, and 0.50%) applied to the face of subjects with moderate to severe facial erythema associated with rosacea.
- To assess the PK of CD07805/47 gel under maximal use conditions with once or twice daily application (one gram of CD07805/47 gel per application) for 4 weeks in subjects with moderate to severe facial erythema associated with rosacea.
- To compare the steady state systemic exposure of CD07805/47 gel (0.07%, 0.18%, and 0.5%) after four weeks treatment to the systemic exposure of brimonidine tartrate ophthalmic solution 0.2% after one day treatment (one drop to each eye every eight hours over a 24-hour period, as per the current label for the ophthalmic solution). The study consisted of four arms:
 - CD07805/47 gel 0.07% applied twice daily (BID)
 - CD07805/47 gel 0.18% applied once daily (QD)
 - CD07805/47 gel 0.18% applied BID
 - CD07805/47 gel 0.50% applied QD

Study design: This was an intra-individual comparative pharmacokinetic study of brimonidine tartrate, ophthalmic solution 0.2% and CD07805/47 gel (0.07%, 0.18%, and 0.50%) under maximal use conditions.

On Day 1, study personnel were to administer one drop of brimonidine tartrate ophthalmic solution 0.2% to each eye of study subjects every eight hours over a 24-hour period. Following a two-day washout period, subjects were to return to the clinic every morning from Day 4 (Baseline day for topical gel) to Day 32 for facial application of CD07805/47 gel by gloved study personnel. Subjects in the BID dosing groups were to return for the second application six hours after the first application. To ensure maximal use conditions of CD07805/47, one gram of CD07805/47 gel QD or BID was to be applied to the entire face (3% of body surface area) for four weeks (total daily dose: one or two grams).

Total number of subjects: 100 subjects planned; 102 subjects were randomized; 93 subjects completed

Key inclusion criteria:

- Male and female subjects, 18 years of age or older.
- Clinical diagnosis of rosacea.
- Clinician's Erythema Assessment (CEA) score of ≥ 3 (Moderate).

Key exclusion criteria:

- Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression

- Abnormality at the ocular examination

Table 3 Test Product Dosage Form (revised from Study synopsis)

	Investigational Product	Investigational Product	Investigational Product	Investigational Product
Trade Name or equivalent	Brimonidine tartrate ophthalmic	Not applicable	Not applicable	Not applicable
Name of Drug Substance	Brimonidine tartrate	Brimonidine tartrate	Brimonidine tartrate	Brimonidine tartrate
Internal code	Not applicable	CD07805/47	CD07805/47	CD07805/47
Pharmaceutical Form	Solution	Gel	Gel	Gel
Concentration	0.2%	0.07%	0.18%	0.5%
Dosage (total daily)	3 drops to each eye	2 g	1 g or 2 g	1 g
Dose regimen				
Route	Ophthalmic	Dermal	Dermal	Dermal
Frequency	1 drop in each eye every 8 hours over a	Twice daily (6 hours apart)	Once daily or twice daily (6 hours apart)	Once daily
Duration of administrati	1 day	4 weeks	4 weeks	4 weeks
Location of treated	Eye	Face	Face	Face

Pharmacokinetic assessment

The schedules for PK sampling are provided in the following table.

Table 4 Flow Chart for PK Sampling Times (Table 2 from study report)

PK Sampling Day	Day 1	Day 2	Day 4/Baseline	Day 5	Day 10	Day 18	Day 19	Day 24	Day 32/ET	Day 33	Day 34	Day 35
Treatment	Ophthalmic Solution	-	CD07805/47 Gel							-	-	-
Time Points	40 minutes, 1, 2, 3, 4, 8, 10, 11, 14, and 16 and 18 hours after the initial dose	24 hours after the initial dose on Day 1	Predose, 2, 3, 5, 6, 8, 9, 10, 11, 12, and 16 hours after the initial dose	Predose	Predose	Predose, 2, 3, 5, 6, 8, 9, 10, 11, 12, and 16 hours after the initial dose	Predose	Predose	Predose, 2, 3, 5, 6, 8, 9, 10, 11, 12, and 16 hours after the initial dose	24 hours after initial dose on Day 32	48 hours after initial dose on Day 32	72 hours after initial dose on Day 32

Demographics and Baseline Characteristics

The Safety Population was 60.8% females and 97.1% Caucasian. Mean age was 41.6 years.

Pharmacokinetic results

The PK parameters for the brimonidine tartrate ophthalmic solution 0.2% and the brimonidine tartrate gel 0.5% are presented in the following table from p.3 of Dr. Lu’s review:

Table 5 PK parameters for the brimonidine tartrate ophthalmic solution 0.2% and the brimonidine tartrate gel 0.5% (Clinical Pharmacology review Table 1)

		Brimonidine tartrate ophthalmic solution 0.2%, TID, at Day 1	Brimonidine tartrate topical gel 0.5% QD		
			Day 4 (after first application)	Day 18 (after 15 th application)	Day 32 (after 29 th application)
C _{max} (pg/mL)	Mean ±SD ^a	54 ± 28	19.4 ± 11.7	46.2 ± 61.5	25.5 ± 24.3
	Range	16-134	10-52	10-254.6	10-117.9
	N (N quantifiable ^b)	96 (96)	23(17)	21(20)	19(15)
AUC _{0-24h} (pg.hr/mL)	Mean ±SD	568 ± 277	262.1 ± 209.4	417.3 ± 263.6	290 ± 241.8
	Range	124-1490	10-732.9	10-1077.4	10-949.1
	N (N quantifiable)	96 (96)	23(17)	21(20)	19(15)

a. SD=standard deviation

b. BLQ data value replaced by LOQ (10 pg/mL) for mean C_{max} calculation; AUC_{0-24hr} were calculated only if there is at least one quantifiable time point. However, for statistical analysis not reportable AUC_{0-24hr} were replaced by the lowest AUC_{0-24hr} calculated in this trial (i.e. 10 pg.hr/mL)

From Dr. Lu’s table, 96 subjects (100%) who received the brimonidine tartrate ophthalmic solution had quantifiable systemic exposure after receiving three doses in one day. A total of 15 subjects (79%) of subjects who received brimonidine tartrate topical gel 0.5% had quantifiable systemic exposure after 29 days of treatment.

Dr. Lu presented the mean accumulation ratios for brimonidine tartrate gel 0.5% between the 15th and 1st application, 29th and 1st application, and 29th and 15th application. Dr. Lu described the results as depicting that, “The accumulation ratios for both AUC_{0-24hr} and C_{max} of 15th/1st application are higher than those of 29th/1st and 29th/15th application, and indicate that there was a small degree of accumulation after 15 applications of brimonidine tartrate topical gel, 0.5% once daily.”

Table 6: Mean AUC_{0-24hr} and C_{max} Accumulation Ratio (Clinical Pharmacology review Table 2)

		15 th / 1 st application	29 th / 1 st application	29 th / 15 th Application
Mean _a AUC _{0-24hr}	Mean	1.4±0.6	1.2±0.8	0.9±0.3
	Range	0.7-3.1	0.3-3.6	0.4-1.7
	N	16	12	15
Mean _b C _{max}	Mean	2.8±4.5	1.4±1.4	0.8±0.6
	Range	0.0-19.4	0.0-6.3	0.2-2.8
	N	21	21	20

^a: unquantifiable AUC were not used for calculation of accumulation ratios.

^b: BLQ values replaced by the LOQ (10 pg/mL)

Dr. Lu calculated the relative bioavailability of brimonidine tartrate topical gel, 0.5%, QD (Test) compared to brimonidine tartrate ophthalmic solution 0.2% (Reference) based on the AUC_{0-24h} and C_{max}. Those results are shown in the following tables from Dr. Lu's review:

Table 7: Brimonidine Tartrate Gel 0.5% Relative bioavailability in Reference to Ophthalmic Route (Based on AUC_{0-24h}) (Clinical Pharmacology review Table 3)

	Geometric Mean AUC _{0-24h} (CV%) (pg.hr/mL)	Ratio of AUC _{0-24h} (Test/Reference)	90% Confidence interval for ratio of AUC _{0-24h}
Reference (Day 1)	521 (33%) N=19	-----	-----
Test (Day 18, after 15 th application)	370 (69%) N=20	71%	54%-92%
Test (Day 32, after 29 application)	313 (40%) N=15	63%	46%-86%

Table 8: Brimonidine Tartrate Gel 0.5% Relative bioavailability in Reference to Ophthalmic Route (Based on C_{max}) (Clinical Pharmacology review Table 4)

	Geometric Mean C _{max} (CV%) (pg/mL)	Ratio of C _{max} (Test/Reference)	90% Confidence interval for ratio of C _{max}
Reference (Day 1)	48 (40%) N=19	-----	-----
Test (Day 18, after 15 th application)	32 (95%) N=20	66%	47%-94%
Test (Day 32, after 29 th application)	24 (62%) N=15	55%	38%-79%

The results of those calculations allowed the following observations:

- The systemic exposure of brimonidine tartrate gel 0.5% QD was higher after the 15th application than after the 29th application.
- After the 15th application, the mean relative bioavailability of AUC_{0-24h} and C_{max} were 71% and 66%, respectively. The 90% confidence intervals for the relative bioavailability of both C_{max} and AUC_{0-24h} were below 100%.

Adverse Events

Adverse events were reported by 65 subjects (63.7%). Adverse events reported in at least two subjects in any treatment group are presented in Table 9.

Two serious adverse events occurred during the ophthalmic solution treatment period: an acute hypotensive event and chest pain. No serious adverse events were reported during the CD07805/47 gel treatment period. Five subjects discontinued from the study due to adverse events, and three of these subjects reported the events during the ophthalmic solution treatment period (and withdrew prior to exposure to CD07805/47 gel). Two of the adverse events were acute hypotension, and one serious adverse event of chest pain (previously mentioned). The other two subjects who withdrew during the CD07805/47 gel treatment period for the following adverse events: cold/flu symptoms (0.5% QD regimen) and “achy bilateral eyes” (0.07% BID).

Table 9 Summary of Adverse Events Reported for 2 or More Total Subjects by System Organ Class and Preferred Term, Safety Population (Applicant Table 27 from study report)

System Organ Class Preferred Term ^a	Ophthalmic Solution N=102 n (%)	CD07805/47 Gel				Total N=102 n (%)
		0.5% QD N=24 n (%)	0.18% BID N=26 n (%)	0.18% QD N=25 n (%)	0.07% BID N=27 n (%)	
Total Number of AE(s)	41	27	35	38	50	193
Total Number (%) of Subjects with AE(s) ^b	23 (22.5)	12 (50.0)	14 (53.8)	14 (56.0)	16 (59.3)	65 (63.7)
Nervous system disorders	13 (12.7)	5 (20.8)	5 (19.2)	7 (28.0)	10 (37.0)	33 (32.4)
Headache	9 (8.8)	3 (12.5)	3 (11.5)	5 (20.0)	8 (29.6)	24 (23.5)
Dizziness	2 (2.0)	2 (8.3)	1 (3.8)	1 (4.0)	1 (3.7)	7 (6.9)
Syncope vasovagal	2 (2.0)	1 (4.2)	0	0	1 (3.7)	5 (4.9)
Migraine	1 (1.0)	0	1 (3.8)	1 (4.0)	0	3 (2.9)
Infections and infestations	0	5 (20.8)	4 (15.4)	4 (16.0)	5 (18.5)	18 (17.6)
Nasopharyngitis	0	2 (8.3)	1 (3.8)	2 (8.0)	1 (3.7)	6 (5.9)
Upper respiratory tract infection	0	0	1 (3.8)	2 (8.0)	1 (3.7)	4 (3.9)
Influenza	0	0	0	0	2 (7.4)	2 (2.0)
Vascular disorders	8 (7.8)	1 (4.2)	1 (3.8)	5 (20.0)	3 (11.1)	18 (17.6)
Hypotension	8 (7.8)	0	0	2 (8.0)	0	10 (9.8)
Flushing	0	1 (4.2)	1 (3.8)	2 (8.0)	2 (7.4)	6 (5.9)
Orthostatic hypotension	0	0	0	2 (8.0)	1 (3.7)	3 (2.9)
General disorders and administration site conditions	3 (2.9)	4 (16.7)	4 (15.4)	2 (8.0)	4 (14.8)	16 (15.7)
Fatigue	1 (1.0)	1 (4.2)	3 (11.5)	1 (4.0)	1 (3.7)	7 (6.9)
Chest pain	1 (1.0)	1 (4.2)	0	0	1 (3.7)	3 (2.9)
Pyrexia	1 (1.0)	0	0	0	1 (3.7)	2 (2.0)
Skin and subcutaneous tissue disorders	0	3 (12.5)	6 (23.1)	2 (8.0)	3 (11.1)	14 (13.7)
Pruritus	0	1 (4.2)	3 (11.5)	0	0	4 (3.9)
Erythema	0	0	2 (7.7)	0	0	2 (2.0)
Acne	0	0	1 (3.8)	0	1 (3.7)	2 (2.0)
Skin burning sensation	0	1 (4.2)	1 (3.8)	0	0	2 (2.0)
Rash papular	0	1 (4.2)	0	0	1 (3.7)	2 (2.0)
Skin warm	0	0	1 (3.8)	1 (4.0)	0	2 (2.0)
Gastrointestinal disorders	4 (3.9)	1 (4.2)	2 (7.7)	3 (12.0)	3 (11.1)	13 (12.7)
Vomiting	1 (1.0)	0	0	1 (4.0)	1 (3.7)	3 (2.9)
Stomach discomfort	1 (1.0)	1 (4.2)	0	1 (4.0)	0	3 (2.9)
Nausea	1 (1.0)	0	1 (3.8)	0	1 (3.7)	3 (2.9)
Gastroesophageal reflux disease	0	0	1 (3.8)	0	1 (3.7)	2 (2.0)
Eye disorders	5 (4.9)	1 (4.2)	0	1 (4.0)	3 (11.1)	9 (8.8)
Eye pruritus	4 (3.9)	0	0	1 (4.0)	0	5 (4.9)

Eye pain	2 (2.0)	0	0	0	1 (3.7)	2 (2.0)
Immune system disorders	0	1 (4.2)	1 (3.8)	2 (8.0)	0	5 (4.9)
Seasonal allergy	0	1 (4.2)	1 (3.8)	2 (8.0)	0	5 (4.9)
Respiratory, thoracic and mediastinal disorders	0	1 (4.2)	1 (3.8)	1 (4.0)	2 (7.4)	5 (4.9)
Pharyngolaryngeal pain	0	0	1 (3.8)	1 (4.0)	1 (3.7)	3 (2.9)
Cardiac disorders	0	0	2 (7.7)	1 (4.0)	1 (3.7)	4 (3.9)
Tachycardia	0	0	2 (7.7)	1 (4.0)	1 (3.7)	4 (3.9)
Blood and lymphatic system disorders	0	0	1 (3.8)	0	2 (7.4)	3 (2.9)
Anaemia	0	0	1 (3.8)	0	1 (3.7)	2 (2.0)

^a Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.

^b A subject was counted once even if the subject experienced more than 1 AE during the study.

Intraocular pressure (IOP) and ophthalmic assessment

On Day 1 (ophthalmic solution dosing day), the applicant reported that lowest and highest mean IOP values were comparable across subjects randomized to the CD07805/47 gel treatment groups. On Days 4, 18, and 32 (the dosing period for CD07805/47 gel), the mean lowest and highest IOP values were reported as also comparable across treatment groups. There was no notable IOP lowering effect for the highest concentration of CD07805/47 gel. There were no clinically meaningful reductions in mean IOP observed after 1, 15, or 29 daily applications in any of the gel treatment groups. Also see section 7.3.5 of this review for additional discussion of IOP measurements in the development program.

Vital signs

Blood pressure data were collected on Day 1, Day 4, Day 18, and Day 32, at pre-specified time points. No clinically meaningful differences in mean blood pressure or heart rates were observed among the treatment groups.

Conclusions

Dr. Lu concluded that the PK data establish that “the systemic exposure of once daily topical use of brimonidine tartrate topical gel, 0.5%, (1 gram applied to the face) was less than the exposure of brimonidine tartrate ophthalmic solution 0.2% at its approved dose of 1 drop into each eye TID.”

Based on the comparative bioavailability data, the Medical Officer concluded that, the applicant had adequately established a “clinical bridge” to brimonidine tartrate ophthalmic solution, 0.2% which permitted the applicant to rely on the agency’s findings of safety for the solution to support the approval of brimonidine topical gel, 0.33%.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for brimonidine tartrate gel included 18 clinical trials conducted: 13 conducted by the applicant (“CD07805/47 Gel”); five conducted by CollaGenex (“COL-118 Gel”).

Ten trials evaluated a brimonidine tartrate 0.5% gel. The two brimonidine tartrate 0.5% gel formulations evaluated in these trials differed only in the amount of methylparaben, as discussed in Section 4.1 (b) (4).

Table 10 Tables of All Clinical Trials (Source: Table 01-Integrated Summary of Safety Statistical Analysis Plan)

Study Category	Study No.	Population	Study Objective	Study Design	Exposure Dose	Exposure Duration	# Subjects Treated
Well-controlled Study	RD.06.SRE.18140	patients	Efficacy and Safety (Phase 3)	Randomized, double-blind, vehicle-controlled, Parallel Group Study	0.5% BT Gel Vehicle Gel	29	260
	RD.06.SRE.18141	patients	Efficacy and Safety (Phase 3).	Randomized, double-blind, vehicle-controlled, Parallel Group Study	0.5% BT Gel Vehicle Gel	29	293
Long Term Study	RD.06.SRE.18142	patients	Long-term Safety and Efficacy (Phase 3)	open-label	0.5% BT Gel	365	449
Dose Finding Study	RD.06.SRE.18161	patients	Efficacy and Safety study (Phase 2b).	Randomized, double-blind, vehicle-controlled, Parallel Group Study	0.18% BT Gel QD 0.18% BT Gel BID 0.5% BT Gel QD Vehicle Gel BID Vehicle Gel QD	29	269
	COL-118-Rose-101	patients	Dose-response	Intra-individual Study (6 confined 1cm ² area on face)	diluent 0.0125% BT ophthalmic solution 0.025% BT ophthalmic solution 0.05% BT ophthalmic solution 0.10% BT ophthalmic solution 0.20% BT ophthalmic solution	1	22
	COL-118-Rose-102	patients	Pharmacodynamic (PD)	Intra-individual Study (6 confined 1cm ² area on face)	0.10% BT Gel A 0.10% BT Gel B 0.10% BT Gel C 0.10% BT Cream A 0.10% BT Cream B 0.10% BT Cream C	1	20
	COL-118-Rose-201	patients	Dose-response and PD	Randomized, double-blind, vehicle-controlled, Parallel Group Study	0.2% BT Gel 0.07% BT Gel 0.02% BT Gel Vehicle Gel	29	110

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Study Category	Study No.	Population	Study Objective	Study Design	Exposure Dose	Exposure Duration	# Subjects Treated
	RD.06.SRE.18144	patients	Dose-finding, PD and safety	Randomized, double-blind, vehicle-controlled, Parallel Group Study	0.07% BT Gel 0.18% BT Gel 0.5% BT Gel Vehicle Gel	1	122
PK Study	COL-118-BAPK-101	Healthy subjects	Relative bioavailability	2-way crossover	0.2% BT Gel 0.2% BT ophthalmic solution	1 day per period	16
	RD.06.SRE.18139	Healthy subjects	Thorough QTc	3-way crossover, positive and placebo controlled, double-blind,	Treatment A = Brimonidine = 2 drops 0.2% BT ophthalmic solution + 1 placebo moxifloxacin capsule; Treatment B = Placebo = 2 drops placebo ophthalmic solution (Advanced Eye Relief)+1 placebo moxifloxacin capsule; Treatment C = Moxifloxacin = 2 drops placebo ophthalmic solution (Advanced Eye Relief)+1 moxifloxacin capsule 400 mg	2 day per period	60
	RD.06.SRE.18126 (COL-118-ROSE-202)	patients	Relative systemic bioavailability	2-way crossover	Treatment A = 0.18% BT Gel + placebo ophthalmic solution (Advanced Eye Relief) (equivalent to 0.18%BID (2nd at 4hr)) Treatment B = Vehicle Gel + 0.2% BT ophthalmic Solution	1 day per period	20
	RD.06.SRE.18143	patients	Comparative bioavailability and PK	Day 1: 0.2% BT Ophth Soln (B&L), Day 4: Randomized, evaluator-blinded,	0.2% BT ophthalmic Solution + 0.07% BT Gel 0.2% BT ophthalmic Solution + 0.18% BT Gel 0.2% BT ophthalmic Solution + 0.5% BT Gel	1 day BT ophthalmic Solution; 29 days BT Gels	102

Study Category	Study No.	Population	Study Objective	Study Design	Exposure Dose	Exposure Duration	# Subjects Treated
Dermal Safety Study	COL-118-Phototoxicity-104	Healthy subjects	Phototoxicity	Intra-individual study (4 sites per subject; 2 irradiated sites, 2 unirradiated controlled sites)	0.2% BT Gel Vehicle Gel	2 days	30
	RD.06.SRE.18123	Healthy subjects	Local Tolerance (sensitization); RIPT(repeated Insult patch test)	Intra-individual study (5 sites per subject). Induction, challenge, rechallenge.	0.07% BT Gel 0.18% BT Gel 0.5% BT Gel Vehicle Gel White petrolatum	19 days in induction phase	247
	RD.06.SRE.18124	Healthy subjects	Local Tolerance (photosensitization)	Intra-individual study (5 sites per subject). Induction, challenge, rechallenge.	0.07% BT Gel 0.18% BT Gel 0.5% BT Gel Vehicle Gel White petrolatum	19 days in induction	57
	RD.06.SRE.18125	Healthy subjects	Local Tolerance (cumulative irritancy)	Intra-individual study (6 sites per subject)	0.07% BT Gel 0.18% BT Gel 0.5% BT Gel Vehicle Gel White petrolatum Sodium lauryl sulfate	22 days	38
	RD.06.SRE.18137	Healthy subjects	SPF determination (vehicle with titanium dioxide excipient, no active brimonidine DS used).	intra-individual study (3 sites per subject)	Vehicle Gel Homosalate 8% Lotion Untreated area	1 day	25
	RD.06.SRE.18189	Healthy subjects	Phototoxicity	Intra-individual study (10 sites per subjects, 5 irradiated sites, 5 non-irradiated sites)	0.07% BT Gel 0.18% BT Gel 0.5% BT Gel Vehicle Gel Untreated area	3 days	35

BT = Brimonidine tartrate

5.2 Review Strategy

The applicant cited five trials in support of efficacy:

- one dose-finding study: Phase 2a Study (RD.06.SRE.18144) (single application),
- one Phase 2b efficacy and safety study (RD.06.SRE.18161),
- two Phase 3 adequate and well-controlled safety and efficacy studies (RD.06.SRE.18140 and RD.06.SRE.18141), and
- one Phase 3 long-term safety and efficacy study (RD.06.SRE.18142).

The applicant relied on efficacy data from the Phase 3 pivotal trials 18140 and 18141 to establish efficacy, and the review of efficacy will focus on these trials.

The other trials provided supportive evidence of efficacy and are discussed elsewhere in the review. Discussion of 18161 and 18142 is largely in the context of safety as the applicant integrated data from 18161 with those from 18140 and 18141 for the integrated safety database (termed the “Controlled Core Studies”). Study 18142 was an open-label study principally intended to provide information on the long-term safety of brimonidine gel, 0.33%.

5.3 Discussion of Individual Studies/Clinical Trials

Individual trials discussed in various sections the review.

6 Review of Efficacy

Efficacy Summary

The applicant provided substantial evidence of efficacy. The applicant conducted two adequate and well-controlled trials, of identical design, which evaluated brimonidine gel, 0.33% for the treatment of the facial erythema of rosacea. In both trials, the applicant’s product was significantly superior to vehicle in the target population. The primary endpoint was *Composite Success* at Hours 3, 6, 9 and 12 first on Day 29, then on Day 15 and lastly Day 1, where *Composite Success* was defined as 2-grade improvement on both the Clinician Erythema Assessment (CEA) and the Patient Self Assessment (PSA) scales at each time point. The testing on Day 29 was performed first as the primary analysis. If the result was statistically significant, the testing was to continue to Day 15 and then to Day 1. The primary endpoint was agreed upon, as was conveyed in the SPA agreement letter. Brimonidine gel, 0.33% was superior to vehicle at each time point, on each day, and the results were statistically significant for each assessment. The details are discussed in Section 6.1.4.

No statistical issues were identified that would impact the final conclusions regarding efficacy. However, the applicant's primary analyses only considered subjects who completed the Day 29 assessments and did not address missing data. Therefore, the statistical reviewer, Dr. Matthew Guerra, performed analyses on imputed data, and the results remained statistically significant for each assessment under these analyses. Additionally, all results remained statistically significant when performed on a modified intent-to-treat population which excluded all subjects from one site where the research coordinator had falsified data (a blood pressure reading) and, as well, under a sensitivity analysis which excluded sites where the applicant disclosed financial arrangements with investigators (those arrangements raised no questions about data integrity).

The submitted data only allow a conclusion that no evidence of tachyphylaxis was observed with short-term use, as the applicant evaluated for the potential for tachyphylaxis only during the 29-day treatment period.

6.1 Indication

The applicant proposed brimonidine gel, 0.33% "for the topical treatment of facial erythema of rosacea in adults 18 years of age or older."

6.1.1 Methods

The applicant conducted two pivotal trials of identical design. Both were multicenter, randomized, double-blind, parallel-group, vehicle-controlled efficacy and safety trials which evaluated CD07805/47 topical gel in subjects with moderate to severe facial erythema associated with rosacea. The trials were conducted in the United States and Canada. As the trials were identical, this review describes design features and methodology singly, i.e. the methodology described below applies to 18140 and 18141. The efficacy results are discussed separately for each trial.

Title (of both trials): A multicenter, randomized, double-blind, vehicle-controlled, parallel group study to demonstrate the efficacy and assess the safety of CD07805/47 gel 0.5% applied topically once daily in subjects with moderate to severe facial erythema associated with rosacea.

Study objectives:

- Efficacy objective: To demonstrate the efficacy of CD07805/47 gel 0.5% applied topically once daily for 4 weeks versus vehicle control, in the treatment of moderate to severe facial erythema associated with rosacea.
- Safety objective: To assess the safety of CD07805/47 gel 0.5% applied topically once daily for 4 weeks versus vehicle control, in the treatment of moderate to severe facial erythema associated with rosacea.

Inclusion criteria

In order to be eligible for the study, subjects must have fulfilled all of the following criteria.

1. Male or female who is at least 18 years of age or older.
2. A clinical diagnosis of facial rosacea.
3. A Clinician Erythema Assessment (CEA) score of ≥ 3 at Screening and on Baseline/Day 1 (prior to the T0 study drug application).
4. A Patient Self Assessment (PSA) score of ≥ 3 at Screening and on Baseline/Day 1 (prior to the T0 study drug application).
5. Females of childbearing potential with a negative urine pregnancy test (UPT) at Screening and Baseline/Day 1 (prior to the T0 study drug application), or females of non-childbearing potential (post-menopausal [absence of menstrual bleeding for 1 year prior to enrollment], documented hysterectomy, or bilateral oophorectomy).
6. Willing and able to comply with all of the time commitments and procedural requirements of the protocol.
7. Understands and signed an Informed Consent Form at Screening, prior to any investigational procedure being performed.
8. Apprised of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), if in the US or the Personal Information Protection and Electronic Documents Act (PIPEDA), if in Canada and is willing to share personal information and data, as verified by signing a written authorization at Screening.
- 9.

Exclusion criteria per Amendment #1

Any subject who met one or more of the following criteria was not to have been included in this study.

1. Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other concomitant facial dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia.
2. Presence of three (3) or more facial inflammatory lesions of rosacea.
3. Current treatment with monoamine oxidase (MAO) inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, or alpha-agonists.
4. Less than 3 months stable dose treatment with tricyclic anti-depressants, cardiac glycosides, beta blockers or other antihypertensive agents.
5. Current diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression.
6. Any uncontrolled chronic or serious disease or medical condition that would normally prevent participation in a clinical trial, or, in the judgment of the Investigator, would put the subject at undue risk, or might confound the study assessments (e.g. other dermatological diseases), or might interfere with the subject's participation in the study, (e.g. planned hospitalization during the study).
7. Known allergies or sensitivities to any component of the study drugs, including the active ingredient brimonidine tartrate.
8. The subject has received, applied, or taken the following treatments within the specified time frame prior to the Baseline/Day 1 clinic visit:

TOPICAL FACIAL treatments:

- Laser, Photodynamic Therapy or IPL (intense pulsed light) treatment; Electrocoagulation; Dermabrasion; Facial peels; Any other dermatologic/surgical procedure on the face; Prescription medications for the treatment of rosacea (e.g. azelaic acid, metronidazole, etc.); Prescription medications for treatment of acne; Immunomodulators; Corticosteroids: 4 weeks.
- Antibiotics: 2 weeks.
- Over-the-counter (OTC) medications for treatment of acne: 1 week.
- Astringents or abrasives: 2 days.

SYSTEMIC treatments:

- Isotretinoin: 6 months.
 - Immunomodulators: 12 weeks.
 - Prescription medications for the treatment of rosacea (e.g. doxycycline, tetracycline, macrolides); Prescription medications for treatment of acne; Corticosteroids (oral or injectable); Phototherapy; Antibiotics: 4 weeks.
 - Prescription anti-inflammatory medications: 2 weeks.
 - Chronic, daily use of OTC anti-inflammatory medications (e.g. ibuprofen, naproxen) for more than 1 week (does not include low-dose aspirin for cardiac prophylaxis): 1 week.
 - Niacin \geq 500 mg per day: 1 week.
9. Female who was pregnant or is lactating.
 10. Female who intended to conceive a child during the course of the study.
 11. Exposed to excessive ultraviolet (UV) radiation within 1 week prior to Baseline and/or subject was unwilling to refrain from excessive exposure to UV radiation during the course of the study.
 12. Presence of beard or excessive facial hair at Screening which would interfere with the study treatments or study assessments and refusal to remove for duration of study.
 13. Refusal to submit to blood and urine sampling for laboratory analysis.
 14. Prior treatment with CD07805/47 gel.
 15. Treatment at the time of eligibility assessment (Screening/Day 1) with brimonidine tartrate ophthalmic solution.
 16. Treatment at the time of eligibility assessment (Screening/Day 1) with any topical facial formulation containing brimonidine tartrate or oxymetazoline.
 17. Participation at the time of eligibility assessment (Screening/Day 1) in any other investigational drug or device study or participated within 30 days prior to Baseline.

Overall study design and methodology

Screening and Baseline assessments of erythema were performed on two different days to confirm the presence of stable moderate to severe non-transient erythema.

Approximately two hundred and sixty (260) subjects were to have been randomized at the Baseline/Day1 visit in a 1:1 ratio to one of the following treatment arms:

- CD07805/47 gel 0.5% applied once daily for four weeks
- CD07805/47 vehicle gel applied once daily for four weeks

Subjects were assessed over a 12- hour post-dose evaluation period on Day 1, Day 15, and Day 29 at the investigational site. On non-clinic days (through Day 28) subjects applied study drug as directed and completed daily subject assessments. Subjects returned to the clinic sites on Week 6 and Week 8/Early Termination for post-treatment follow-up evaluations.

The evaluator completed the Clinician Erythema Assessment (CEA) at each clinic visit (Screening, Baseline/Day 1, Day 15, Day 29, and Follow-up visits).

Clinician Erythema Assessment (CEA)

The Investigator/evaluator (a board-certified dermatologist) evaluated the subject's rosacea-associated facial erythema by performing a static ("snap-shot") evaluation of erythema severity using the CEA, and reported the one integer that best described the overall severity.

Table 11 Clinician Erythema Assessment (CEA)

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

Patient Self Assessment (PSA)

Subjects performed static (“snap-shot”) evaluations of their rosacea-associated facial erythema severity at Screening, Baseline/Day 1, Day 15, Day 29, and Follow-up visits using the Patient Self Assessment scale (PSA), and reported the one integer that best described the overall severity of their facial redness as seen in a mirror at the time of the evaluation.

Subjects completed a Patient Self Assessment (PSA) at each clinic visit and different PSA on non-clinic Days 2-14 and 16-28 (on non-clinic days the subject completed a PSA once daily just before bedtime and captured daily status by subject recall).

Table 12 Clinic Day Assessment Patient Self Assessment (Screening, Day 1, Day 15, Day 29, Week 6, and Week 8/ET)

Circle the number that best describes your rosacea-related facial redness RIGHT NOW.	
0	No redness
1	Very mild redness
2	Mild redness
3	Moderate redness
4	Severe redness

Note: The PSA used on non-clinic days was the same scale, but instructed subjects to “Circle the number that best describes your rosacea-related facial redness TODAY since first applying the study medication this morning.”

Investigators and subjects completed several other assessments which were designated as tertiary endpoints (six) or “other” endpoints (ten). The review will generally not discuss these endpoints, as the reviewer considered them to be exploratory. See Section 6.1.6.

Concomitant therapies

Subjects were prohibited from using therapies listed in the Exclusion Criteria. On non-clinic days, subjects could use facial products such as lotions, creams, ointments, cosmetics, and sunscreens, unless specifically excluded. Study drug was to be applied prior to any other facial product.

Vital signs were assessed at Screening, Day 1, Day 15, Day 29, and Week 8/ET. Laboratory safety tests (hematology, blood chemistry, urinalysis) were conducted at Screening and Day 29. Adverse event assessments were done at every clinic visit.

Efficacy and safety assessments were performed on Baseline/Day 1 and at each subsequent post-baseline visit. For each clinic visit, subjects were instructed to wait until they arrived at the investigational site to apply the study drug. The time of application (T0) was recorded. Post-application assessments were performed at 30 min, 3, 6, 9, and 12 hours, after T0.

The **primary endpoint** was *Composite Success* at Hours 3, 6, 9 and 12 first on Day 29, then on Day 15 and lastly Day 1, where *Composite Success* was defined as 2-grade improvement on both CEA and PSA at each time point.

The protocol defined two secondary endpoints, and these are discussed in Section 6.1.5.

6.1.2 Demographics

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.

Table 13: Demographics (Statistical review Table 8)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	Mirvaso Gel (N=148)	Vehicle Gel (N=145)
Age				
Mean (SD)	49.5 (11.8)	48.1 (12.8)	48.5 (11.9)	46.5 (12.1)
Range	20 - 76	18 - 87	22 - 77	19 - 78
Gender				
Male	25 (19.4%)	29 (22.1%)	43 (29.1%)	37 (25.5%)
Female	104 (80.6%)	102 (77.9%)	105 (70.9%)	108 (74.5%)
Race				
White	127 (98.4%)	129 (98.5%)	145 (98.0%)	144 (99.3%)
Black	2 (1.6%)	1 (0.8%)	2 (1.3%)	1 (0.7%)
Asian	0	1 (0.8%)	1 (0.7%)	0
Ethnicity				
Hispanic or Latino	7 (5.4%)	11 (8.4%)	8 (5.4%)	10 (6.9%)
Not Hispanic or Latino	122 (94.6%)	120 (91.6%)	140 (94.6%)	135 (93.1%)

SD: Standard Deviation
 Source: Reviewer's Analysis

Table 14: Baseline Disease Characteristics (ITT) (Statistical review Table 9)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	Mirvaso Gel (N=148)	Vehicle Gel (N=145)
CEA				
3 - Moderate	111 (86.0%)	113 (86.3%)	108 (73.0%)	115 (79.3%)
4 - Severe	18 (14.0%)	18 (13.7%)	40 (27.0%)	30 (20.7%)
PSA				
1 - Very Mild	0	1 (0.8%)	0	0
3 - Moderate	107 (82.9%)	114 (87.0%)	129 (87.2%)	122 (84.1%)
4 - Severe	22 (17.1%)	16 (12.2%)	19 (12.8%)	23 (15.9%)
Skin Phototype				
I	19 (14.7%)	8 (6.1%)	12 (8.1%)	13 (9.0%)
II	65 (50.4%)	74 (56.5%)	88 (59.5%)	84 (57.9%)
III	38 (29.4%)	37 (28.2%)	36 (24.3%)	38 (26.2%)
IV	6 (4.7%)	11 (8.4%)	11 (7.4%)	9 (6.2%)
V	1 (0.8%)	1 (0.8%)	1 (0.7%)	1 (0.7%)

Source: Reviewer's Analysis

Demographic and baseline disease characteristics were generally well-balanced between treatment groups for 18140. However, there were > twice as many subjects with skin type I in the brimonidine group compared to vehicle in 18140 and nearly twice as many subjects with skin type IV in the vehicle group compared to brimonidine. There was balance between treatment groups in assessment of moderate and severe erythema on CEA in 18140. More subjects in the brimonidine group in 18140 rated their redness as severe compared to the vehicle group. The opposite pattern was seen with "moderate" redness.

Demographic and baseline disease characteristics were generally balanced between treatment groups in 18141. On the CEA, more subjects in the vehicle group were graded as moderate erythema relative to the brimonidine group, while more subjects were graded as severe in the active group compared to vehicle. On the PSA, the opposite pattern was seen (although to a lesser extent than with the CEA). More subjects were baseline disease as “severe” by the CEA in 18141 compared to 18140.

Concomitant Therapies

In 18140, 43 subjects (16.5%) in the combined treatment groups used “other emollients and protectives” (not otherwise specified). A total of 14 subjects (5.4%) in the combined treatment groups used sunscreen.

In 18141, 22 subjects (7.5%) in the combined treatment groups used “other emollients and protectives” (not otherwise specified). A total of 18 subjects (6.1%) used “protectives against UV-Radiation.”

6.1.3 Subject Disposition

18140

A total of 260 subjects were randomized and included in the ITT Population in 18140.

Table 15 Summary of Subject Disposition 18140, ITT Population (Applicant Table 16 of study report)

Completion Status	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	Total (N=260)
Normal Completion	127 (98.4%)	127 (96.9%)	254 (97.7%)
Premature Discontinuation	2 (1.6%)	4 (3.1%)	6 (2.3%)
Lack of Efficacy	0	0	0
Adverse Event	2 (1.6%)	1 (0.8%)	3 (1.2%)
Subject's Request	0	1 (0.8%)	1 (0.4%)
Protocol Violation	0	1 (0.8%)	1 (0.4%)
Lost to Follow-up	0	1 (0.8%)	1 (0.4%)

Six subjects discontinued prematurely: two in the brimonidine group and four in the vehicle group. The three subjects who discontinued due to adverse events are discussed in Section 7.3.3 of the review.

18141

A total of 293 subjects were randomized and included in the ITT Population in 18141.

Table 16 Summary of Subject Disposition, ITT Population (Applicant Table 17 of study report)

Completion Status	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)	Total (N=293)
Normal Completion	141 (95.3%)	142 (97.9%)	283 (96.6%)
Premature Discontinuation	7 (4.7%)	3 (2.1%)	10 (3.4%)
Adverse Event	1 (0.7%)	1 (0.7%)	2 (0.7%)
Subject's Request	2 (1.4%)	0	2 (0.7%)
Protocol Violation	3 (2.0%)	2 (1.4%)	5 (1.7%)
Other	1 (0.7%)	0	1 (0.3%)

The two subjects who discontinued due to adverse events are discussed in Section 7.3.3.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable for the study was 2-grade Composite Success at Hours 3, 6, 9, and 12 first on Day 29, then on Day 15, and then on Day 1. Composite Success was defined as 2-grade improvement on both the CEA and PSA at each time point.

The testing on Day 29 was performed first as the primary analysis. If the result was statistically significant, the testing was to continue to Day 15 and then to Day 1. The primary analyses were performed based on the intent-to-treat (ITT) Population. The applicant defined a modified intent-to-treat (mITT) population which excluded all subjects from site 8283 (further discussed below; also see Section 3.2).

The agency had advised the applicant during the pre-submission period that because the treatment effect on erythema was non-durable, efficacy should be measured by a co-primary endpoint which reflected the investigator (objective) assessment and the subject (subjective) assessment. Also, because of lack of durability of effect, the primary endpoint should reflect assessment over the course of treatment. The applicant was also advised that primary efficacy should be based on repeated measurements to capture a clinically-meaningful treatment effect over time.

The applicant and the agency agreed on the primary efficacy endpoint and sequential testing under the Special Protocol Assessment process.

The applicant's analyses only considered subjects who completed the Day 29 assessments (observed data) and did not address missing data. Dr. Guerra based his analyses on imputed data (imputing missing data), and it is these analyses that will be used in the label. Dr. Guerra recommended "including those subjects with missing evaluations by using the averages over the 5 imputed datasets generated by the

Multiple Imputation (MI) approach, as efficacy results are usually presented for all randomized subjects enrolled in the trial (ITT) and not for observed cases only.”

18140

The results for the primary endpoint “Composite Success” for 18140 are presented in the following table from Dr. Guerra’s review. The table presents the applicant’s and Dr. Guerra’s analyses. In both analyses, brimonidine gel, 0.33% (Mirvaso) was superior to vehicle at each time point on all days, i.e. Days 1, 15 and 29, and the results were statistically significant ($p < 0.001$).

Table 17: Composite Success⁽¹⁾ Rates by Hours and Days for Study 18140 (ITT) (Statistical review Table 10)

	Observed Data		Imputed Data ⁽²⁾		p-value ⁽³⁾
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	
Day 29					
Hour 3	40/127 (31.5%)	14/128 (10.9%)	40.2 (31.2%)	14.4 (11.0%)	<0.001
Hour 6	39/127 (30.7%)	12/128 (9.4%)	39 (30.2%)	12.6 (9.6%)	
Hour 9	33/127 (26.0%)	13/128 (10.2%)	33 (25.6%)	13.4 (10.2%)	
Hour 12	29/127 (22.8%)	11/128 (8.6%)	29 (22.5%)	11.6 (8.9%)	
Day 15					
Hour 3	32/128 (25.0%)	4/128 (3.1%)	32 (24.8%)	4.4 (3.4%)	<0.001
Hour 6	35/128 (27.3%)	8/128 (6.3%)	35 (27.1%)	9.4 (7.2%)	
Hour 9	25/128 (19.5%)	7/128 (5.5%)	25 (19.4%)	7.2 (5.5%)	
Hour 12	21/128 (16.4%)	3/128 (2.3%)	21 (16.3%)	3.4 (2.6%)	
Day 1					
Hour 3	21/129 (16.3%)	4/131 (3.1%)	*	*	<0.001
Hour 6	30/129 (23.3%)	3/131 (2.3%)	*	*	
Hour 9	25/129 (19.4%)	5/131 (3.8%)	*	*	
Hour 12	17/129 (13.2%)	4/130 (3.1%)	*	4.2 (3.2%)	

Source: Reviewer’s Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

(3) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point.

(*) No missing data, therefore no imputation of missing data.

18141

The results for the primary endpoint “Composite Success” for 18141 are presented in the following table from Dr. Guerra’s review. The table presents the applicant’s and Dr. Guerra’s analyses. Again, under both analyses, brimonidine gel, 0.33% (Mirvaso) was superior to vehicle at each time point on all days, i.e. Days 1, 15 and 29, and the results were statistically significant ($p < 0.001$). Dr. Guerra’s Table below presents both analyses.

Table 18: Composite Success (1) Rates by Hours and Days for Study 18141 (ITT)
(Statistical review Table 11)

	Observed Data		Imputed Data ⁽²⁾		p-value ⁽³⁾
	Mirvaso Gel (N=148)	Vehicle Gel (N=145)	Mirvaso Gel (N=148)	Vehicle Gel (N=145)	
Day 29					
Hour 3	36/142 (25.4%)	13/142 (9.2%)	37.4 (25.3%)	13.2 (9.1%)	<0.001
Hour 6	36/142 (25.4%)	13/142 (9.2%)	37.4 (25.3%)	13 (9.0%)	
Hour 9	25/142 (17.6%)	15/142 (10.6%)	26.2 (17.7%)	15.2 (10.5%)	
Hour 12	30/142 (21.1%)	14/142 (9.9%)	31.8 (21.5%)	14 (9.7%)	
Day 15					
Hour 3	36/143 (25.2%)	5/141 (3.5%)	37 (25.0%)	5 (3.4%)	<0.001
Hour 6	37/143 (25.9%)	6/141 (4.3%)	37.8 (25.5%)	6 (4.1%)	
Hour 9	31/143 (21.7%)	7/141 (5.0%)	32 (21.6%)	7 (4.8%)	
Hour 12	22/143 (15.4%)	10/141 (7.1%)	23.2 (15.7%)	10 (6.9%)	
Day 1					
Hour 3	29/148 (19.6%)	0/145 (0%)	*	*	<0.001
Hour 6	44/148 (29.7%)	3/145 (2.1%)	*	*	
Hour 9	27/148 (18.2%)	1/144 (0.7%)	*	1 (0.7%)	
Hour 12	20/148 (13.5%)	2/144 (1.4%)	*	2 (1.4%)	

Source: Reviewer's Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

(3) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point. For Day 1, as no missing data in the Mirvaso arm and only 1 subject with missing data in the vehicle arm, MI produced the same 5 datasets; therefore the p-value is based on one imputed dataset (i.e. not based on all five identical datasets).

(*) No missing data, therefore n

For the 18141 trial, the applicant defined a mITT population which excluded all 33 subjects from site 8283 (see Section 3.2). Dr. Guerra analyzed the primary endpoint for the mITT population, and those analyses are presented with the applicant's in the following table. The results remain statistically significant:

Table 19: Composite Success⁽¹⁾ Rates by Hours and Days for Study 18141 (mITT) (Statistical review Table 13)

	Observed Data		Imputed Data ⁽²⁾		p-value ⁽³⁾
	Mirvaso Gel (N=131)	Vehicle Gel (N=129)	Mirvaso Gel (N=131)	Vehicle Gel (N=129)	
Day 29					
Hour 3	27/125 (21.6%)	13/127 (10.2%)	28.4 (21.7%)	13.2 (10.2%)	<0.001
Hour 6	29/125 (23.2%)	13/127 (10.2%)	30.4 (23.2%)	13 (10.1%)	
Hour 9	23/125 (18.4%)	15/127 (11.8%)	24.2 (18.5%)	15.2 (11.8%)	
Hour 12	24/125 (19.2%)	14/127 (11.0%)	25.8 (19.7%)	14 (10.9%)	
Day 15					
Hour 3	30/126 (23.8%)	5/126 (4.0%)	31 (23.7%)	5 (3.9%)	<0.001
Hour 6	30/126 (23.8%)	6/126 (4.8%)	30.8 (23.5%)	6 (4.7%)	
Hour 9	28/126 (22.2%)	7/126 (5.6%)	29 (22.1%)	7 (5.4%)	
Hour 12	19/126 (15.1%)	10/126 (7.9%)	20.2 (15.4%)	10 (7.8%)	
Day 1					
Hour 3	23/131 (17.6%)	0/129 (0%)	*	*	0.004
Hour 6	36/131 (27.5%)	3/129 (2.3%)	*	*	
Hour 9	24/131 (18.3%)	1/128 (0.8%)	*	1 (0.8%)	
Hour 12	15/131 (11.5%)	2/128 (1.6%)	*	2 (1.6%)	

Source: Reviewer's Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

(3) P-value calculated using imputed data and based on a GEE model with treatment, analysis center and time point. For Day 1, as no missing data in the Mirvaso arm and only 1 subject with missing data in the vehicle arm, MI produced the same 5 datasets; therefore the p-value is based on one imputed dataset (i.e. not based on all five identical datasets).

(*) No missing data, therefore no imputation of missing data.

For each pivotal trial, Dr. Guerra also considered the day response rates, averaging the rates from each time point (hour 3, 6, 9, and 12) for each day. Those results are presented in the following table:

Table 20: Average Composite Success Rates⁽¹⁾ on Days 29, 15, and 1 (ITT) (Statistical review Table 12)

	Study 18140		Study 18141	
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)	Mirvaso Gel (N=148)	Vehicle Gel (N=145)
Day 29	27.4%	9.9%	22.4%	9.6%
Day 15	21.9%	4.7%	22.0%	4.8%
Day 1	18.0%	3.1%	20.3%	1.0%

Source: Reviewer's Analysis

(1) Composite success is defined as 2-grade improvement on both CEA and PSA. Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over hours 3, 6, 9, and 12, and over the 5 imputed datasets.

Dr. Guerra also conducted a sensitivity analysis in which missing data for brimonidine gel, 0.33% were imputed as failures and missing data for vehicle imputed as successes. In these most conservative analyses, 0.5% gel remained superior to vehicle at a level of statistical significance.

Table 21: Reviewer’s Sensitivity Analysis⁽¹⁾ for Composite Success⁽²⁾ Rates by Hours and Days (ITT) (Statistical review Table 14)

	Study 18140		p-value ⁽²⁾	Study 18141		p-value ⁽²⁾
	Mirvaso Gel (N=129)	Vehicle Gel (N=131)		Mirvaso Gel (N=148)	Vehicle Gel (N=145)	
Day 29						
Hour 3	40 (31.0%)	17 (13.0%)	<0.001	36 (24.3%)	16 (11.0%)	<0.001
Hour 6	39 (30.23%)	15 (11.5%)		36 (24.3%)	16 (11.0%)	
Hour 9	33 (25.6%)	16 (12.2%)		25 (16.9%)	18 (12.4%)	
Hour 12	29 (22.5%)	14 (10.7%)		30 (20.3%)	17 (11.7%)	
Day 15						
Hour 3	32 (24.8%)	7 (5.3%)	<0.001	36 (24.3%)	9 (6.2%)	<0.001
Hour 6	35 (27.1%)	11 (8.4%)		37 (25.0%)	10 (6.9%)	
Hour 9	25 (19.4%)	10 (7.6%)		31 (20.9%)	11 (7.6%)	
Hour 12	21 (16.3%)	6 (4.6%)		22 (14.9%)	14 (9.7%)	
Day 1						
Hour 3	21 (16.3%)	4 (3.1%)	<0.001	29 (19.6%)	0 (0%)	0.002
Hour 6	30 (23.3%)	3 (2.3%)		44 (29.7%)	3 (2.1%)	
Hour 9	25 (19.4%)	5 (3.8%)		27 (18.2%)	2 (1.4%)	
Hour 12	17 (13.2%)	5 (3.8%)		20 (13.5%)	3 (2.1%)	

Source: Reviewer’s Analysis

(1) Missing data for Mirvaso gel imputed as failures and missing data for vehicle gel was imputed as successes.

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

(2) P-value calculated using a GEE model with treatment, analysis center and time point.

6.1.5 Analysis of Secondary Endpoints(s)

The protocols for the pivotal trials described two secondary endpoints:

- CEA Initial Effect is defined as 1-grade improvement on CEA at 30 minutes on Day 1.
- PSA Initial Effect is defined as 1-grade improvement on PSA at 30 minutes on Day 1.

However, the Statistical Analysis Plan dated May 4, 2011 described a single secondary endpoint, the “30-minute Effect”, defined as 1-grade Composite Success (1-grade improvement on CEA and PSA) at 30 minutes on Day 1.

In the study reports for the pivotal trials, the applicant presented analyses for the composite endpoint, “30-minute Effect” (defined above). Dr. Guerra found the brimonidine gel, 0.33% to be superior to vehicle, and the results were statistically significant.

Table 22: 30 Minute Effect⁽¹⁾ on Day 1 (Statistical review Table 15)

Population	Study 18140			Study 18141		
	Mirvaso Gel	Vehicle Gel	p-value ⁽²⁾	Mirvaso Gel	Vehicle Gel	p-value ⁽²⁾
ITT	36/129 (27.9%)	9/131 (6.9%)	<0.001	42/148 (28.4%)	7/145 (4.8%)	<0.001
MITT	--	--	--	37/131 (28.2%)	6/129 (4.7%)	<0.001
PP	32/113 (28.3%)	8/118 (6.8%)	<0.001	33/119 (27.7%)	4/120 (3.3%)	<0.001

Source: Reviewer's Analysis

(1) 30 minute effect is defined as a 1-grade improvement on CEA and PSA at 30 minutes on Day 1.

(2) P-value based on a CMH test stratified by analysis center.

The agency advised the applicant in the Special Protocol Agreement letter that success defined as 1-grade improvement on the CEA or PSA scale might not be clinically meaningful. Therefore, the results of this analyses will not support a labeling claim.

6.1.6 Other Endpoints

The protocols for the Phase 3 trials defined six tertiary endpoints and ten "other" endpoints. The reviewer considers these to be exploratory endpoints, and they generally will not be discussed. This review will discuss two "other" endpoints.

Investigator's Global Assessment (IGA) of Lesions

Among the "other endpoints" was the Investigator's Global Assessment (IGA) of Lesions. During development of the product, the agency advised the applicant that an investigator global assessment of overall disease should be included in the study assessments to ensure that treatment of erythema does not worsen other manifestations of the disease. The IGA of Lesions assessment was performed by the following scale:

Table 23 Investigator's Global Assessment of Lesions

Grade	Score	Clinical Description
Clear	0	No Papules/Pustules; No Nodules
Almost Clear	1	Few Small Papules/Pustules; No Nodules
Mild	2	Some Small Papules/Pustules; No Nodules
Moderate	3	Several Small and Medium Sized Papules/Pustules; One Nodule May Be Present
Severe	4	Numerous Small, Medium, and Large Sized Papules/Pustules; Two or More Nodules Present

For the Controlled Core Studies (the two pivotal trials and the Phase 2b trial), the applicant concluded that there was no significant worsening in mean IGA score at any post-baseline visit. Given that subjects were required to have ≤ two inflammatory

lesions to be study eligible, it would seem that all subjects would have been 0 (clear) or 1 (almost clear) on the IGA of Lesions at enrollment, i.e. the reviewer notes that several subjects were graded as “moderate” on Day 1 (and one “severe”). The reviewer concludes that there was no apparent significant worsening in the mean IGA score under these analyses.

Table 24 IGA of Lesions during treatment/follow-up; Studies 18161, 18140, 18141; ITT Population (Applicant Summary of Clinical Efficacy Table 30)

IGA of Lesions	18161		18140		18141	
	CD07805/47 Gel 0.5% (N=53)	Vehicle Gel (N=55)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Day 1: Hour 0						
0=Clear	25 (47.2)	35 (63.6)	95 (73.6)	94 (71.8)	102 (68.9)	102 (70.3)
1=Almost Clear	26 (49.1)	18 (32.7)	31 (24.0)	33 (25.2)	36 (24.3)	40 (27.6)
2=Mild	0	0	2 (1.6)	2 (1.5)	2 (1.4)	1 (0.7)
3=Moderate	2 (3.8)	2 (3.6)	1 (0.8)	2 (1.5)	7 (4.7)	2 (1.4)
4=Severe	0	0	0	0	1 (0.7)	0
Mean (SD)	0.6 (0.69)	0.4 (0.69)	0.3 (0.54)	0.3 (0.59)	0.4 (0.80)	0.3 (0.57)
Day 29: Hour 12						
Mean Change (SD)	-0.3 (0.84)	0.1 (0.92)	0.1 (0.74)	0.0 (0.86)	0.1 (0.91)	0.3 (0.93)
Follow-up: Day 30						
Mean Change (SD)	-0.2 (0.89)	0.1 (0.85)	NA	NA	NA	NA
Follow-up: Week 5						
Mean Change (SD)	-0.3 (0.83)	0.0 (0.84)	NA	NA	NA	NA
Follow-up: Week 6						
Mean Change (SD)	-0.2 (0.76)	0.0 (0.73)	0.0 (0.74)	-0.0 (0.67)	-0.0 (0.99)	0.1 (0.84)
Follow-up: Week 8						
Mean Change (SD)	-0.2 (0.86)	0.1 (0.86)	0.0 (0.77)	-0.0 (0.67)	-0.0 (0.92)	0.2 (0.83)

IGA of Lesions Scores: 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe

Patient Assessment of Whitening (PAW)

The Patient Assessment of Whitening (PAW) was also an “other” endpoint. Subjects completed self-assessments of potential over-extended pharmacodynamic effect of the study drug. This effect was also evaluated in the Phase 2b, 18161. The PAW is mentioned as the applicant did include some assessment of the potential for excessive drug effect in the development program. The PAW was a two-question, yes/no questionnaire which subjects completed at the clinic and on non-clinic days.

Patient Assessment of Whitening (PAW) Clinic Day Assessment (Day 1, Day 15, Day 29)

PART A: Do you have too much whitening (blanching) or blotching of your skin due to the study medication RIGHT NOW? (Circle one answer)	
Yes	
No	
PART B: If you answered YES in PART A, are you bothered by this effect? (Check one box)	<input type="checkbox"/> Yes <input type="checkbox"/> No

The results for the PAW assessments on Clinic Days are presented in Table 25. A higher proportion of brimonidine-treated subjects reported being bothered by “too much whitening.” However, up to 3.1% of subjects in the vehicle group reported this as well.

Table 25 PAW during treatment; Studies 18161, 18140, 18141; ITT Population (Applicant Summary of Clinical Efficacy Table 33)

PAW	18161		18140		18141	
	CD07805/47 Gel 0.5% (N=53)	Vehicle Gel (N=55)	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Day 1: Hour 3						
Bothered by Too Much Whitening	7 (13.2)	1 (1.8)	12 (9.3)	4 (3.1)	7 (4.7)	1 (0.7)
Day 1: Hour 6						
Bothered by Too Much Whitening	10 (18.9)	0	8 (6.2)	1 (0.8)	6 (4.1)	2 (1.4)
Day 1: Hour 9						
Bothered by Too Much Whitening	5 (9.4)	0	6 (4.7)	3 (2.3)	8 (5.4)	2 (1.4)
Day 1: Hour 12						
Bothered by Too Much Whitening	3 (5.7)	0	7 (5.4)	2 (1.5)	3 (2.0)	1 (0.7)
Day 15: Hour 3						
Bothered by Too Much Whitening	7 (13.5)	0	5 (3.9)	1 (0.8)	0	2 (1.4)
Day 15: Hour 6						
Bothered by Too Much Whitening	6 (11.5)	0	5 (3.9)	1 (0.8)	2 (1.4)	1 (0.7)
Day 15: Hour 9						
Bothered by Too Much Whitening	4 (7.7)	0	4 (3.1)	1 (0.8)	2 (1.4)	1 (0.7)
Day 15: Hour 12						
Bothered by Too Much Whitening	3 (5.8)	0	3 (2.3)	1 (0.8)	1 (0.7)	2 (1.4)
Day 29: Hour 3						
Bothered by Too Much Whitening	3 (5.9)	0	3 (2.4)	2 (1.6)	0	2 (1.4)
Day 29: Hour 6						
Bothered by Too Much Whitening	4 (7.8)	0	4 (3.1)	2 (1.6)	2 (1.4)	1 (0.7)
Day 29: Hour 9						
Bothered by Too Much Whitening	2 (3.9)	0	3 (2.4)	2 (1.6)	3 (2.1)	1 (0.7)
Day 29: Hour 12						
Bothered by Too Much Whitening	2 (3.9)	0	4 (3.1)	2 (1.6)	3 (2.1)	2 (1.4)

The reviewer notes that there were no reports of “pallor” in any of the three Controlled Core Studies per ISS Table 2.2 (Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Core Studies)).

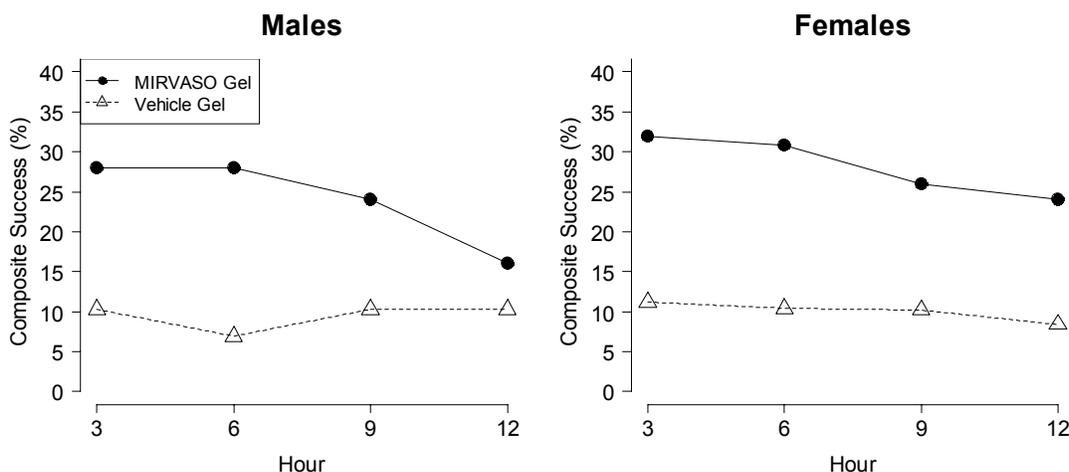
6.1.7 Subpopulations

The applicant prepared descriptive summaries for 2-grade Composite Success by gender, age group (18-64 years vs ≥ 65 years) and race (Caucasian vs. non-Caucasian).

Males constituted 20.8% of the study population in Study 18140 and 27.3% in trial 18141. Efficacy outcomes were similar for both genders. The study population was primarily Caucasian (98.5% in trial 18140 and 98.6% in trial 18141), thus severely limiting the meaningfulness of assessments for any potential differences in efficacy that could have been associated with race. Similarly, a majority of subjects (90.0% in Study 18140 and 92.2% in Study 18141) were 18 to 64 years old. The numbers of subjects in the older age group were too few to permit a meaningful assessment of differences in efficacy responses that may have been related to age.

Dr. Guerra’s analyses of Composite Success rates by sub-groups of gender and age group are presented in the following figures.

Figure 1: Composite Success⁽¹⁾ Rates by Hours and Gender on Day 29 for Study 18140 (ITT) (Statistical review Figure 1)

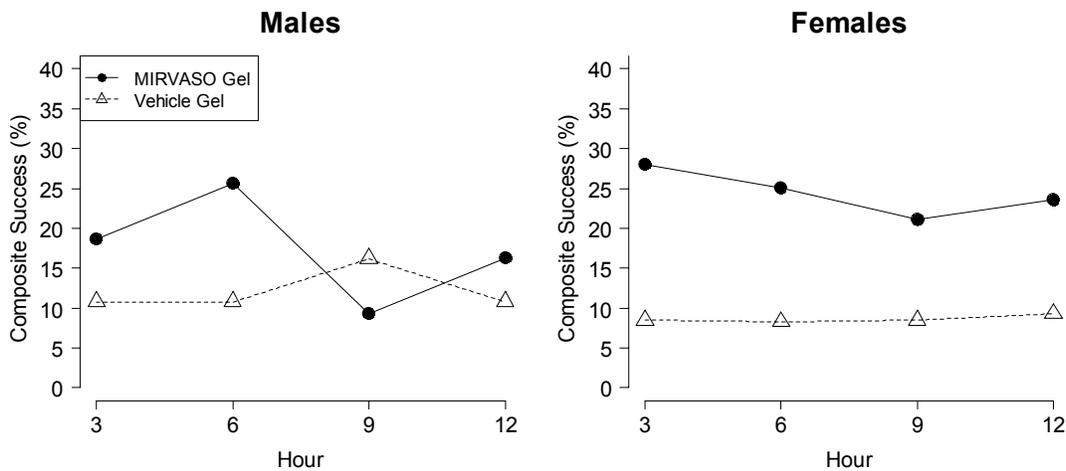


Source: Reviewer’s Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

Figure 2: Composite Success⁽¹⁾ Rates by Hours and Gender on Day 29 for Study 18141 (ITT)
 (Statistical review Figure 2)

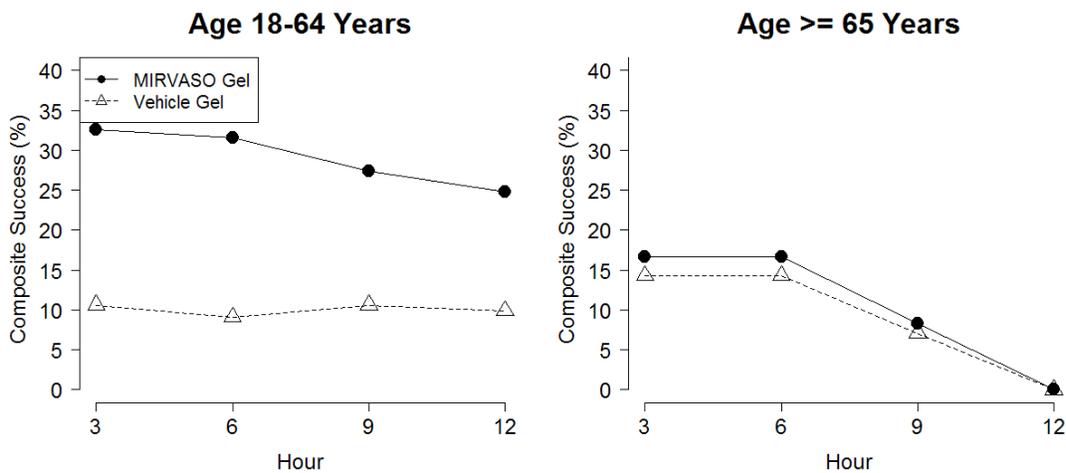


Source: Reviewer's Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

Figure 3: Composite Success⁽¹⁾ Rates by Hours and Age on Day 29 for Study 18140 (ITT)
 (Statistical review Figure 3)

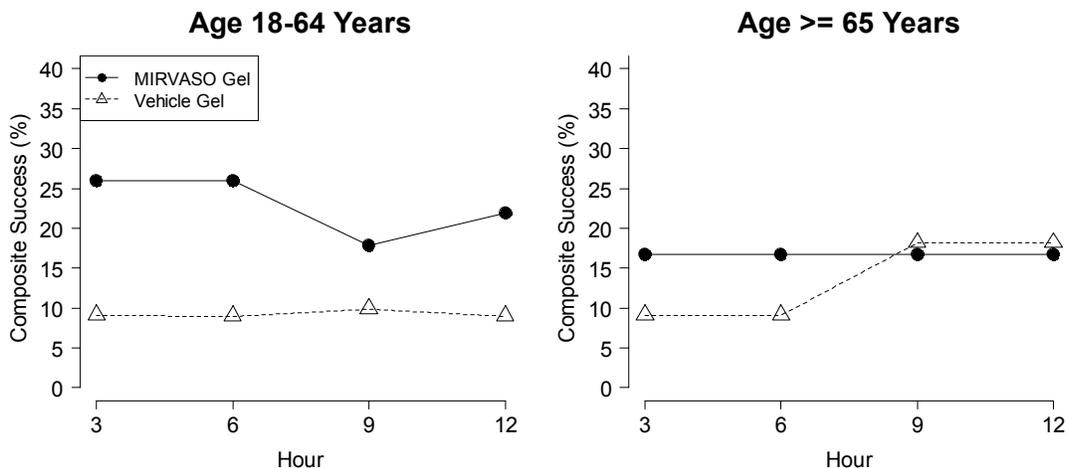


Source: Reviewer's Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

Figure 4: Composite Success⁽¹⁾ Rates by Hours and Age on Day 29 for Study 18141 (ITT)
 (Statistical review Figure 4)



Source: Reviewer's Analysis

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

(2) Multiple Imputation (MI) was used to impute missing data. The rates displayed are the averages over the 5 imputed datasets.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant considered three trials conducted by Collagenex as preliminary dose-finding trials (COL-118-ROSE-101, COL-118-ROSE-102, and COL-118-ROSE-201). See Section 4.4.2. These trials did not evaluate brimonidine tartrate gel 0.5%. The three trials that the applicant considered as being the most informative in providing information relevant to dosing recommendations were: 18144, 18143 and 18161 (See Table 26).

Table 26: Summary of relevant clinical trials contributing to dose selection
 (Source: Applicant Table 39 Summary of Clinical Efficacy)

Study Number	Study Design	Number of subjects Gender Mean Age	Doses and Treatment Duration	Results
Subjects with Rosacea				
RD.06.SRE.18144	Randomized, double-blind, parallel-group, vehicle-controlled, multicenter, dose-finding study	122 subjects 30M, 92F 45.7 years	Brimonidine Tartrate Gel (0.5%, 0.18%, 0.07%) Gel or Vehicle Gel Single dose	Brimonidine Tartrate Gel was found to be effective in the treatment of facial erythema of rosacea. The effect was superior to Vehicle Gel and consistently dose-dependent with the highest concentration (0.5%) being the most effective. Safety and tolerability were good and comparable between the groups treated with Brimonidine Tartrate Gel and Vehicle Gel.
RD.06.SRE.18161	Randomized, double-blind, parallel-group, vehicle-controlled, multicenter, efficacy and safety study	269 subjects 52M, 217F 44.3 years	Brimonidine Tartrate Gel (0.5%, 0.18% QD or BID) Gel or Vehicle Gel (QD or BID) 29 days	Brimonidine Tartrate 0.5% gel was statistically superior to Vehicle Gel for the primary endpoint. No evidence of tachyphylaxis was observed. All Brimonidine Tartrate Gel concentrations/regimens were well-tolerated with an acceptable safety profile during the treatment and follow-up phases.
RD.06.SRE.18143	Intra-individual, double-blind, randomized, multicenter, comparative, maximal use PK study	102 subjects 40M, 62F 41.6 years	Day 1: 1 drop of brimonidine tartrate 0.2% ophthalmic solution instilled in each eye every 8 hours over a 24-hour period Days 2-3: washout Days 4 to 32 (29 days): Topical administration of Brimonidine Tartrate Gel (0.07% BID, 0.18% QD or BID, and 0.5% QD). For the BID groups, the second application of Brimonidine Tartrate Gel was 6 hours after the first dose	Systemic bioavailability of Brimonidine Tartrate 0.5% Gel administered topically QD for 29 days was lower in comparison to ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution administered for a single day (3 times at 8 hour intervals over a 24-hour period)

RD.06.SRE.18144 was a single-application trial that evaluated three concentrations of brimonidine tartrate gel: 0.07%, 0.18%, and 0.5%, “in a geometric progression (approximately multiples of three).” Brimonidine tartrate gel 0.07% and 0.18% demonstrated clinical effect in previous trials. Single applications of brimonidine tartrate gel reduced facial erythema in subjects with rosacea. The actives were superior to vehicle, in a dose-dependent fashion. Based on the duration of the response of the one application, the applicant decided that a four-week treatment period was sufficiently long to evaluate efficacy and “short-term” safety in the Phase 2b (18161) and pivotal trials.

RD.06.SRE.18143 was the comparative bioavailability, maximal use trial, and 0.5% was significantly effective. The safety margin was favorable with regard to the systemic exposure. Efficacy was assessed by at least a 1-grade improvement in the CEA and/or PSA for 12 hours post dosing, with the ability for the effect to be achieved and maintained daily. This trial is primarily discussed in its context as the “bridging” trial. See Section 4.4.3.

RD.06.SRE.18161: “A 4-week, randomized, double-blind, parallel-group, vehicle-controlled, multicenter study investigating the efficacy and safety of CD07805/47 gel 0.5% applied topically once daily (QD), and CD07805/47 gel 0.18% applied topically once daily (QD) or twice daily (BID), in subjects with moderate to severe facial erythema associated with rosacea”

Study design: This was a Phase 2b trial in subjects with moderate to severe facial erythema of rosacea. The trial evaluated the efficacy and safety of two concentrations of brimonidine tartrate gel (0.5% and 0.18%) that were tested in trial 18144. Trial 18161

was intended to determine the most safe and effective dose of brimonidine tartrate gel for evaluation in subsequent Phase 3 trials. The treatment period was 29 days, followed by 4 weeks of additional treatment-free follow-up.

Subjects were randomized to receive brimonidine tartrate gel 0.5% QD, brimonidine tartrate gel 0.18% BID, brimonidine tartrate gel 0.18% QD, vehicle gel BID, or vehicle gel QD. Subjects were assessed during a 12-hour post-dose period on Baseline/Day 1, Day 15, and Day 29. Post-treatment follow-up was at Day 30, Week 5, Week 6, and Week 8.

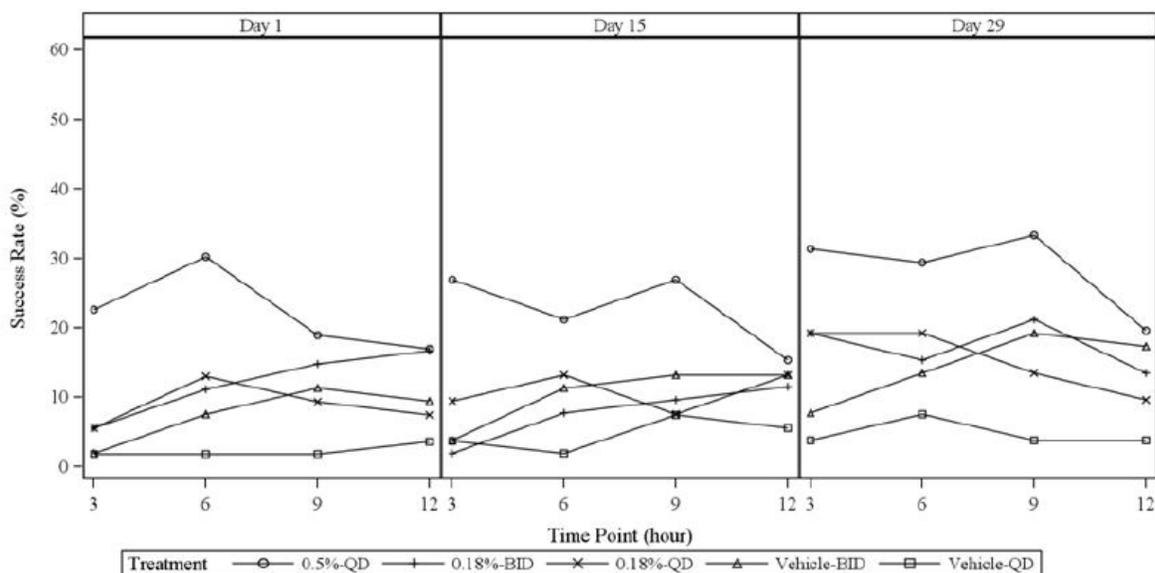
The primary analyses were to test differences between each active treatment (0.5% QD, 0.18% BID, and 0.18% QD) versus the corresponding vehicle gel for Composite Success at Hours 3, 6, 9, and 12 on Day 29. Testing for Composite Success at the time points on Days 15 and 1 was performed to evaluate the early efficacy profile.

Results

A total of 269 subjects were randomized to the following treatment groups: brimonidine tartrate gel 0.5% QD (53 subjects), brimonidine tartrate gel 0.18% BID (54 subjects), brimonidine tartrate gel 0.18% QD (54 subjects), vehicle gel BID (53 subjects), and vehicle gel QD (55 subjects).

The brimonidine tartrate gel 0.5% QD dose regimen was significantly more effective in the treatment of facial erythema than the vehicle gel QD control, brimonidine tartrate gel 0.18% BID and brimonidine tartrate gel 0.18% QD dose regimens.

Figure 5: 2-grade Composite Success during treatment, Study 18161, LOCF, ITT Population (Summary of Clinical Efficacy Figure 2)



Brimonidine tartrate 0.5% gel QD was significantly superior ($p < 0.001$) compared to vehicle gel QD by the primary analysis, 2-grade Composite Success [CEA and PSA-5] at Hours 3, 6, 9, and 12 on Day 29. The results were also statistically significant on Days 15 and 1.

Ultimately, the applicant selected the 0.5% gel for dosing once daily, as the optimal concentration and regimen for achieving the desired treatment effect in the most subjects. The algorithm used by the applicant for selection of the concentration and dose regimen of brimonidine tartrate gel for the Phase 3 program is found in Appendix 5 (algorithm developed by Galderma).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant evaluated the potential for tachyphylaxis with use of their product, as discussed below.

Medication effect was evaluated over a 12-hour observation period on Days 1, 15, and 29 in the Phase 2b trial 18161 and the pivotal trials 18140 and 18141. The three cited trials are the “Controlled Core Studies” (as described for the safety review). The applicant cited the primary efficacy data (2-grade Composite Success on Days 29, 15, and 1) as evidence that tachyphylaxis did not develop. The applicant reported that there was no apparent decrease in efficacy effect during the treatment period and, therefore, concluded that no evidence of tachyphylaxis was seen in the trials. However, an assessment period of 29 days may not have been sufficiently long to assess for tachyphylaxis; 29 days might be considered a relatively short period of observation for development of tachyphylaxis. Therefore, the reviewer concluded that the data allows only for a conclusion that no evidence of tachyphylaxis was observed with short-term use of brimonidine gel, 0.33%.

6.1.10 Additional Efficacy Issues/Analyses

There were no other efficacy issues.

7 Review of Safety

Safety Summary

The applicant provided substantial evidence to support the safety of once daily use of brimonidine gel, 0.33%. The applicant assessed the short-term safety of brimonide gel, 0.33% in trials with treatment periods of 29 days that evaluated subjects with facial erythema of rosacea. Adverse events in the integrated safety database were most

commonly reported in the Skin and subcutaneous tissue disorders system organ class (SOC). “Erythema,” “skin burning sensation,” and “skin warm” were the events in this SOC that were reported by $\geq 1\%$ of brimonidine-treated subjects and at higher frequency relative to the vehicle group. “Flushing” was reported only by brimonidine-treated subjects and was reported by 2.7% of subjects by the reviewer’s assessment.

The applicant assessed the long-term safety of their product in a one-year trial which evaluated subjects in sufficient numbers and with sufficient exposures, consistent with the recommendations in the ICH E1A Guideline for Industry. Also, the long-term trial evaluated a population which may be considered potentially more reflective of real-world use, i.e. that trial evaluated subjects with facial erythema of rosacea, but placed no restrictions on the numbers of inflammatory lesions subjects might have. Also, that trial allowed for use of concomitant rosacea therapies. No new safety concerns were identified in the long-term trial.

No serious adverse events were reported when the product was used as intended. Serious adverse events were reported from accidental ingestion of the product by two children, and the events generally appeared to have been consistent with the pharmacology of the drug. Measures to enhance the safe use of the product in the marketplace include adding a child-resistant container closure and a having Patient Package Insert.

Contact sensitization was documented in three subjects in the development program, two of whom were patch tested with individual product ingredients. One of the two subjects was found to be allergic to brimonidine tartrate and the other subject was found to be allergic to phenoxyethanol, a preservative excipient.

Brimonidine gel, 0.33% did not appear to have any clinically significant effects on intraocular pressure when applied daily in trials from one day to one year in duration.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Subjects considered in the safety analyses had received at least one dose of study drug. Safety data presentation included:

- Adverse events for all trials.
- Laboratory data summaries for trials 18143, 18140, 18141, and 18142.
- Vital signs summaries for trials 18143, 18144, 18161, 18140, 18141, and 18142.
- IOP summaries for trials 18143, 18144, 18161, and 18142.

The applicant conducted four dermal safety studies and a thorough QT study (discussed in Section 7.4.4).

In the data tables, the applicant included a column with data from the first 29 days of the open-label, long-term trial (18142) beside the data from the three Core Controlled Studies, and the applicant termed the grouping of these four trials as the “Core Studies.” The applicant did not integrate the data from the open-label, long-term trial with the data from the controlled trials (“Core Controlled Studies”).

Safety data from all other trials in the development program were discussed individually in the applicant’s safety summary.

7.1.2 Categorization of Adverse Events

The applicant classified adverse events as being “treatment-emergent” if:

- The event occurred on or after the first dose of study treatment but not more than 30 days after last dose of study drug.
- The event occurred prior to randomization and worsened during study treatment.

The applicant used the MedDRA classification system for coding of adverse events. The applicant coded/re-coded all adverse events in the pooled safety database using MedDRA version 11.0 to ensure consistency. Earlier versions of MedDRA were used in some clinical study reports.

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

Pooling strategies for the integrated safety analyses were agreed to at the preNDA meeting (May 16, 2012).

Per the Statistical Analysis Plan, the “Core Studies” were defined as including the following four trials:

- one Phase 2b randomized, controlled dose-finding trial (18161),
- two Phase 3 randomized, controlled efficacy and safety pivotal trials (18140 and 18141), and
- one Phase 3 long-term, open-label safety and efficacy trial 18142.

The applicant pooled the safety data from the three controlled trials in the Core Studies group for the integrated safety database. The applicant termed this grouping of trials 18161, 18140 and 18141 the “Core Controlled Studies.”

Data pooled for the integrated safety analyses included only data from subjects dosed with 0.5% or vehicle once daily for 29 days.

Data from the first 29 days of the long-term trial 18142 were included in some of the tables for comparison to the integrated data from the three controlled trials, 18161, 18140 and 18141. The long-term trial did not restrict the numbers of inflammatory lesions that subjects could have and also allowed for concomitant rosacea therapies. Presentation of data from the first 29 days of the long-term trial alongside that from trials 18161, 18140 and 18141 may allow some comparison of the more restrictive population in those trials to more “real-world” subjects in trial 18142. Trial 18142 is largely discussed in Section 7.5.2 of this review.

7.2 Adequacy of Safety Assessments

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

A total of 2174 subjects were evaluated in the clinical development program. Of these, 1619 subjects were exposed to brimonidine tartrate gel, with 1210 subjects exposed to brimonidine tartrate 0.5% gel QD.

Rosacea is a chronic indication, and the applicant evaluated the long-term safety of their product by conducting the long-term trial 18142, which provided exposures in accordance with ICH Guideline E1A (300-600 subjects treated for six months at dosage levels intended for clinical use and 100 subjects exposed for one year). In study 18142:

- 333 subjects were treated for >180 days, and
- 276 (of those 333) subjects were treated for ≥365 days.

Therefore, the numbers of subjects and durations of exposure are sufficient to address the recommendations in the ICH E1A Guideline.

The mean duration of treatment was 28.6 days for subjects in the Controlled Core Studies, and the mean daily amount of brimonidine tartrate 0.5% gel exposure was 0.8 g.

The mean duration of treatment was 277.9 days for subjects in the long-term study, and the mean daily amount of brimonidine tartrate 0.5% gel exposure was 0.5 g.

A summary table of the demographics of the subjects in the Core Studies is presented in the following table:

ISS Table 27: Summary of Subject Demographics (Core Studies) (Appliant ISS Table 1.5.2)

	Controlled Studies		Open Label
	CD07805/47 0.50% (N = 330)	CD07805/47 Vehicle (N = 331)	CD07805/47 0.50% (N = 449)
Age			
n	330	331	449
mean (sd)	48.3 (11.9)	46.6 (12.6)	50.9 (12.1)
median	49	47	51
min, max	20, 77	18, 87	19, 81
Age Category, n(%)			
18 - 64	305 (92)	305 (92)	395 (88)
>= 65 years	25 (8)	26 (8)	54 (12)
Sex, n(%)			
Male	79 (24)	76 (23)	113 (25)
Female	251 (76)	255 (77)	336 (75)
Race, n(%)			
White	323 (98)	326 (98)	438 (98)
Black or African American	2 (1)	2 (1)	2 (<1)
Asian	5 (2)	3 (1)	6 (1)
Other	0	0	3 (1)
Ethnicity, n(%)			
Hispanic or Latino	17 (5)	22 (7)	32 (7)
Not Hispanic or Latino	313 (95)	309 (93)	417 (93)

7.2.2 Explorations for Dose Response

See Sections 4.4.2 and 6.1.8.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate to explore potential adverse reactions. See Section 4.3.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate in methodology and scheduling. See Section 7.1.1.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Alphagan P label describes that brimonidine is extensively metabolized by the liver. Urinary excretion is the major route of elimination of brimonidine and its metabolites. Specific drug-drug interactions studies have not been conducted with brimonidine gel. However, the Alphagan P label includes information pertaining to drug interactions with anti-hypertensives and/or cardiac glycosides, CNS depressants, tricyclic antidepressants, and monoamine oxidase inhibitors.

This information may (at least in part) be appropriate for the brimonidine gel, 0.33% label. Note: The applicant did revise the Phase 3 protocols (Amendment #1) to be less restrictive regarding tricyclic antidepressants, anti-hypertensives (including beta blockers) and cardiac glycosides to address a non-agreement item in the Special Protocol Assessment agreement letter. However, the protocol continued to carry some restriction, requiring 3 months on a stable dose for these products. The discussion of interaction with tricyclic antidepressants in the Alphagan P label would not appear to apply to the brimonidine gel label. That discussion pertains to potential compromise of hypotensive effect (which may be pertinent in the setting of treatment of systemic hypertension or increased intraocular pressure).

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

The applicant incorporated assessments directed at capturing potential adverse events for similar drugs in the class. Clinical assessments in the development program included vital signs (including sitting and standing blood pressures) and measurement of intraocular pressure.

7.3 Major Safety Results

7.3.1 Deaths

One death was reported in the clinical development program for brimonidine tartrate gel, and the death occurred in the long term study, 18142: Subject 8095-007 was a 65 y/o male smoker who died of complications of squamous cell carcinoma of the lung.

7.3.2 Nonfatal Serious Adverse Events

Other serious adverse events were reported in seven trials across the development program.

Serious adverse events were reported for three subjects in the Core Controlled Studies:

- One subject in the vehicle group in trial 18161 reported deep vein thrombosis.

- One subject in the brimonidine group in trial 18140 (Subject 8076-028) had serious adverse events attributed to her. However, the events occurred in her children who experienced serious adverse events following accidental ingestion of the subject's study product, as discussed below.
- One subject in the brimonidine group in trial 18141 reported appendicitis.

Subject 8076-028

Two young children of this subject experienced seven serious adverse events following accidental ingestion of brimonidine tartrate gel, 0.5%:

Child #1: Accidental Drug Intake by Child; Lethargy; Respiratory Distress

An 18-month-old female reportedly used her mother's study drug as toothpaste on Day (b) (6) of the subject's study drug exposure. The apparently unsupervised child was found lethargic and was transported to the emergency room. Lethargy persisted, and she was in respiratory distress. Respiratory rate was reported as 16 breaths/minute, with apneic episodes. Capillary refill was normal. Her blood pressure was increased (133/74 mmHg). Oxygen therapy (Ventimask) was initiated, with subsequent blood gases showing hypocapnia, and normal PaO₂ and pH. Hyperlactemia (4.13 mmol/L [reference range: 0.5-2.2 mmol/L]) and hyperglycemia (213 mg/dL [reference range: 56-120 mg/dL]) were also reported. She was treated with 5 mg intravenous rocuronium, propofol and intubated, with improvements in blood gases. The lowest measured respiratory rate under intubation was 13 breaths/minute. She was transported via helicopter to another facility, where she was observed overnight. She was discharged the following day without any complications. The child's weight was reported as 14 kg, and the Investigator reported that the child had ingested no more than 0.5g of study drug.

Child #2: Accidental Drug Intake by Child, Heart Rate Irregular, Lethargy, Psychomotor Hyperactivity

A 3-year-old male (sibling of child discussed above) whose mother was enrolled as a subject reportedly used his mother's study drug as toothpaste on Day (b) (6) of the subject's study drug exposure. The child was found lethargic after "a few minutes" unsupervised. He was transported to the emergency room where he was reported as hyperactive on arrival and with an irregular heartbeat. He was reported to be pale, diaphoretic, lethargic, confused, and polypneic. (Hyperactivity and lethargy were reported). He also presented with sinus bradycardia. Blood gases performed showed pH of 7.46 (reference range: 7.35-7.45), PaCO₂ 33.6 mmHg (reference range: 39-51 mmHg), and PaO₂ 54 mmHg (reference range: 30-50 mmHg). Lactate was 2.53 mmol/L (reference range: 0.5-2.2 mmol/L), blood calcium 1.33 mmol/L (reference range: 1.12-1.3 mmol/L) and glucose 143 mg/dL (reference range: 56-120 mg/dL), which subsequently increased to 151 mg/dL. The child rapidly improved in the emergency room with 10 mL/kg bolus of intravenous normal saline and was in stable condition during transport to another facility, where he was observed overnight. He was discharged the following day without any complications. The applicant considered that

“the diagnosis of hyperactivity could have been explained by the stressful context related to the circumstances of the occurrence.” The investigator reported that the child had ingested no more than 0.5 g of study drug.

Therefore, in the Core Controlled Studies, eight serious adverse events were reported for two subjects in the brimonidine group (seven events experienced by the children of one of these two subjects).

The following table also includes the serious adverse events that were reported during the first 29 days of the long-term trial, 18142. Trial 18142 is discussed in Section 7.5.2 of this review.

Table 28 Summary of serious adverse events by System Organ Class and Preferred Term, Safety Population, Core Studies (Applicant Summary of Clinical Safety Table 35)

SYSTEM ORGAN CLASS Preferred Term	Controlled Studies		Open-Label Study (first 29
	Brimonidine Tartrate 0.50% (N = 330)	Vehicle (N = 331)	Brimonidine Tartrate 0.50% (N = 449)
SUBJECTS REPORTING ANY SERIOUS ADVERSE EVENT, N(%)	2 (0.6)	1 (0.3)	1 (0.2)
INFECTIONS AND INFESTATIONS	1 (0.3)	0	1 (0.2)
Appendicitis	1 (0.3)	0	0
Pneumonia primary atypical	0	0	1 (0.2)
Sepsis	0	0	1 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.3)	0	0
Accidental drug intake by child	1 (0.3) ^a	0	0
INVESTIGATIONS	1 (0.3) ^a	0	0
Heart rate irregular	1 (0.3) ^a	0	0
NERVOUS SYSTEM DISORDERS	1 (0.3) ^a	0	0
Lethargy	1 (0.3) ^a	0	0
Psychomotor hyperactivity	1 (0.3) ^a	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3) ^a	0	1 (0.2)
Hypoxia	0	0	1 (0.2)
Respiratory distress	1 (0.3) ^a	0	0
VASCULAR DISORDERS	0	1 (0.3)	0
Deep vein thrombosis	0	1 (0.3)	0

^a Subject 18140-8076-028 was assigned to the 0.50% gel group; her 2 children accidentally ingested the study drug and their mother is counted here.

Other serious adverse events during treatment with brimonidine tartrate gel in the clinical development program were as below:

- Head trauma/injury and hand fracture suffered in an automobile accident were reported for one subject in RD.06.SRE.18124 (photosensitization study)
- Gastroenteritis reported by one subject in RD.06.SRE.18125 (cumulative irritancy study)
- Gastroesophageal reflux disease in one subject receiving brimonidine tartrate gel, 0.18% in a treatment arm of the dose-finding in the Phase 2b trial, 18161 (one of the Controlled Core Studies).

7.3.3 Dropouts and/or Discontinuations

Five subjects discontinued from the Core Controlled Studies due to adverse events: three in the 0.5% group and two in the vehicle group.

For the three subjects in the 0.5% group, all events were in the Skin and Subcutaneous Tissue Disorders SOC. The three subjects reported the following events: contact dermatitis (two) and erythema (one). However, for one subject (Subject 8017-015), the contact dermatitis was described as “poison ivy” and reported as occurring on treated and non- treated areas. The other two cases are discussed below.

Subject 8238-008 was a 51 y/o female who was discontinued on Day 18 for an event that was coded by the preferred term “skin irritation.” The history was somewhat difficult to piece together. Apparently, some of the subject’s signs were self-reported and not confirmed by the investigator, who ultimately coded the event as “skin irritation” and possible allergic contact dermatitis. The subject contacted the study site and reported awakening with a swollen, stinging, itchy face on [REDACTED] ^{(b) (6)}. She had not applied study drug that day and was reportedly told not to apply it. Per the case report form, she presented to her family physician who prescribed oral prednisone, a topical steroid cream (betamethasone is listed in the narrative) and “OTC meds.” The subject apparently obtained no relief, and Eucerin Calming Cream was recommended which was described by subject as “helping.” However, she remained “really swollen” and developed “bumps on her face.” Treatment at some point also included loratadine and diphenhydramine hydrochloride. However, the sequence of treatment was unclear. She refused formal patch testing. She provided photographs for the investigator to review, and the investigator from review of the photographs found the appearance to be more consistent with irritation from a bandage adhesive. The irritation was classified as “severe” and related to study drug. Irritation was favored over allergic reaction. The event was of 14 days duration and resolved without sequelae (14 days after discontinuation of treatment).

Subject 8218-007 was a 43 y/o female in study 18141 who was treated with 0.5% gel and discontinued due to “intermittent rebound erythema” per the case report form. Per the CRF, the event occurred approximately 12 hours “after application daily, resolved by the time subject wakes up” and was reported to be of “sudden onset with no exposure to trigger.” The event was not treated and resolved without sequelae. It was limited to the treated areas. Study treatment was discontinued on Day 11. This subject also experienced a “tingling sensation” in the treated areas, and the subject had not experienced this event prior to the study.

Two subjects discontinued in the vehicle group of the Controlled Core Studies, and the events resulting in discontinuation were intervertebral disc protrusion and deep vein thrombosis).

Twenty-two subjects discontinued from 18142 during the corresponding 29-day period.

Table 29 Summary of treatment-emergent adverse events leading to discontinuation by System Organ Class and Preferred Term, Safety Population, Core (Applicant Summary of Clinical Safety Table 38)

System Organ Class Preferred Term	Controlled Core Studies		Open-Label Study (first 29 days)
	Brimonidine Tartrate 0.5% Gel (N=330)	Vehicle Gel (N=331)	Brimonidine Tartrate 0.5% Gel (N=449)
Subjects Reporting Any Adverse Event Leading to Discontinuation, N(%)	3 (0.9)	2 (0.6)	22 (4.9)
Infections and Infestations	0	0	1 (0.2)
Pneumonia primary atypical	0	0	1 (0.2)
Sepsis	0	0	1 (0.2)
Nervous System Disorders	0	0	2 (0.4)
Headache	0	0	2 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	0	0	1 (0.2)
Hypoxia	0	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders	3 (0.9)	2 (0.6)	13 (2.9)
Dermatitis contact	2 (0.6)	0	0
Erythema	1 (0.3)	0	5 (1.1)
Flushing	0	0	1 (0.2)
Rosacea	0	0	4 (0.9)
Skin burning sensation	0	0	2 (0.4)
Skin hyperpigmentation	0	0	1 (0.2)
Vascular Disorder	0	0	9 (2.0)

Flushing	0	0	8 (1.8)
Hypertension	0	0	1 (0.2)

Subjects reporting a particular adverse event more than once are counted only once for that adverse event.

The number of subjects who discontinued for flushing during the first 29 days of the long term trial is somewhat striking relative to the corresponding period in the Core Controlled Studies during which no subjects discontinued for this event. “Flushing” is further discussed in Section 7.3.5.

7.3.4 Significant Adverse Events

The applicant reported 15 severe treatment-related events that led to discontinuation in the Core Studies, and all but one of these events occurred in the long-term trial (the one event that was not in the long-term trial was discussed above in 7.3.3). Discontinuations from the long-term trial are discussed in Section 7.5.2. The 15 severe events are listed in the table below.

Table 30 Severe treatment-emergent adverse events related to study drug leading to discontinuation, Safety Population, Controlled Core Studies and Long-Term Study (Applicant Summary of Clinical Safety Table 41)

Study Number	Subject Number	Adverse Event (PT)	
RD.06.SRE.18140	8238-008	Dermatitis contact	
RD.06.SRE.18142	8048-012	Dermatitis allergic	
	8073-002	Rosacea	
	8073-016	Erythema	
	8095-021		Flushing (Vascular Disorder)
			Skin burning sensation
	8214-001	Dermatitis allergic	
	8214-011	Erythema	
	8214-013	Dermatitis Contact	
	8241-015	Erythema	
	8326-020	Flushing (Vascular Disorder)	
	8327-004	Rosacea	
	8327-007		Rosacea
			Skin burning sensation
8327-012	Flushing (Vascular Disorder)		

7.3.5 Submission Specific Primary Safety Concerns

The potential for local adverse reactions was evaluated in all clinical trials (e.g. in the collection of adverse event data) and in a battery of dermal safety studies (discussed in Section 7.4.5). The applicant also measured intraocular pressure (IOP) in select trials (per Section 4.1.5 of the Summary of Clinical Safety, the effect of brimonidine tartrate on IOP is locally mediated via direct ocular application).

The potential for events that relate to the pharmacologic class of the product as an alpha-2 adrenergic receptor agonist was evaluated through the collection of adverse event data. In addition to measurement of IOP, vital signs were assessed in the development program (vital signs data are discussed in Section 7.4.3 of this review).

This section will include discussion of two events which were reported more frequently in the brimonidine tartrate, 0.5% group compared to the vehicle group in the Controlled Core Studies: erythema and flushing. In discussing these events in the Summary of Clinical Safety, the applicant stated that both erythema and flushing relate to “rosacea pathophysiology.” However, while that may be true, it is also possible that these events could reflect some measure of a brimonidine effect. This is suggested by the imbalance of the occurrence of erythema and flushing when treatment groups are compared in the Controlled Core Studies.

Erythema

A total of 32 brimonidine-treated subjects (4.1%) and three subjects in the vehicle group (0.9%) reported “erythema” as an adverse event in the Core Studies:

- In the Controlled Core Studies, 12 subjects in the brimonidine group (3.6%) and three subjects in the vehicle group (0.9%) reported this event.
- In the first 29 days of the long term safety study, 20 subjects (4.5%) reported erythema.

The applicant offered a possible explanation for the erythema as being that, “The effect of Brimonidine Tartrate 0.5% Gel can begin to diminish several hours after application. Particularly noted in the (long-term) study, but also in other studies in the development program, it is possible that the subjects’ perception of this diminishment of effect late in the day could also have contributed to the frequency of reporting of erythema...by subjects” (Section 2.1.5.1.1.1 of the Summary of Clinical Safety). The applicant did not present information to support that an onset late in the day generally characterized the erythema that was reported in association with brimonidine gel treatment.

Six of the above subjects treated with brimonidine gel in the Core Studies discontinued treatment due to erythema, and one of those subjects was in pivotal trial 18141. For that subject (8212-007; also see Section 7.3.3), the event was indeed reported as “occurring approximately 12 hours after application daily.” However, the investigator specifically described the event as “intermittent *rebound* erythema” (emphasis added), suggesting a

worsened status and not just a returning of her baseline state. Therefore, the erythema appeared to represent more than just a reappearance of the condition from decrease in medication effect late in the day.

Eight subjects discontinued the long-term study due to erythema. Additionally, in the subject narratives for these subjects, “simple” erythema does not appear to represent the extent of what some subjects experienced. That is, some narratives describe a “worsening of erythema” or “rebound redness.” These descriptions do not suggest to this reviewer a decrease in medication effect and return to baseline status; these descriptions suggest a status worse relative to baseline. (Also see Section 7.6.4 for a discussion of rebound.) Summary descriptions of the course of erythema for subjects who discontinued the long-term study due to erythema are provided in Table 31.

Table 31 Discontinuations due to Erythema from Long-Term Study (all subjects received 0.5% gel)
 (Source: Subject narratives 18142)

Subject ID	Onset/Course	Action/Outcome	Concomitant rosacea therapy; any triggers?
8048-017:	“worsening erythema” on Day 21; “permanent and lasted 1 week”	d/c'd* med Day 21; resolved Day 29	No; no triggers
8073-016	“worsening erythema” on Day 30; severe when awakening; onset relative to gel variable	d/c'd med Day 90; resolved Day 94	No; no triggers
8155-006	“erythema (rebound redness)” on Day 5; onset 8 hrs after application; “very red, worse than before applying”	d/c'd med on Day 7; resolved Day 15	Doxycycline
8197-012	“erythema (increased erythema)” on Day 8; “it was not a flush response”	d/c'd on Day 9; resolved Day 9	No; no triggers
8214-005	Two episodes (“recurrent worsening of erythema and one of blotchy skin”) on Day 15; 4-5 hrs after application of 0.5%; intermittent	d/c'd on Day 28; resolved Day 35	Metrogel no triggers
8214-011	“erythema bilateral cheeks” on Day 7; intermittent 6-12 hrs after application; “were not flushing reactions”	d/c'd on Day 291; resolved Day 295	No; no triggers
8214-015	Two episodes (one to forehead and nose; and one to cheeks) on Day 58; “reaction time was unknown; lasted 3 to 6 hours; no change in reaction with “reduced daily application” on Day 100	d/c'd on Day 159; resolved Day 160	No; no triggers
8294-006	“erythema (intermittent rebound redness)” on Day 34	d/c'd on Day 44; resolved Day 45	Metrocream

*d/c'd= day 0.5% gel was discontinued

In Section 12.2.2 of the study report for 18140, the applicant stated that “Because this study was designed to assess the effect of CD07805/47 0.5% Gel on treatment of facial erythema of rosacea, it is presumed that the few subjects with (adverse events) of rosacea and erythema showed a worsening relative to their baseline condition.” This reviewer agrees with the applicant’s presumption regarding the reports erythema

representing a worsened status compared to baseline, and subject narratives also appear to support this thinking.

Flushing

Pertaining to flushing, the applicant concluded that, “The lack of appreciable difference between controlled active and vehicle groups suggests that the higher frequencies of flushing overall and related to study drug in the (long-term study) study might be more indicative of occurrence in the target population and not due to exposure to the active compound” (Section 2.1.5.1.3.1 of the Summary of Clinical Safety). However, all reports of flushing in the Controlled Cores Studies were in brimonidine-treated subjects; none were reported in the vehicle group. The extent of the imbalance between treatment groups in the reports of flushing would appear to suggest some role for brimonidine, e.g. contributory.

The applicant listed six reports of flushing in the summary table of treatment-emergent adverse events occurring at frequency $\geq 1\%$ in the Summary of Clinical Safety (Table 22). However, the applicant stated that three reports of flushing in brimonidine-treated subjects were coded as “alcohol intolerance” under the Metabolic and nutrition disorders SOC, rather than as “flushing” under the Vascular disorders SOC. Therefore, this reviewer considered that the number of flushing events should have been counted as nine rather than six, e.g. for purposes of labeling. Therefore, in the reviewer’s opinion nine subjects (2.7%) reported flushing in the brimonidine group in the Controlled Core Studies, and no subjects (0%) reported this event in the vehicle group. The reviewer agrees with the applicant that flushing is common to the pathophysiology of rosacea. However, the association of this event only with brimonidine treatment may represent more than a coincidence and may be clinically relevant.

A total of 47 subjects (10.4%) reported flushing over the course of the long-term (one year) trial, and 18 subjects (4%) discontinued the trial due to this event. From review of subject narratives for those subjects who discontinued, the onset of flushing relative to 0.5% gel application appeared to range from approximately 30 minutes to 23 hours (post application). It was described by some as intermittent, and the duration varied. It generally was not reported to be in association with any triggers, e.g. sunlight. The flushing appeared to resolve with discontinuation of brimonidine gel treatment.

Contact Sensitization

The applicant assessed for the potential for contact sensitization in all 12 trials that they conducted (i.e. the applicant did not assess the six CollaGenex trials for evidence of sensitization). The applicant identified contact sensitization reactions in two of the 12 trials. Contact sensitization was documented by patch testing of two subjects in the long-term safety trial (Section 7.5.2) and in one subject in the contact sensitization dermal safety study (Section 7.4.5).

Other Select Cutaneous Events

“Skin burning sensation” and “Skin warm” were also reported in a higher proportion of subjects in the brimonidine group compared to the vehicle group in the Controlled Core Studies: “Skin burning sensation”: five brimonidine subjects (1.5%) and two (0.6%) vehicle subjects; “Skin warm” three (0.9%) brimonidine subjects and no (0%) vehicle subjects. Pruritus occurred in a similar a frequency between treatment groups during the controlled period: eight (2.4%) brimonidine subjects and seven (2.1%) vehicle subjects. Skin irritation was reported by three (0.9%) brimonidine subjects and five (1.5%) vehicle subjects. The cumulative irritancy study did not demonstrate 0.5% to be a dermal irritant.

In the Controlled Core Studies, a higher proportion of subjects in the vehicle group [5 subjects (1.5%) reported “Rosacea” compared to those in the brimonidine group 3 subjects (0.9%). The reports of this event by a similar proportion of subjects in each treatment group may be consistent with the applicant’s theory that this event would be reflective the target population (“rosacea pathophysiology”).

Intraocular pressure (IOP) measurements

The applicant measured intraocular pressures (IOP) in trials 18161 (4-week dose-finding trial), 18144 (one-day dose finding trial), 18143 (4-week PK trial), and 18142 (the long-term trial) and summarized results for each trial separately. Complete IOP data were collected in 18161 and 18143. For trial 18143, only IOP data from the gel treatment phase were summarized for these analyses (this trial also evaluated the ophthalmic solution), and the applicant analyzed these data only for the 0.50% gel and vehicle gel QD arms (the trial also evaluated BID dosing). The applicant did not measure IOP in the two pivotal trials.

The applicant constructed shift tables representing the number of subjects with values below, within, or above the normal range (10 mm Hg to 21 mm Hg) from Hour 0 to post-dose time points at each visit. For trials 18144 and 18161, Hour 12 at each visit was used as the post-dose time point (it was the only post dose time point for IOP measurement in these trials). For trial 18142 (the long-term trial), the applicant created shift tables from Day 1 (Hour 0) to each post-treatment visit (i.e. Month 1, Month 6, and Month 12) to show potential trends over the long-term.

Table 32 Study visit/time point schedule for intraocular pressure parameters (Applicant Summary of Clinical Safety Table 52)

Study ID	18161	18144	18143 ^a	18142
Time Point	Day 1 (0h, 12h) Day 15 (0h, 12h) Day 29 (0h, 12h)	Day 1 (0h, 12h)	Day 1 (0h, 2h, 3h, 4h, 8h, 9h, 10h) Day 15 (0h, 2h, 3h, 4h, 8h, 9h, 10h) Day 29 (0h, 2h, 3h, 4, 8h, 9h, 10h)	Day 1 (0h) Month 1 (0h) Month 6 (0h) Month 12 (0h)

^a In study 18143, 0.2% ocular solution administered at 3 days prior to gel applications and IOPs not included in this table. Day 1 is the first day

of gel application.

The reference range for normal IOP was 10-21 mm Hg (per the Summary of Clinical Safety).

18142

IOP data were collected at Month 1, Month 6, and Month 12. Mean IOPs in both eyes of subjects generally trended towards slight decrease from Day 1 through Month 12. The largest mean change from Baseline occurred at Month 12 for both eyes: -0.45 mm Hg in the right eye and -0.22 mm Hg in the left eye. The mean values remained within the normal range for both eyes through the last post baseline visit.

Table 33 Summary of intraocular pressure measurements, change from Baseline, Safety Population, RD.06.SRE.18142 (Applicant Summary of Clinical Safety Table 53)

Statistic (mm Hg)	Day 1		Month 1		Month 6		Month 12		Last Post-Baseline Visit	
	Right Eye	Left Eye	Right Eye	Left Eye						
N (change from Baseline)	448	445	436	432	355	353	296	294	437	433
Mean (SD)	16.81 (3.12)	16.58 (3.01)	16.43 (3.27)	16.48 (3.84)	16.37 (2.84)	16.44 (2.96)	16.24 (2.69)	16.19 (2.72)	16.27 (2.70)	16.24 (2.96)
Mean change from Baseline (SD)	N/A	N/A	-0.41 (3.19)	-0.11 (3.54)	-0.35 (3.09)	-0.08 (3.17)	-0.45 (3.01)	-0.22 (2.86)	-0.56 (2.98)	-0.34 (2.96)

The shift table below shows the numbers of subjects with normal IOPs whose reading shifted above or below the normal range at each post-treatment visit at Hour 0 (Table 34).

Table 34 Intraocular pressure shifts from Day 1 by visit, Safety Population, RD.06.SRE.18142 (Applicant Summary of Clinical Safety Table 54)

Visit Day Type of Shift	From Day 1 Brimonidine Tartrate 0.5% Gel QD (N=449)	
	Right Eye	Left Eye
Month 1		
Normal to High	8	6
Normal to Low	1	2
Month 6		
Normal to High	4	5
Normal to Low	2	3
Month 12		
Normal to High	1	2
Normal to Low	0	0

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Last Post-Baseline Visit		
Normal to High	2	3
Normal to Low	0	1

From Table 34, at each time point, more subjects had IOP readings that shifted from normal to high than from normal to low. Most reports of normal to high shift were observed at the Month 1 assessment.

From these analyses, the applicant concluded that no clinically meaningful changes in mean IOP measurements were observed over the course of the trial. The review concurs.

18143

Trial 18143 evaluated dosing of ophthalmic solution in the first phase of the study. Day 1 of the topical gel treatment period was Study Day 4. Study Day 18 was Day 15 of gel treatment, and Study Day 32 was Day 29 of gel treatment.

On Days 4, 18 and 32 (gel treatment phase), the mean lowest and highest IOP values were comparable across treatment groups. No clinically meaningful reductions in mean IOP were observed. See Table 35.

Table 35 Shifts in intraocular pressure by visit, Safety Population, RD.06.SRE.18143 (Applicant Summary of Clinical Safety Table 78)

Visit Day Type of Shift	Lowest Post-Hour 0 Value Within Visit							
	Brimonidine Tartrate Gel 0.50% QD (N=23)		Brimonidine Tartrate Gel 0.18% Gel BID (N=24)		Brimonidine Tartrate Gel 0.18% Gel QD (N=25)		Brimonidine Tartrate Gel 0.07% Gel BID (N=26)	
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye
Day 4								
Normal to Low	0	0	2	1	1	1	0	1
Day 18								
Normal to Low	0	0	0	0	0	1	0	1
Day 32								
Normal to Low	0	0	1	1	2	1	0	0

18144

This was a one-day study of three concentrations of brimonidine tartrate: 0.5%, 0.18% and 0.07%. IOP was measured pre-dose and Hour 12. Mean reductions of 1 to 2 mm were similar across treatment groups and similar when right and left eyes were compared.

Table 36 Intraocular pressure measurements, Safety Population, RD.06.SRE.18144 (Applicant Summary of Clinical Safety Table 55)

IOP Measurements (mm Hg)	Brimonidine Tartrate Gel						Vehicle Gel (N=32)	
	0.50% (N=31)		0.18% (N=31)		0.07% (N=28)		Right Eye	Left Eye
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye		
Pre-Dose Mean (SD)	17.9 (3.03)	17.3 (3.24)	17.2 (3.08)	17.7 (2.90)	18.0 (3.43)	18.0 (2.97)	17.9 (2.28)	17.6 (2.54)
Hour 12								
Mean (SD)	16.8 (3.13)	16.5 (2.96)	15.3 (3.14)	15.5 (3.68)	16.4 (3.80)	16.6 (3.41)	15.7 (3.30)	16.2 (3.15)
Mean Change (SD)	-1.06 (2.58)	-0.84 (3.31)	-1.90 (3.49)	-2.23 (3.40)	-1.61 (3.75)	-1.39 (3.02)	-2.16 (3.38)	-1.44 (3.56)

There were two reports of IOP above the normal range in the 0.07% gel dose group. Two subjects had IOPs below the normal range: one in the 0.18% gel group, and one in the 0.50% gel group, right eye). The decreases in IOP were reported as being transient and reversible.

18161

This study evaluated 0.5% once daily, 0.18% twice daily, 0.18% once daily and vehicle once and twice daily. The applicant summarized mean changes in IOP for the brimonidine tartrate gel 0.5% daily and vehicle groups for each assessment time point.

At each visit (Days 1, 15 and 29), mean IOP decreased from Hour 0 to Hour 12 in each treatment group, except for the vehicle once daily group at Day 29 (IOP in right eye remained constant; IOP in the left eye increased). Mean reductions from Baseline (Day 1/Hour 0) for the study ranged from 0 to 1.8 mm Hg and were similar across treatment groups, and in each eye. There was no apparent correlation with changes in IOP and dose concentration or frequency or between active and vehicle groups.

Conclusions

Brimonidine tartrate gel did not appear to have clinically significant effects on intraocular pressure when applied daily in studies for one day (18144) to up to one year (18142). The applicant considered that the rare cases of transient lowering of IOP below normal levels probably resulted from accidental ocular exposure to the gel and of little clinical significance. This appears to be a reasonable conclusion.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the Controlled Core Studies, 109 subjects (33%) in the brimonidine group and 91 subjects (27.5%) in the vehicle group reported at least one adverse event. Adverse events were most commonly reported in the Skin and subcutaneous tissue disorders SOC. “Erythema,” “skin burning sensation,” and “skin warm” were the events in this SOC that were reported by $\geq 1\%$ of brimonidine-treated subjects and at higher frequency relative to the vehicle group. “Flushing,” in the Vascular Disorders SOC, was reported in approximately 6 (1.8%) brimonidine subjects and none in the vehicle group. However, the three reports of flushing reported as alcohol intolerance, are not reflected in the applicant’s table (see Section 7.3.5 above). Therefore, the total number of flushing events is 9 (2.7%). Overall, headache was the most commonly reported adverse event in the Controlled Core Studies, and it was reported with similar frequency between treatment groups 15 (4.5%) in the brimonidine group and 12 (3.6%) in the vehicle group. Table 37 presents events that occurred at $\geq 1\%$ in the Core Studies.

Table 37 Treatment-emergent adverse events by System Organ Class and Preferred Term occurring at $\geq 1\%$ frequency, Safety Population, Core Studies (Applicant Summary of Clinical Safety Modified Table 22)

SYSTEM ORGAN CLASS Preferred Term	Controlled Core Studies		LTS* Study (First 29)
	Brimonidine Tartrate 0.5% Gel (N = 330) n,%	Vehicle Gel (N = 331) n,%	Brimonidine Tartrate 0.5% Gel (N = 449) n,%
SUBJECTS REPORTING ANY ADVERSE EVENT, N(%) ^a	109 (33.0)	91 (27.5)	133 (29.6)
INFECTIONS AND INFESTATIONS	28 (8.5)	22 (6.6)	15 (3.3)
Nasopharyngitis	8 (2.4)	7 (2.1)	2 (0.4)
Sinusitis	1 (0.3)	4 (1.2)	2 (0.4)
Upper respiratory tract infection	4 (1.2)	1 (0.3)	2 (0.4)
INVESTIGATIONS	8 (2.4)^a	12 (3.6)	7 (1.6)
Intraocular pressure increased	7 (2.1)	9 (2.7)	5 (1.1)
NERVOUS SYSTEM DISORDERS	19 (5.8)^a	15 (4.5)	23 (5.1)
Headache	15 (4.5)	12 (3.6)	15 (3.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	43 (13.0)	31 (9.4)	61 (13.6)
Erythema	12 (3.6)	3 (0.9)	20 (4.5)
Pruritus	8 (2.4)	7 (2.1)	6 (1.3)

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Rosacea	3 (0.9)	5 (1.5)	10 (2.2)
Skin burning sensation	5 (1.5)	2 (0.6)	8 (1.8)
Skin irritation	3 (0.9)	5 (1.5)	3 (0.7)
Skin warm	3 (0.9)	0	6 (1.3)
Dry skin	1 (0.3)	0	5 (1.1)
VASCULAR DISORDERS^b	11 (3.3)	4 (1.2)	34 (7.6)
Flushing ^b	9 (2.7)	0	26 (5.8)

* Long-term, open-label, safety study

^a Subject 18140-8076-028 was assigned to the 0.50% gel group; her 2 children accidentally ingested the study drug and their mother is counted here (PTs not in this table).

^bReviewer include the three reports of flushing reported as alcohol intolerance.

During the corresponding period of the long-term study, 133 subjects (29.6%) experienced adverse events. The four most frequently reported adverse events in the first month of the long term study, (presented in order of decreasing frequency) were flushing (5.8%), erythema (4.5%), headache (3.3%), and rosacea (2.2%).

7.4.2 Laboratory Findings

Laboratory data (chemistry, hematology, and urinalysis testing) were collected in the following trials: 18140, 18141, 18142 and 18143. In the analyses of laboratory data, the applicant pooled the data from the pivotal trials (18140, 18141) and analyzed the data from the long term trial (18142) separately. The applicant considered laboratory data from trial 18143 to be supportive, since this was a PK trial. This review will focus on the data from the pivotal trials and the long-term trial.

In the Phase 3 pivotal trials, blood and urine specimens were obtained at Screening and Day 29 (or end of treatment if prior to Day 29). Lab work was also obtained at unscheduled visits, according to investigator's judgment. In the long term study, blood and urine specimens were obtained at Screening, Month 3, Month 6, Month 12/Early Termination, and unscheduled visits (prior to study drug application), if deemed necessary by the Investigator.

Results

Hematology:

No apparent pattern was identified with changes (normal to low or normal to high shifts) in any hematologic parameter from pooled trials (18140 and 18141) to suggest a drug effect. One subject (54 y/o female in vehicle group; trial 18141) had a potentially significant low platelet count at Screening, and the platelet count was normal at Day 29. No trends were apparent for hematology data over the course of the study long-term trial, 18142.

Chemistry

In the pooled data from the Phase 3 trials, no apparent pattern was identified with changes (normal to low or normal to high shifts) in any chemistry parameter to suggest a drug effect. Changes were similar between treatment groups. Two subjects in 18141 had critically clinically significant chemistry values: one 55 y/o male in the brimonidine group (history of diabetes) had an elevated non-fasting glucose value on Day 29/ET. A 48 y/o female in the vehicle group had elevated potassium levels on Day 29/ET, which had normalized by follow-up testing in the post-treatment period.

Two subjects in 18142 had critically clinically significant glucose values (one low glucose and one high). No apparent patterns or trends were observed to suggest a drug-effect in 18142.

No critically clinically significant urinalysis data were obtained for any individual subjects in the pivotal trials, 18140 and 18141 or the long-term trial, 18142.

7.4.3 Vital Signs

The applicant prepared an integrated summary of vital signs from the Core Studies. These analyses were limited to subjects exposed to brimonidine tartrate gel 0.5% or vehicle gel QD (study 18161 also evaluated 0.18% and BID dosing). Vital sign parameters analyzed were systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR), for both standing and sitting measurements, when available. The schedule of assessments was as presented in Table 38.

The applicant summarized vital sign measurements, changes from Baseline (Day 1/pre-dose) at post-dose time points and changes from Hour 0 at each visit.

The applicant separately prepared descriptive summaries of vital signs data for trials 18143 (maximal use PK trial), 18144 (single-dose trial) and the non-target treatment groups in trial 18161.

Table 38 Study visit/time point schedule for vital sign parameters (Applicant Summary of Clinical Safety Table 59)

Study ID	18161	18140/18141	18142	18144	18143
Time point	Day 1 (0h, 6h, 12h) Day 15 (0h, 6h, 12h) Day 29 (0h, 6h, 12h) Week 8 FU/ET	Day 1 (0h, 30min, 3h, 6h, 9h, 12h) Day 15 (0h, 30min, 3h, 6h, 9h, 12h) Day 29 (T0, 30min, 3h, 6h, 9h, 12h) Week 6 FU Week 8 FU/ET	Day 1 (0h, 3h) Week 1 (0h, 3h) Month1 (0h, 3h) Month3 (0h, 3h) Month6 (0h, 3h) Month9 (0h, 3h) Month12/ET(0h, 3h)	Day 1 (0h, 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h)	Day 1 (0h, 6h, 12 h) Day 15 (0h, 6h, 12 h) Day 29 (0h, 6h, 12 h)
Parameter	sitting SBP sitting DBP sitting HR	sitting SBP sitting DBP sitting HR standing SBP standing DBP standing HR	sitting SBP sitting DBP sitting HR standing SBP standing DBP standing HR	sitting SBP sitting DBP sitting HR	sitting SBP sitting DBP sitting HR

FU=follow up

For the pivotal trials, the applicant summarized pooled mean changes in sitting and standing systolic and diastolic blood pressures and heart rates from Baseline (Day1/Hour 0) and from Hour 0 of the given trial visit to post-dose times of 30 minutes, Hour 3, Hour 6, Hour 9, and Hour 12 on Days 1, 15, and 29. Mean changes from Baseline were also summarized at follow-up visits at Week 6 and Week 8. No clinically meaningful differences in mean blood pressures or heart rates were observed over time within either dosage group or between the 0.50% gel and vehicle treatment groups.

For the long-term trial (18142), the applicant summarized mean changes in standing and sitting systolic and diastolic blood pressures and heart rates from Baseline (Day 1/Hour 0) and from the respective visit day's Hour 0. These changes were measured at Hour 3 post-dose on Day 1 and then at Hour 0 and Hour 3 at Month 1, Month 3, Month 6, Month 9, and Month 12. No clinically meaningful differences in mean blood pressure were observed over the course of the trial. No clinically meaningful differences in mean heart rates from Baseline to on the particular visit day were noted.

7.4.4 Electrocardiograms (ECGs)

The applicant conducted a thorough QT/QTc (TQT) study. That report will be discussed in this section of the review. The Interdisciplinary Review Team for QT Studies (QT-IRT) reviewed the protocol. The QT-IRT also reviewed the study report for the investigation conducted under that protocol (DARRTS signature date of QT-IRT review of study report: October 22, 2010). References to QT-IRT review below refer to their review of the study report. Per the SPA agreement letter, the applicant did not perform routine ECGs in the pivotal trials (the applicant had proposed not to obtain routine ECGs).

The study was entitled "A Positive and Placebo Controlled, Double-Blind, Single-Dose, Three-Way Cross-Over, Thorough QTc Study of Brimonidine Tartrate at a Supra-

Therapeutic Dose in Healthy Subjects” (RD.06.SRE.18139). The study design was as reflected in the study title.

Study objective(s)

- The primary objectives of this thorough QTc study were to evaluate the effect of a single ocular administered dose of brimonidine tartrate (two drops of a 0.2% solution to each eye), on ventricular repolarization in healthy subjects compared to placebo, and to evaluate the change from baseline of QT/QTc interval corrected by QTcB, QTcF, and QTci (subjects specific) at the Tmax using 12-lead electrocardiograms (ECGs).
- The secondary objective was to determine if there was a pharmacodynamic relationship between the duration of the QT/QTc intervals and the plasma concentration of brimonidine.

Number of subjects: Planned: 60 subjects with no fewer than 27 subjects of the same gender; Randomized: 60 subjects (27 males and 33 females); Analyzed: 60 subjects (safety population)

Diagnosis and inclusion criteria

Male and female subjects, of any race, 18-55 years of age, a body mass index (BMI) between 18 and 30 kg/m², inclusive, normal blood pressure (\leq 140 mmHg systolic and \leq 90 mmHg diastolic), normal 12-lead ECG (QTc interval $<$ 450 msec for males and $<$ 470 msec for females), no clinically significant sinus arrhythmias or conduction disorders, pulse rate (PR) interval between 120 and 230 msec, heart rate (HR) \leq 100 bpm and \geq 40 bpm, and QRS interval \leq 110 msec.

Brimonidine tartrate Ophthalmic Solution 0.2% (Bausch and Lomb) was used in the study rather than the applicant’s product. The usual dose of the Ophthalmic Solution is one drop, and two drops were applied for the supra-therapeutic dose. In the study report, the applicant discussed their rationale for using an ocular dose of brimonidine in the TQT, rather than a dermal dose, the dosing route for their product. The applicant stated that clinical studies of facial application of brimonidine tartrate 0.2% gel resulted in exposure too low to permit calculation of the pharmacokinetic parameters. Plasma concentrations measured with brimonidine tartrate gel were below the level of quantitation. The applicant therefore concluded that facial application of brimonidine (CD07805/47) gel would not likely provide meaningful systemic exposure to brimonidine. However, the applicant discussed several human pharmacokinetic studies which demonstrated quantifiable plasma levels of brimonidine tartrate following ocular administration.

Per the QT-IRT review: “According to ICH Guideline E14, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure. Thus, Galderma

proposed to perform a thorough QTc study using brimonidine tartrate administered by the ocular route in a single supra-therapeutic dose.” Additionally, “The C_{max} values in the thorough QT study were 5.4-fold higher following administration of 0.2% mg brimonidine supra compared with the lower limit of quantitation. Exposures from the intended clinical dose did not exceed the lower limit of quantitation (10 pg/mL). The intended clinical dose for ocular use is 1 drop of 0.2% Brimonidine tartrate. This study used 2 drops and the C_{max} for the supra-therapeutic dose (54 pg/mL) was 1.3-fold greater than the C_{max} for the intended ocular dose (41.4 pg/mL).”

The applicant concluded that:

- At a supra-therapeutic dose brimonidine tartrate did not increase QTc.
- There were no clinically important changes in ECG results from screening, pre-dose, or postdose.
- The results of the study meet the criteria of a negative TQT study in accordance with ICH E-14 Guidance for Industry.

The QT-IRT found the applicant’s dosing approach to be acceptable. They also found the timing of ECGs and PK assessments to be acceptable. The results from the QT-IRT’s independent analyses aligned with those of the applicant. The QT-IRT detected no significant QTc prolongation effect of brimonidine tartrate in this TQT study.

Dr. An-Chi Lu discussed the dosing approach in her review of the TQT study and concluded that the dose was appropriate. From her review, the two-drop supra-therapeutic dosed by the ocular route was expected to “result in a higher systemic concentration than topically applied brimonidine tartrate gel, 0.5% for the following two reasons:

1. In the maximal use PK trial 18143, one drop of brimonidine tartrate ophthalmic solution 0.2% to each eye resulted in a systemic exposure with mean C_{max} 54 pg/mL, which is higher than the highest systemic concentration of brimonidine tartrate topical gel, 0.5% applied for 29 days with mean C_{max} 46.2 pg/mL after 15th application.
2. Compared to the highest mean C_{max} from topical administration of brimonidine tartrate gel, 0.5% in the maximal use PK trial 18143 (after the 15th administration), the mean C_{max} in this TQT trial (Trial 18139) was 1.2-times higher.”

“Following ocular administration of Brimonidine tartrate 0.2% two drops in each eye, the mean C_{max} was 54 ± 24 pg/mL. Compared to the highest mean peak plasma level (C_{max}) from topical administration of brimonidine tartrate gel, 0.5% in the maximal use PK trial 18143 (after the 15th administration), the mean C_{max} in this TQT trial was 1.2-times higher. In addition, in the maximal use PK trial 18143, following topical administration of Brimonidine tartrate 0.5% gel once a day for 29 days, the mean C_{max} was the highest on Day 18 (15th application) with a value of 46.2 ± 61.5 pg/mL; following ocular administration of Brimonidine tartrate solution 0.2% one drop to each eye TID for one

day, the mean C_{max} was 54 ± 28 pg/mL. Since one drop of brimonidine tartrate ocular solution, 0.2% to each eye resulted in a mean C_{max} already higher than the highest mean C_{max} obtained from once a day topical administration of brimonidine tartrate gel for 29 days, it is reasonable to use the dose of two drops ocular solution to each eye in this TQT trial to establish a C_{max} at least as high as the C_{max} obtained from one drop administration of ocular solution if not higher. Therefore, the dose in this TQT trial was considered appropriate.”

7.4.5 Special Safety Studies/Clinical Trials

The applicant’s dermal safety studies will be discussed in this section.

7.4.5.1 Contact Sensitization Potential

RD.06.SPR.18123: “Evaluation of the Sensitization Potential and Local Tolerability of Three Concentrations of CD07805/47 topical gel (0.07%, 0.18%, and 0.5%) Following Repeated Applications to the Skin of Healthy Subjects (Repeated Insult Patch Test Study or RIPT)”

Objectives: To determine the sensitization potential and local tolerability of CD07805/47 topical gel 0.07%, 0.18% and 0.5% after repeated applications.

Design/Plan: This was a single-center, randomized, vehicle- and negative-controlled, evaluator-blinded, intra-individual study enrolling healthy male and female subjects.

Test products were:

- CD07805/47 topical gel 0.07%, 0.18% and 0.5%,
- gel vehicle and
- white petrolatum USP (negative control).

Induction Phase

Approximately 0.1 mL of each test product was applied under occlusive patches to a designated site on one side of the subject’s back three times a week (Monday, Wednesday, and Friday) for three consecutive weeks. The patches were to be removed at each subsequent visit. A Skin Reaction Assessment (below) of each test site was performed approximately 15 to 30 minutes after patch removal on Days 3, 5, 8, 10, 12, 15, 17, 19, and 22. After the assessment, test products were reapplied to the same sites except at Day 22 when there was no reapplication of patches.

Table 39 Skin Reaction Assessment (Table 4 of protocol for RD.06.SPR.18123)

0	No reaction	No reaction
1	Mild erythema	Slight redness
2	Moderate erythema	Definite redness easily recognized
3	Severe erythema OR erythema with edema	Intense redness or redness associated with local swelling
4	Erythema with vesicles or erosion or bullae	Redness with small or large blisters or skin abrasion (can be accompanied by weeping/oozing, crusting)

Rest Phase: A two-week Rest Phase began after patch removal on Day 22 of the Induction Phase. No patch applications or clinical evaluations occurred during this phase.

Challenge Phase

A Challenge Phase followed the Rest Phase. On Day 36, approximately 0.1 mL of each test product was applied under occlusive patches to naïve skin on the opposite side of the back from the Induction Phase patch sites. Approximately 48 hours later (Day 38), the patches were removed, and a Skin Reaction Assessment of the patch sites was performed approximately 15 to 30 minutes after patch removal. Test products were not reapplied on Day 38.

On Day 40 (48 hours after patch removal), the Skin Reaction Assessment and the Sensitization Reaction Evaluation (below) of the test sites were performed. If a Sensitization Reaction Evaluation score of 1 (equivocal) was obtained, a second reading could be performed, at the Investigator’s discretion, 96 to 120 hours (Days 42 and 43, respectively) after patch removal.

Table 40 Sensitization Reaction Evaluation (Table 5 of protocol for RD.06.SPR.18123)

0	Negative*
1	Equivocal
2	Positive

*A negative sensitization reaction might include a skin reaction grade greater than 0. In that case, the severity of the skin reaction should be reported and color photographs taken. The Investigator was to justify and document the negative sensitization reaction evaluation.

Re-challenge Phase

A Re-challenge Phase was completed for subjects who had a Sensitization Reaction Evaluation score of 1 or 2 (equivocal or positive, respectively) at the 48-hour Challenge Phase evaluation. The Re-challenge Phase began at least 2 weeks after the end of the

Challenge Phase. Subjects were patch tested with the test product and, possibly, with individual ingredients. On the first day of the Re-challenge Phase, approximately 0.1 mL of each ingredient was to be applied under occlusive patches to previously un-patched sites on the subject's back for 48 hours.

A Skin Reaction Assessment of the designated skin sites was performed approximately 15 to 30 minutes and 48 hours after patch removal (Visits 16 and 17, respectively). A Sensitization Reaction Evaluation of the sites was performed approximately 48 hours after patch removal.

Results

Disposition of subjects

Two hundred forty-seven (247) subjects were enrolled and comprised the Safety Population. A total of 207 subjects (83.8%) completed the study. Subject 216 completed the Induction, Challenge, and Re-challenge phases (per protocol) but was unavailable for a second Re-challenge and consequently categorized as a prematurely discontinued subject in the "Withdrawal by Subject" category. Subject 216 is further discussed below. (Note: The reviewer did not find provisions for a second re-challenge in the protocol.)

Table 41: Disposition of Subjects (Applicant Table 7 of study report)

Category	Safety Population N=247
Enrolled (Screened Subjects)	247
Treated (Safety Population)	247
Premature Discontinuation, n (%)	40 (16.2%)
Withdrawal by Subject	34 (13.8%)
Adverse Event	3 (1.2%)
Protocol Violation	2 (0.8%)
Pregnancy	1 (0.4%)
Completed, n (%)	207 (83.8%)

Demographic and other baseline characteristics

A total of 237 subjects (96%) were Caucasian. A total of 171 (69%) were female. The mean age of subjects was 41 years. Most subjects had Fitzpatrick skin types of either III (39%) or IV (40%).

Extent of exposure

All subjects were to have received ten applications (nine during Induction and one at Challenge) of all five test products during the study unless irritation required discontinuation. Test products were to have been in contact with the subjects' skin for 21 days during Induction and two days during Challenge.

During Induction, 140 to 149 subjects (57% to 60%) were exposed to 21 days of CD07805/47 at each of the three concentrations tested as well as the gel vehicle and 152 subjects (62%) were exposed to 21 days of the negative control (white petrolatum).

During the Challenge Phase, 199 to 201 subjects (81%) completed the two-day challenge exposure to the three concentrations of CD07805/47 gel, gel vehicle, and the negative control. During the Rechallenge Phase, six subjects (2%) completed an additional two days of exposure to the five test products.

Adverse events

No serious adverse events were reported during the study. A total of 21 subjects (8.5%) reported 26 adverse events during the study. Three of these adverse events (increase in blood pressure, influenza, and hypertension) resulted in discontinuation from the study. There were two reports of each of the following events: influenza, nasopharyngitis, skin laceration, and skin test positive at challenge. The two adverse events of positive sensitization scores at Challenge occurred in one subject, Subject 216. During the Challenge Phase, this subject demonstrated reactions to CD07805/47 gel 0.07% and the gel vehicle patch that were graded as positive for sensitization. During the Re-challenge, reactions to these test products were graded as equivocal, and the subject was unavailable to participate in a second Re-challenge (to confirm sensitization).

Skin Reaction Assessments

During the Induction Phase, most test sites received skin reaction scores of 0 (no reaction) on each evaluation day (Days 1 to 9) for each test product. Table 42 below presents a summary of the highest (or worst) scores, i.e. the number of subjects who reported the particular score at some point during the nine-day induction period. Note: No reactions were scored as Grade 3.

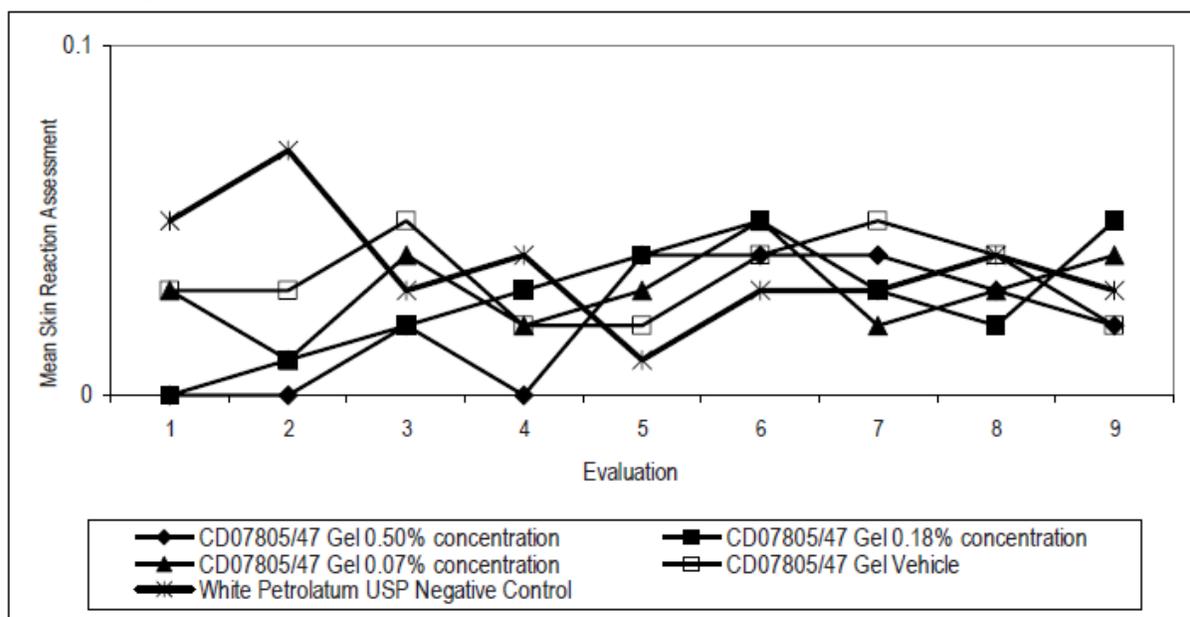
Table 42: Summary of Worst Skin Reaction Score by Test Product – Induction Phase (Applicant Table 17 of study report)

Worst Score (includes imputed scores for missing data)	Treatment									
	CD07805/47 Gel 0.50%		CD07805/47 Gel 0.18%		CD07805/47 Gel 0.07%		Gel Vehicle		White Petrolatum USP Negative Control	
	N	%	N	%	N	%	N	%	N	%
0	211	87.92	206	85.83	205	85.42	202	84.17	193	80.42
1	27	11.25	28	11.67	30	12.50	33	13.75	46	19.17
2	1	0.42	5	2.08	5	2.08	2	0.83	0	0
4	1	0.42	1	0.42	0	0	3	1.25	1	0.42
Total	240	100	240	100	240	100	240	100	240	100

Scale:0=no reaction; 1=mild erythema, 2=moderate erythema; 3=severe erythema OR erythema with edema; 4 =erythema with vesicles or erosion or bullae.

Grade 4 (severe) reactions were most commonly reported with vehicle. One Grade 4 reaction was reported with white petrolatum (occurred at one test site and on Day 10). The applicant computed the mean irritation scores for each patch scoring for each day that an evaluation was performed and for each treatment that was applied. Mean irritation scores were < one for each evaluation/day (where a score of one on the Skin Reaction Assessment scale was “mild erythema”). See Figure 6 and Table 43

Applicant Figure 6: Mean Skin Reaction Scores at Each Patch Scoring – Induction Phase (Applicant Figure 1)



Data Source: Figure generated from data in Section 14.4, Table 14.3.4.2

Table 43: Mean Skin Reaction Score by Test Product and Visit – Induction Phase (Applicant Table 19 of study report)

Visit	Treatment				
	CD07805/47 Gel 0.50%	CD07805/47 Gel 0.18%	CD07805/47 Gel 0.07%	Gel Vehicle	White Petrolatum USP Negative Control
Evaluation 1	0.00	0.00	0.03	0.03	0.05
Evaluation 2	0.00	0.01	0.01	0.03	0.07
Evaluation 3	0.02	0.02	0.04	0.05	0.03
Evaluation 4	0.00	0.03	0.02	0.02	0.04
Evaluation 5	0.04	0.04	0.03	0.02	0.01
Evaluation 6	0.04	0.05	0.05	0.04	0.03
Evaluation 7	0.04	0.03	0.02	0.05	0.03
Evaluation 8	0.03	0.02	0.03	0.04	0.04
Evaluation 9	0.02	0.05	0.04	0.02	0.03

Scale: 0=no reaction; 1=mild erythema, 2=moderate erythema; 3=severe erythema OR erythema with edema; 4 =erythema with vesicles or erosion or bullae

Challenge and Re-Challenge

A total of 209 subjects participated in the Challenge Phase. No subject reported a score > 2 (moderate erythema) at any assessment. Six subjects who were assessed with equivocal or positive results at Challenge participated in a Re-challenge. One subject (Subject 216) had two positive re-challenge reactions (see below). Equivocal responses were reported for six subjects (Subjects 044, 076, 111, 129, 145, and 166) as below:

- at two sites for CD07805/47 gel 0.50%,
- at five sites for CD07805/47 gel 0.18%,
- at three sites for CD07805/47 gel 0.07%,
- at two sites for the gel vehicle and
- at two sites for the negative control.

To confirm sensitization, Subjects 044, 076, 111, 129, 145 and 216 participated in a Re-challenge with the five test products. (Subject 166 was unable to complete Re-challenge). Re-challenge Sensitization Reaction Assessments were negative, with the exception of the equivocal results for Subject 216 (at sites patched with CD07805/47 0.07% and the gel vehicle). The subject was unavailable to participate in a second Re-challenge to confirm sensitization and was therefore graded as positive for sensitization.

Table 44: Summary of Sensitization Reaction Assessment Data by Test Product –Challenge and Re-challenge Phases (Applicant Table 21)

Sensitization	Treatment – n (%) of Total Safety Population N=247				
	CD07805/47 Gel 0.50%	CD07805/47 Gel 0.18%	CD07805/47 Gel 0.07%	Gel Vehicle	White Petrolatum USP Negative Control
CHALLENGE					
Negative	207 (83.8)	204 (82.6)	205 (83.0)	206 (83.4)	207 (83.8)
Equivocal	2 (0.8)	5 (2.0)	3 (1.2)	2 (0.8)	2 (0.8)
Positive	0	0	1 (0.4)	1 (0.4)	0
Total	209 (84.6)	209 (84.6)	209 (84.6)	209 (84.6)	209 (84.6)
38 (15.3%) subjects have no sensitization evaluation due to discontinuation.					
RE-CHALLENGE					
Negative	6 (2.4)	6 (2.4)	5 (2.0)	5 (2.0)	6 (2.4)
Equivocal	0	0	1 (0.4)	1 (0.4)	0 (0)
Total	6 (2.4)	6 (2.4)	6 (2.4)	6 (2.4)	6 (2.4)
Subject 166 was unable to complete Re-challenge. Subject 216 was unavailable for a second Re-challenge.					

Conclusions: Irritation did not increase with increase concentration of the active ingredient (CD07805/47). Irritation from exposures to the active ingredient (CD07805/47) was generally comparable to vehicle and white petrolatum. Most test products produced no reaction. There were few reactions graded higher than Grade 2 (“moderate erythema”), and Grade 4 reactions (“erythema with vesicles or erosion or

bullae”), when observed, were most often reported with vehicle exposure (three observations) and included one report with white petrolatum. Under the conditions of this study, one subject (Subject 216) presented evidence of contact sensitization.

7.4.5.2 Photosensitization Potential

RD.06.SRE.18124: “Evaluation of the Photosensitization Potential of Three Concentrations of CD07805/47 Topical Gel (0.07%, 0.18%, and 0.50%) and Corresponding Vehicle Gel Following Repeated Applications to the Skin of Healthy Subjects”

Study objectives: to determine the photosensitization potential of three concentrations of CD07805/47 topical gel (0.07%, 0.18%, and 0.50%) and corresponding vehicle gel after repeated applications.

Study design: single-center, randomized, vehicle- and negative-controlled, Investigator/evaluator-blinded, intra-individual photoallergenicity study in healthy subjects

Study periods were a 3-week Induction Phase, a 2-week Rest Phase, a 1-week Challenge Phase, and if applicable, a 3-week Rechallenge Phase.

MED

The subject’s minimal erythema dose (MED) was determined prior to testing for photoallergenicity. The MED was determined 24 ±2 hours after irradiation on Day 1, and was defined as the smallest dose of energy that produced a perceptible homogeneous redness reaching the borders of the irradiated site.

Number of subjects: 50 planned; 57 subjects randomized, 53 subjects (93%) completed the Induction Phase, and 52 subjects (91%) completed the Challenge Phase.

Diagnosis and key enrollment criteria: healthy male and female subjects 18 to 65 years of age, inclusive, with Fitzpatrick skin types I through IV.

Table 45 Test Product and Exposure Procedures (modified from Synopsis)

	CD07805/47 Gel			CD07805/47 Vehicle Gel	White Petrolatum
	0.07%	0.18%	0.50%	0%	100%
Name of Active Ingredient (INN)	Brimonidine tartrate			Not applicable	Petroleum jelly (Vaseline®)
Internal code	CD07805/47			CD07805/47 Vehicle Gel	Not applicable
Pharmaceutical Form	Gel			Gel	Ointment
Dosage/Site	0.20 mL per application (topical)/back				
Frequency:	Induction Phase: Twice weekly for 3 weeks (two-week Rest Phase before Challenge) Challenge Phase: 2 applications				
Duration	24 ± 2 hours (each application)				
Test Patch Site UV Irradiation Dosage					
Week 1:	2 x MED of UVA/UVB				
Weeks 2 and 3:	3 x MED of UVA/UVB				

Safety assessments

- Induction: Skin Reaction Assessments: All assigned scores of skin reactions were summarized using frequency counts and percentages by visit and by study product for the irradiated side. The worst (largest) score for each subject during the Induction Phase was summarized.
- Challenge Phase (and Rechallenge Phase, if applicable): Skin reaction assessments, Sensitization Reaction Evaluations; Photosensitization reactions on Day 39 and Day 40 were assessed according to the Sensitization Reaction Evaluation criteria (i.e., 0=Negative; 1=Equivocal; 2=Positive). If a score of 1 (Equivocal) was obtained on Day 40, a facultative reading could be performed approximately 96 or 120 hours after patch removal at the Investigator's discretion.

Skin Reaction Assessment (same as used in contact sensitization study 18123)

0 = No reaction

1= Mild erythema (slight redness)

2= Moderate erythema (definite redness easily recognized)

3= Severe erythema OR erythema with edema (intense redness or redness associated with local swelling)

4= Erythema with vesicles or erosion or bullae (redness with small or large blisters or skin abrasion; can be accompanied by weeping/oozing, crusting)

Sensitization Reaction Evaluation (same as used in contact sensitization study 18123)

0= negative; 1= equivocal; 2= positive

Results

Demographics and Extent of Exposure

The study population was 86% female, 94.7% Caucasian, and the mean age was 46.9 years. The reason for the predominance of females is unclear, since this study did not enroll subjects with rosacea (a population where there is a female predominance).

A total of 53 subjects (93.0%) completed the Induction Phase, and these subjects received six applications (two 0.2 mL applications per week for three weeks) of CD07805/47, i.e. two applications each of 0.07%, 0.18% and 0.05%. Subjects also received six applications of vehicle gel and white petrolatum during the Induction Phase. One application of each study product was placed on each side of the subject's back. A total of 52 subjects (91.2%) completed the Challenge Phase, and these subjects received two applications of each of the five test products.

Each patch application was for 24 hours.

Adverse events

Eight subjects (14%) reported ten adverse events. One subject reported two serious adverse events (head injury and a hand fracture sustained in an automobile accident), and this subject discontinued the study. No other subjects discontinued the study due to adverse events. Nasopharyngitis [three subjects (5.3%)] and headache [two subjects (3.5%)] were the most commonly reported events. There were single reports of the remaining adverse events: lymphadenopathy, face edema and oropharyngeal pain.

Skin reactions

Of the 52 subjects who completed the Challenge Phase, 100% had a negative photosensitization score as determined by the Investigator based on the Sensitization Reaction Evaluation. During Challenge, no subject had any skin reaction greater than mild erythema (Grade 1) at any of the irradiated sites. A total of 50 subjects (94%) had mild erythema at least one skin site. Of these subjects, 49 (92.5%) had mild erythema at the white petrolatum (negative control) site, which the applicant reported as consistent with physiologic responses to repeated MED levels of UV exposure. Mean skin reaction scores ranged from 0.48 in the CD07805/47 gel 0.50% group to 0.55 in the vehicle gel group.

Conclusion: None of the subjects showed a pattern of response suggestive of a photosensitivity to the study products. Based on the study results, there was no evidence of a photosensitization reaction to CD07805/47 gel (0.07%, 0.18%, 0.50%) or vehicle.

7.4.5.3 Cumulative Irritancy Potential

RD.06.SRE.18125: “Evaluation of the Cumulative Irritancy Potential of Three Concentrations of CD07805/47 Topical Gel (0.07%, 0.18%, and 0.5%) Following Repeated Applications to the Skin of Healthy Subjects”

Study objective: To determine the cumulative irritancy potential of repeated applications of three concentrations of CD07805/47 topical gel (0.07%, 0.18%, and 0.5%) to the skin of healthy subjects.

Study Design: This was a phase 1, single-center, randomized, vehicle-, negative-, and positive-controlled, evaluator-blinded, intra-individual design study enrolling healthy male and female subjects. Test products were three concentrations of CD07805/47 topical gel (0.07%, 0.18%, and 0.5%), CD07805/47 gel vehicle, white petrolatum USP as a negative control, and 0.25% sodium lauryl sulphate sulfate (SLS) solution as a positive control.

Treatment and Assessment Period

Test products were applied under occlusive patches to designated skin sites on the subject’s back Monday through Friday for three consecutive weeks. Patches remained in place over the weekends. Treatment duration was 22 days.

A Skin Reaction Assessment (5 point scale as used in studies above) was performed approximately 15 to 30 minutes after patch removal for each designated skin site daily.

Number of subjects: 40 subjects planned; 38 subjects enrolled and randomized to treatment, and 35 subjects completed the study.

Diagnosis and key inclusion criteria: Healthy male or female, 18 to 65 years;
Skin phototype of I to IV

Results

Demographics and Extent of Exposure

Thirty-eight subjects were enrolled. All subjects were White (100%); 26 (68.4%) were female; age ranged from 18 to 64 years (mean age was 40.2 years).

The extent of exposure was measured by the number of subjects exposed to the treatment gel for each concentration. At least 24 subjects (63.2%) of subjects were exposed to 21 days of treatment with CD07805/47 at each of the three concentrations tested. Approximately 27 subjects (71.1%) of subjects were exposed to 21 days of applications of the white petrolatum (negative control), and approximately four subjects (10.5%) were exposed to 21 days of SLS (positive control) applications.

Adverse Events

A total of eight subjects (21.1%) subjects reported an adverse event during the study. One subject reported a serious adverse event of gastroenteritis, and this subject discontinued the study. There were two reports of gastroenteritis; there were single reports of all other adverse events, which included nasopharyngitis, nasal congestion, and headache.

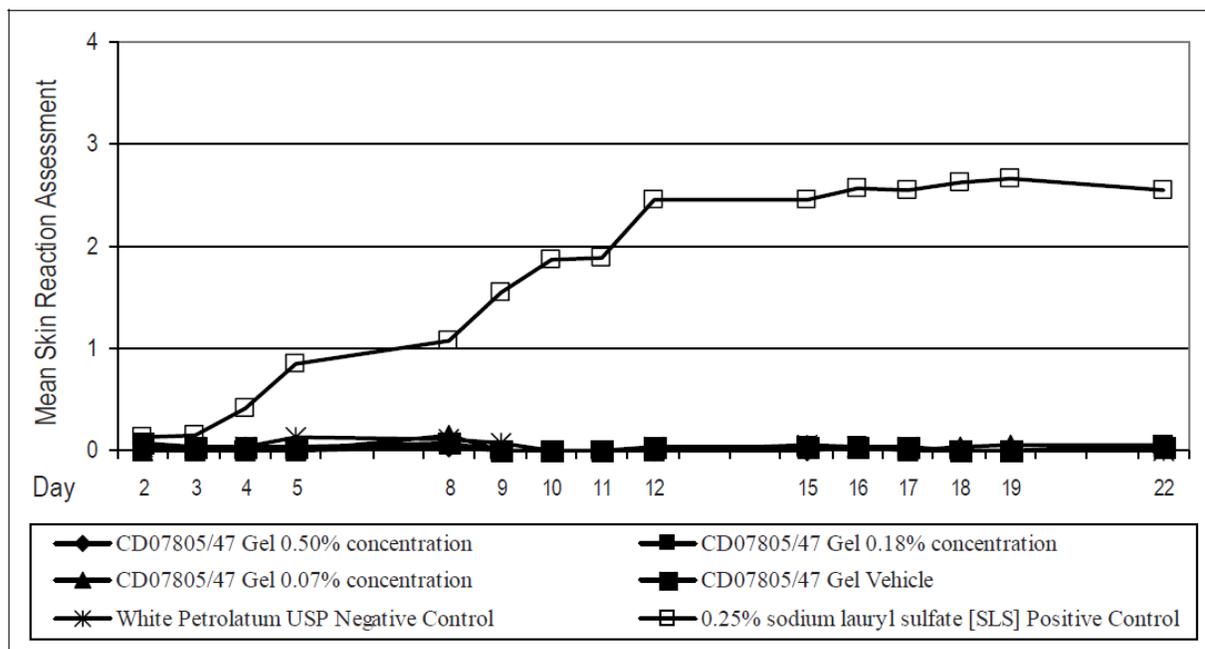
Skin Reaction Assessment

The reaction scores for each test article during the study were as follows:

- Sites patched with CD07805/47 Gel (0.50%) received scores of 0 (no reaction) and 1 (mild erythema).
- Sites patched with CD07805/47 Gel (0.18%) received scores of 0 and 1.
- Sites patched with CD07805/47 Gel (0.07%) received scores of 0, 1 and one instance of a score of 3 (severe erythema on Evaluation 5).
- Sites patched with CD07805/47 Gel vehicle (0.0%) received scores of 0 and 1.
- Sites patched with the negative control, white petrolatum USP, received scores of 0, 1 and one score of 2 (moderate erythema on Evaluation 4).
- Sites patched with the positive control, 0.25% SLS, received scores ranging from 0 through 4 (erythema with vesicles or erosion or bullae).

The mean irritation scores for each test article and each time point are presented in Figure 1.

Figure 7 Mean Irritation Scores at Each Patch Scoring (Applicant Figure 1 of study report)



Evaluation Key:

Day 2=Eval. 1 Day 5=Eval. 4 Day 10=Eval. 7 Day 15=Eval. 10 Day 18=Eval. 13; Day 3=Eval. 2 Day 8=Eval. 5 Day 11=Eval. 8 Day 16=Eval. 11 Day 19=Eval. 14; Day 4=Eval. 3 Day 9=Eval. 6 Day 12=Eval. 9 Day 17=Eval. 12 Day 22=Eval. 15

Mean cumulative irritancy index (MCII or average of irritancy scores across all study visits) for sites patched with the CD07805/47 0.5% and 0.18% was 0.01. MCII for the 0.07% concentration and Gel Vehicle were 0.02. The three concentrations of CD07805/47 and the Gel Vehicle elicited less irritation than the negative control (MCII=0.03) and the positive control (MCII=1.69).

Conclusion: Under the conditions of the study, brimonidine gels and vehicle did not demonstrate signs of clinically significant irritancy. There was no apparent correlation between the increase in the concentration of active ingredient CD07805/47 and irritation. Mean irritation scores for the three CD07805/47 gels, the gel vehicle, and the white petrolatum negative control were similar and near zero at all evaluation points during the treatment period.

7.4.5.4 Phototoxic Potential

RD.06.SRE.18189: “Evaluation of the Phototoxic Potential of Three Concentrations of CD07805/47 Gel (0.07%, 0.18%, and 0.50%) and Corresponding Vehicle Gel Following Application to the Skin of Healthy Subjects”

Study objectives: to determine the potential of a single application of CD07805/47 gel (0.07%, 0.18%, and 0.50%) and corresponding vehicle gel to induce a phototoxic (photoirritation) reaction (i.e. when dermal application was followed by ultraviolet (UV) light exposure) in healthy subjects.

Study design: This was a single-center, randomized, investigator/evaluator-blinded, controlled, intra-individual comparison study.

Each subject received two dermal applications of each study drug, one application on the left side of the back and the other application on the right side of the back. One additional test site was left untreated on each side of the back (to allow an evaluation of the reaction caused by the UV irradiation and patch occlusion alone in order to help eliminate the interpretation of false-positive drug reactions). The test sites were covered with an occlusive covering for approximately 24 hours, after which one set of test sites was irradiated with UVA and UVA/UVB radiation, while the contralateral set remained non-irradiated. The Investigator evaluated the test sites for local skin reactions at 30 minutes, 24 ± 2 hours, and 48 ± 2 hours after irradiation and rated the signs of cutaneous irritation, e.g. erythema, edema. Phototoxic (photoirritation) reactions (graded as negative, equivocal, or positive; see scales previously discussed) were assessed 48 ± 2 hours after irradiation.

Number of subjects:

Thirty-five subjects were enrolled, and 34 subjects completed the study. One subject was discontinued for a protocol violation (the subject removed the test patches prematurely).

Diagnosis and key enrollment criteria

The study enrolled healthy male and female subjects 18 to 65 years of age with Fitzpatrick skin types I through IV.

Safety assessment:

Phototoxic (photoirritation) reactions and local skin reactions were assessed as discussed above.

Results

Demographics and baseline disease characteristics

The population was 97.1% female, 100% Caucasian, and the mean age was 47.7 years. The majority of subjects were of Fitzpatrick skin type 2 (34.3%) or 3 (51.4%).

Extent of exposure

The 35 randomized subjects received a total of six patches containing CD07805/47 gel and two patches of vehicle gel (200 μ L per patch). Exposure to the patches was 24 ± 2 hours for 34 subjects (97.1%).

Adverse events:

There were no serious adverse events and no subject discontinued the study due to an adverse event.

Three subjects (8.6%) reported four adverse events. Two subjects reported nasopharyngitis. Subject 4 reported pruritus at the CD07805/47 gel 0.07% and vehicle gel application sites during a rechallenge procedure performed to investigate potential phototoxicity of the study products. The subject reported no pruritus at 0.18% or 0.50% CD07805/47 application sites.

Skin reactions:

The erythema responses at post-irradiation time points are presented in the following table. The responses were similar across treatment groups, i.e. at brimonidine, vehicle and untreated sites. The responses are consistent with radiation-induced erythema and do not show evidence of an additive effect from the brimonidine.

Table 46 Incidence of Erythema Response Post-Irradiation, Safety Population (Applicant Table 13 study report for 18189)

Time Post-Irradiation	CD07805/47 0.07% Gel		CD07805/47 0.18% Gel		CD07805/47 0.50% Gel		Vehicle Gel		Untreated	
	I	NI	I	NI	I	NI	I	NI	I	NI
30 minutes, n (%)										
Unknown	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)
0 = No reaction	28 (80.0)	27 (77.1)	28 (80.0)	25 (71.4)	30 (85.7)	27 (77.1)	21 (60.0)	28 (80.0)	20 (57.1)	28 (80.0)
1 = Mild erythema	5 (14.3)	7 (20.0)	5 (14.3)	8 (22.9)	3 (8.6)	6 (17.1)	12 (34.3)	6 (17.1)	14 (40.0)	6 (17.1)
2 = Moderate erythema	1 (2.9)	0	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	0	0	0
24 ± 2 hours, n (%)										
Unknown	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)
0 = No reaction	23 (65.7)	33 (94.3)	26 (74.3)	33 (94.3)	25 (71.4)	33 (94.3)	25 (71.4)	33 (94.3)	23 (65.7)	34 (97.1)
1 = Mild erythema	10 (28.6)	1 (2.9)	7 (20.0)	1 (2.9)	9 (25.7)	0	9 (25.7)	1 (2.9)	11 (31.4)	0
2 = Moderate erythema	1 (2.9)	0	1 (2.9)	0	0	1 (2.9)	0	0	0	0
48 ± 2 hours, n (%)										
Unknown	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)
0 = No reaction	31 (88.6)	33 (94.3)	31 (88.6)	33 (94.3)	31 (88.6)	33 (94.3)	31 (88.6)	33 (94.3)	32 (91.4)	34 (97.1)
1 = Mild erythema	3 (8.6)	1 (2.9)	3 (8.6)	1 (2.9)	3 (8.6)	1 (2.9)	3 (8.6)	1 (2.9)	2 (5.7)	0

I=irradiated; N=non-irradiated; Note: The Safety Population comprised 35 subjects

The moderate erythema was observed in Subject 4, a 53-year-old female with Fitzpatrick skin type II.

Conclusion

Under the conditions of this study, CD07805/47 gel (0.07%, 0.18%, and 0.50%) and vehicle gel showed no evidence of inducing phototoxicity.

7.4.5.5 Evaluation of the Static Sun Protection Factor

RD.06.SRE.18137: “Evaluation of the Static Sun Protection Factor (SPF) of CD07805/47 Vehicle Gel Following Application to the Skin of Healthy Subjects”

The study objective was to determine the static sun protection factor (SPF) value of CD07805/47 vehicle gel when applied to human subjects (the product includes titanium dioxide).

Study design

This was a single-center, randomized, Investigator/evaluator blinded, intra-individual comparison study that enrolled healthy male and female subjects, 18 to 65 years of age inclusive, with Fitzpatrick skin types I, II, or III. The investigative product was CD07805/47 vehicle gel. Homosalate 8% lotion (sunscreen) was used as an active

control. One site was left untreated as a control for radiation sensitivity. The study consisted of 2 components: MED determination and static SPF determination.

Under the conditions of the study, the applicant determined that the static SPF for CD07805/47 vehicle gel was 1. These results demonstrate that the amount of titanium dioxide within the formulation did not function as a sunscreen. The static SPF of the active control, homosalate 8% lotion, was determined to be 4. The applicant concluded that these findings confirmed the validity of this study and the 0.625% w/w of 10% TiO₂ in the CD07805/47 gel formulation is not sufficient to give the product a SPF \geq 2. Therefore, the product cannot be classified as a sunscreen.

The applicant conducted based on presubmission discussions with the agency. See Section 2.5.

7.4.6 Immunogenicity

This section is not applicable.

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 open-label, long-term trial.

RD.06.SRE.18142: “A Multicenter, Open-Label Study to Evaluate the Long-Term Safety and Efficacy of CD07805/47 Gel 0.5% Applied Topically Once Daily for up to 52 Weeks in Subjects with Moderate to Severe Facial Erythema Associated with Rosacea”

Study objectives:

The primary objective of this trial was to evaluate the long-term safety of CD07805/47 gel 0.5% applied once daily, for up to 52 weeks (no less than 365 days), in subjects with moderate to severe facial erythema associated with rosacea. The long-term efficacy of CD07805/47 gel 0.5% applied once daily was evaluated as a secondary objective,.

Per section 4.2 of the protocol: “The study population, as defined by the Inclusion and Exclusion Criteria, is representative of the population intended to be treated with CD07805/47 gel 0.5% once the product is marketed.” Unlike with the pivotal trials, there

were no Enrollment Criteria pertaining to numbers of inflammatory lesions (e.g. no exclusions). Concomitant rosacea therapies were permitted (as further discussed below).

Study design: A long-term, open-label, non-comparative safety and efficacy study of CD07805/47 gel 0.5% once daily in subjects with moderate to severe facial erythema associated with rosacea.

Subjects were male or female, of any race, 18 years of age or older. Subjects were to apply CD07805/47 gel 0.5% once daily to the entire face. Approximately 450 subjects were planned; 449 enrolled.

Subjects were treated for up to 12 months and returned to the investigational site for evaluations at Baseline, Week 1, and at Months 1, 3, 6, 9, and 12/Early Termination. Laboratory sampling for blood and urine will be taken at Screening, Month 3, Month 6, and Month 12/ET (discussed in Section 7.4.2). IOP was measured at the Baseline, Month 1, Month 6, and Month 12/ET visits (discussed in Section 7.3.5).

Key inclusion criteria:

- Male or female who is at least 18 years of age or older.
- A clinical diagnosis of facial rosacea.
- A Clinician Erythema Assessment (CEA) score of ≥ 3 at Screening and at Baseline
- A Patient Self Assessment (PSA) score of ≥ 3 at Screening and at Baseline

Key exclusion criteria:

- rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or other concomitant dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, or actinic telangiectasia.
- Current diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression.
- Previous refractive eye surgery such as photorefractive keratectomy (PRK), laser-assisted sub-epithelial keratectomy (LASEK), or laser-assisted in situ keratomileusis (LASIK).
- Current treatment with monoamine oxidase (MAO) inhibitors.
- Current treatment with, barbiturates, opiates, sedatives, systemic anesthetics, alpha-agonists (as revised under Amendment #1)

Concomitant therapies

Concomitant standard of care treatments for subjects with inflammatory lesions of rosacea were allowed in all phases of the study. Subjects on active treatments for

lesions at the time of enrollment continued their current regimen for the duration of the study with modification of the regimen as deemed appropriate by the Investigator during the study. Subjects requiring new therapy for the treatment of inflammatory lesions (at enrollment or during the study) could be prescribed standard- of-care treatment at the Investigator’s discretion.

On non-clinic days, subjects could use facial products such as lotions, creams, ointments, cosmetics, and sunscreens after they applied study drug.

Safety Assessments included: Adverse events, vital signs (blood pressure and heart rate standing and the sitting) position at Screening, Baseline, and all post-baseline visits, IOP (Baseline, Month 1, Month 6, and Month 12/ET (prior to study drug application), Laboratory Safety Tests (Blood and urine samples will be obtained for evaluation of blood chemistry, hematology, and urinalysis at Screening visit, Month 3, Month 6, Month 12/ET, and unscheduled visits).

Efficacy Assessments included: PSA and CEA at Screening, Baseline clinic visit (prior to and 3 hours after study drug application), and all post-baseline clinic visits (prior to and 3 hours after study drug application).

Per Flow Chart of procedures in protocol, on-treatment study visits were at Week 1 and Months 1, 3, 6, 9, and 12.

Results

Disposition of subjects

A total of 449 subjects were enrolled. A total of 279 subjects (62.1%) completed the study (up to the Month 12 visit) and 170 subjects (37.9%) prematurely discontinued the study. A total of 335 subjects (74.6%) completed at least 6 months of treatment.

Table 47 Summary of Subject Disposition, Safety Population (Applicant Table 18 of study report)

Completion Status	CD07805/47 Gel 0.5% n (%)
Normal Completion	279 (62.1)
Premature Discontinuation	170 (37.9)
Adverse Event	75 (16.7)
Subject’s Request	52 (11.6)
Protocol Violation	16 (3.6)
Lost to Follow-up	22 (4.9)
Pregnancy	2 (0.4)
Other	3 (0.7)

Demographic and other Baseline characteristics

The majority of subjects were female (74.8%) and Caucasian (97.6%). Mean age was 50.9 years. A total of 395 subjects (88%) were in the 18 to 64 years age group, and 54 subjects (12.0%) were \geq 65 years.

Skin Phototypes ranged from I to VI, with the majority of subjects (approximately 80%) having Skin Phototype II or III. Six subjects (1.3%) had skin type V, and one (0.2%) had skin type VI.

Table 48 Summary of Subject Baseline Characteristics, Safety Population (Excerpt from Applicant Table 20 of study report)

Patient Self-Assessment (PSA) at Baseline (Day 1, Hour 0), n (%)	
2=Mild redness	2 (0.4)
3=Moderate redness	379 (84.4)
4=Severe redness	68 (15.1)
Total	449 (100)
Clinician's Erythema Assessment (CEA) at Baseline (Day 1, Hour 0), n (%)	
3=Moderate erythema, marked redness	394 (87.8)
4=Severe erythema, fiery redness	55 (12.2)
Total	449 (100)

Note: The two subjects who had a baseline PSA of 2 had met the PSA criterion of \geq 3 at Screening.

Concomitant therapies

Concomitant therapies were taken by 84.9% of subjects. The most commonly-reported concomitant therapies (>10% of total subjects) were

- metronidazole- route not specified; presumed topical (70 subjects, 15.6%),
- ibuprofen (58 subjects, 12.9%), and
- multivitamins (56 subjects, 12.5%).

The applicant stated that 131 subjects (29.2%) were taking concomitant therapies for inflammatory lesions of rosacea. From review of the summary table of concomitant therapies taken by > 3% of subjects (Table 21 of the study report), therapies for treatment of inflammatory lesions of rosacea may have included (the reviewer did not find the treatments that were prescribed specifically for rosacea identified): metronidazole 70 subjects (15.6%), azelaic acid 27 subjects (6.0%), doxycycline 45 subjects (10.0%), and tetracycline 18 subjects (4.0%). "Other emollients and protectives" (not otherwise specified) were used by 21 subjects (4.7%). Also see Section 7.5.5 of this review.

Measurements of treatment compliance

Subjects were instructed to bring the study drug tubes and dosing calendar to the investigational site at the Month 3, 6, 9, and 12/ET visits. Subjects were queried regarding the frequency of application and missed doses. Over the course of the study, the mean subject compliance was 95.18% and the mean number of missed applications of study drug was 9.49.

Quantity of product used

The mean total study drug usage was 130.35 g and the mean daily study drug usage was 0.53 g/day.

Efficacy

The primary objective of this study was the assessment of long term safety. Efficacy was a secondary objective. The composite endpoint was not assessed in this study.

Duration of study treatment

The mean duration of treatment was 277.9 days. Two hundred seventy six subjects (61.5%) had a treatment duration of \geq 365 days.

Table 49 Summary of Duration of Treatment, Safety Population (Applicant Table 34 of the study report-Modified)

Parameter	CD07805/47 Gel 0.5% (N=449)
Treatment Duration (Day) ^a	
N	449
Mean (SD)	277.9 (132.53)
Median	366.0
Minimum, Maximum	1, 408
1 to 14 days, n (%)	17 (3.8)
15 to 29 days, n (%)	17 (3.8)
30 to 90 days, n (%)	40 (8.9)
91 to 180 days, n (%)	42 (9.4)
181 to 270 days, n (%)	30 (6.7)
271 to 364 days, n (%)	27 (6.0)
\geq 365 days, n (%)	276 (61.5)

^a Treatment Duration=Date of the last application - date of the first application

Overall Adverse events

Per the study report, a total of 275 subjects (61.2%) reported 749 adverse events over the entire study. The incidence of adverse events was highest during the first quarter of the study (the first 90 days) with adverse events reported by 41.9% of subjects.

Approximately 24.6%, 24.3% and 19.5% of remaining subjects reported adverse events for the second, third and fourth quarters, respectively.

Serious adverse events

A total of 16 serious adverse events were reported in 12 subjects over the entire course of the one-year study. There were no multiple reports of any serious adverse event, i.e. no particular type of serious adverse event was reported more than once.

Table 50 Summary of serious adverse events by System Organ Class and Preferred Term, Safety Population, RD.06.SRE.18142 (Applicant Summary of Clinical Safety Table 36)

SYSTEM ORGAN CLASS Preferred Term ^a	Brimonidine Tartrate 0.5% Gel N=449 n (%)
Total Number of Adverse Event(s)	16
Total Number (%) of Subjects with Adverse Event(s) ^b	12 (2.7)
Cardiac Disorders	2 (0.4)
Angina Unstable	1 (0.2)
Ventricular Tachycardia	1 (0.2)
Infections and Infestations	2 (0.4)
Periodontal Infection	1 (0.2)
Pneumonia Primary Atypical	1 (0.2)
Sepsis	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	2 (0.4)
Osteoarthritis	1 (0.2)
Synovitis	1 (0.2)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	2 (0.4)
Breast Cancer	1 (0.2)
Lung Squamous Cell Carcinoma Stage Unspecified	1 (0.2)
Reproductive System and Breast Disorders	2 (0.4)
Ovarian Cyst	1 (0.2)
Uterine Hemorrhage	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.4)
Chronic Obstructive Pulmonary Disease	1 (0.2)
Hypoxia	1 (0.2)
Gastrointestinal Disorders	1 (0.2)
Acquired Oesophageal Web	1 (0.2)
Injury, Poisoning and Procedural Complications	1 (0.2)
Tendon Rupture	1 (0.2)
Nervous System Disorders	1 (0.2)
Encephalopathy	1 (0.2)

^a: Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.

^b: A subject was counted once even if the subject experienced more than 1 AE during the study. MedDRA version 11.0.

Discontinuations Due to Adverse Events

A total of 75 subjects (16.7%) discontinued the year-long study due to adverse events. The majority of the adverse events leading to discontinuation were in the Skin and subcutaneous tissue disorders SOC. The adverse event that was most frequently reported as leading to discontinuation was “flushing” with 18 reports (17 reports in the Vascular disorders SOC and one in the Skin and subcutaneous tissue disorders SOC). The highest incidence of adverse events leading to discontinuation was during the first quarter of the study, and 8.0% of subjects discontinued during this period. Approximately 2.9% of subjects discontinued the study during the fourth quarter due to an adverse event.

Table 51 Treatment-emergent adverse events leading to discontinuation by System Organ Class and Preferred Term, Safety Population, RD.06.SRE.18142 (Applicant Summary of Clinical Safety Table 37)

	Entire Study (N=449)	By Day 29 (N=449)	First Quarter (N=449)	Second Quarter (N=382)	Third Quarter (N=337)	Fourth Quarter (N=308)
System Organ Class Preferred Term						
Subjects Reporting Any Adverse Event Leading to Discontinuation, N(%)	75 (16.7)	22 (4.9)	36 (8.0)	17 (4.5)	14 (4.2)	9 (2.9)
Immune System Disorders	1 (0.2)	0	0	0	1 (0.3)	0
Hypersensitivity	1 (0.2)	0	0	0	1 (0.3)	0
Infections and Infestations	2 (0.4)	1 (0.2)	1 (0.2)	0	1 (0.3)	0
Cellulitis	1 (0.2)	0	0	0	1 (0.3)	0
Pneumonia primary atypical	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Sepsis	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	1 (0.2)	0	0	1 (0.3)	0	0
Breast Cancer	1 (0.2)	0	0	1 (0.3)	0	0
Nervous System Disorders	2 (0.4)	2 (0.4)	2 (0.4)	0	0	0
Headache	2 (0.4)	2 (0.4)	2 (0.4)	0	0	0
Psychiatric Disorders	1 (0.2)	0	0	0	0	1 (0.3)
Depression	1 (0.2)	0	0	0	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Hypoxia	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0

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Skin and Subcutaneous Tissue Disorders	57 (12.7)	13 (2.9)	24 (5.3)	14 (3.7)	11 (3.3)	8 (2.6)
Acne	1 (0.2)	0	0	0	1 (0.3)	0
Dermatitis	2 (0.4)	0	0	1 (0.3)	0	1 (0.3)
Dermatitis allergic	7 (1.6)	0	1 (0.2)	3 (0.8)	2 (0.6)	1 (0.3)
Dermatitis contact	7 (1.6)	0	1 (0.2)	2 (0.5)	1 (0.3)	3 (1.0)
Dry skin	1 (0.2)	0	0	0	0	1 (0.3)
Eczema weeping	1 (0.2)	0	0	1 (0.3)	0	0
Erythema	8 (1.8)	5 (1.1)	8 (1.8)	0	0	0
Face oedema	1 (0.2)	0	0	1 (0.3)	0	0
Flushing	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Pain of skin	1 (0.2)	0	0	0	1 (0.3)	0
Pruritus	3 (0.7)	0	0	2 (0.5)	1 (0.3)	0
Rash papular	1 (0.2)	0	0	0	1 (0.3)	0
Rash pruritic	1 (0.2)	0	0	0	1 (0.3)	0
Rosacea	11 (2.4)	4 (0.9)	7 (1.6)	2 (0.5)	1 (0.3)	1 (0.3)
Skin burning sensation	8 (1.8)	2 (0.4)	5 (1.1)	3 (0.8)	0	0
Skin hyperpigmentation	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Skin irritation	8 (1.8)	1 (0.2)	1 (0.2)	3 (0.8)	3 (0.9)	1 (0.3)
Vascular Disorders	19 (4.2)	9 (2.0)	14 (3.1)	3 (0.8)	2 (0.6)	0
Flushing	17 (3.8)	8 (1.8)	12 (2.7)	3 (0.8)	2 (0.6)	0
Hypertension	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0
Orthostatic hypotension	1 (0.2)	0	1 (0.2)	0	0	0

Subjects reporting a particular adverse event more than once are counted only once for that adverse event

Data Source: Table 2.5.C in ISS Tables in Section 5.3.5.3

Common Adverse Events

Over the course of the study, adverse events were most commonly reported in the Skin and subcutaneous tissue disorders SOC, and, per the study report 137 subjects (30.5%) reported adverse events in this SOC. Flushing was the most frequently reported event, with 46 subjects reporting this event (10.2%). Erythema was the second most frequently-reported event: 35 subjects (7.8%). Other events reported in ≥ 4% of subjects were rosacea (5.3%), nasopharyngitis (4.9%), skin burning sensation (4.2%), increased IOP (4.2%), and headache (4.0%).

Table 52 Summary of Adverse Events in >1% of Subjects for the Entire Study by System Organ Class and Preferred Term, Safety Population (Applicant Table 37 of study report)

System Organ Class/ Preferred Term ^a	Entire Study N=449 n (%)	Day 29 N=449 n (%)	1 st Quarter N=449 n (%)	2 nd Quarter N=382 n (%)	3 rd Quarter N=337 n (%)	4 th Quarter N=308 n (%)
Total Number of AE(s)	749	232	368	136	125	107
Total Number (%) of Subjects with AE(s) ^b	275 (61.2)	133 (29.6)	188 (41.9)	94 (24.6)	82 (24.3)	60 (19.5)
Skin and Subcutaneous Tissue Disorders	137 (30.5)	61 (13.6)	79 (17.6)	36 (9.4)	26 (7.7)	19 (6.2)
Erythema	35 (7.8)	20 (4.5)	27 (6.0)	7 (1.8)	3 (0.9)	2 (0.6)
Rosacea	24 (5.3)	10 (2.2)	13 (2.9)	4 (1.0)	5 (1.5)	2 (0.6)
Skin Burning Sensation	19 (4.2)	8 (1.8)	12 (2.7)	6 (1.6)	1 (0.3)	0
Dermatitis Contact	15 (3.3)	1 (0.2)	2 (0.4)	6 (1.6)	3 (0.9)	4 (1.3)
Skin Irritation	15 (3.3)	3 (0.7)	3 (0.7)	5 (1.3)	5 (1.5)	3 (1.0)
Pruritus	11 (2.4)	6 (1.3)	6 (1.3)	3 (0.8)	1 (0.3)	1 (0.3)
Dermatitis Allergic	10 (2.2)	0	1 (0.2)	3 (0.8)	4 (1.2)	2 (0.6)
Skin Warm	8 (1.8)	6 (1.3)	6 (1.3)	1 (0.3)	1 (0.3)	0
Acne	6 (1.3)	4 (0.9)	5 (1.1)	0	1 (0.3)	0
Dry Skin	6 (1.3)	5 (1.1)	5 (1.1)	0	1 (0.3)	1 (0.3)
Rash Papular	6 (1.3)	1 (0.2)	2 (0.4)	1 (0.3)	1 (0.3)	2 (0.6)
Urticaria	5 (1.1)	1 (0.2)	1 (0.2)	0	3 (0.9)	1 (0.3)
Infections and Infestations	72 (16.0)	15 (3.3)	30 (6.7)	19 (5.0)	24 (7.1)	18 (5.8)
Nasopharyngitis	22 (4.9)	2 (0.4)	6 (1.3)	7 (1.8)	6 (1.8)	6 (1.9)
Sinusitis	10 (2.2)	2 (0.4)	4 (0.9)	2 (0.5)	3 (0.9)	2 (0.6)
Impetigo	6 (1.3)	0	0	2 (0.5)	3 (0.9)	1 (0.3)
Urinary Tract Infection	6 (1.3)	2 (0.4)	3 (0.7)	0	2 (0.6)	2 (0.6)
Gastroenteritis	5 (1.1)	3 (0.7)	5 (1.1)	0	1 (0.3)	1 (0.3)
Vascular Disorders	61 (13.6)	34 (7.6)	46 (10.2)	8 (2.1)	7 (2.1)	4 (1.3)
Flushing	46 (10.2)	26 (5.8)	36 (8.0)	7 (1.8)	6 (1.8)	1 (0.3)
Investigations	40 (8.9)	7 (1.6)	18 (4.0)	10 (2.6)	8 (2.4)	8 (2.6)
Intraocular Pressure Increased	19 (4.2)	5 (1.1)	11 (2.4)	4 (1.0)	3 (0.9)	2 (0.6)
Intraocular Pressure Decreased	5 (1.1)	2 (0.4)	2 (0.4)	2 (0.5)	1 (0.3)	0
Nervous System Disorders	33 (7.3)	23 (5.1)	29 (6.5)	3 (0.8)	0	1 (0.3)
Headache	18 (4.0)	15 (3.3)	17 (3.8)	1 (0.3)	0	0
Dizziness	7 (1.6)	4 (0.9)	6 (1.3)	1 (0.3)	0	0
Gastrointestinal Disorders	32 (7.1)	14 (3.1)	16 (3.6)	6 (1.6)	6 (1.8)	6 (1.9)
Nausea	8 (1.8)	3 (0.7)	3 (0.7)	3 (0.8)	1 (0.3)	1 (0.3)
Toothache	6 (1.3)	3 (0.7)	3 (0.7)	0	2 (0.6)	1 (0.3)
Eye Disorders	27 (6.0)	10 (2.2)	17 (3.8)	5 (1.3)	1 (0.3)	5 (1.6)
Eye Pain	6 (1.3)	3 (0.7)	5 (1.1)	1 (0.3)	0	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	25 (5.6)	6 (1.3)	12 (2.7)	5 (1.3)	7 (2.1)	1 (0.3)
Back Pain	7 (1.6)	2 (0.4)	4 (0.9)	1 (0.3)	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	21 (4.7)	5 (1.1)	8 (1.8)	6 (1.6)	4 (1.2)	3 (1.0)
Cough	6 (1.3)	0	1 (0.2)	4 (1.0)	1 (0.3)	0
Pharyngolaryngeal Pain	6 (1.3)	2 (0.4)	3 (0.7)	0	1 (0.3)	0
Sinus Congestion	5 (1.1)	0	0	3 (0.8)	2 (0.6)	0

a Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.

b A subject was counted once even if the subject experienced more than one AE during the study. MedDRA dictionary version 11.0. 1st Quarter: Study days 1 to 90; 2nd Quarter: Study days 91 to 180; 3rd Quarter: Study days 181 to 270; 4th Quarter: Study days ≥271.

N is the number of subjects at the beginning of each period.

AE(s) with onset date(s) prior to the first application are only included in the "Entire Study" column.

Six subjects (1.3%) reported events in the Cardiac disorders SOC over the course of the long term study: two subjects (0.4%) reported palpitations, and one subject (0.2%) each reported unstable angina, atrial fibrillation, tachycardia, and ventricular

tachycardia. One subject reported orthostatic hypotension in the study (Vascular disorders SOC).

Twenty-four subjects (5.3%) developed adverse reactions that were sufficiently suspicious for allergic contact dermatitis that investigators recommended patch testing. A total of 17 of the 24 subjects agreed to patch testing, and 14 subjects had a negative patch test result, while three subjects had a positive patch test result. Of the three positive cases, two subjects agreed to further testing with individual study product ingredients. One of the two subjects was found to be allergic to brimonidine tartrate and the other subject was found to be allergic to phenoxyethanol, a preservative excipient. Note: The subject who had a positive patch test to phenoxyethanol was coded as “contact dermatitis,” and two subjects who had negative rechallenge patch tests were mistakenly coded to the Preferred term “allergic dermatitis.”

See Section 7.3.5 for discussion of IOP measurements. Vital sign data are discussed in Section 7.4.3. and laboratory values in Section 7.4.2.

Conclusions

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.

7.5.3 Drug-Demographic Interactions

Gender

Of the 661 subjects in the Controlled Core Studies, 506 (77%) were female and 155 (23%) were male. In the Controlled Core Studies, 36% of females in the brimonidine group experienced \geq one adverse event compared to 24% of males in the active group. In the vehicle group, 31% of females experienced \geq one adverse event compared to 17% of males. The proportions of males and females who experienced at least one adverse event were higher in the brimonidine group compared to the vehicle group. In the long term study, 32% of females reported at least one adverse event compared to 22% of males, and the proportions were similar to those observed in the Controlled Core Studies.

Adverse events were most commonly reported in the Skin and subcutaneous tissue disorders SOC for both genders. In this SOC, 14% of females and 10% of males treated with the 0.50% gel in the controlled studies reported an adverse event compared to 11% of females and 4% of males treated with vehicle. In the long term study, the proportions were 15% female and 10% male. Erythema was reported by approximately 4.4% of females in the 0.5% group in the controlled studies and 1.3% of males (one subject). In the vehicle group, erythema was reported by 1.2% of females and no males. Erythema was more commonly reported in females in the long term study also (first 29

days). All six reports of events coded as “flushing” in the Controlled Core Studies occurred in females (2.4%) in the 0.5% gel group. All three reports of “alcohol intolerance” (which represented transient flushing) occurred in females (1.2%) in the 0.5% gel group. In the first 29 days of the long term safety trial, 25 females (7.4%) reported flushing, and one male did (1%). Aside from flushing, no apparent difference was identified in the occurrence of adverse events by gender.

Race

Analyses of adverse events by race were limited by the small number of non-Caucasians enrolled in the Core Studies, with the total being 23 subjects: 12 in the Controlled Core Studies (seven in the 0.5% group and five in the vehicle group) and 11 in the long term study. Of these 23, seven subjects reported adverse events: two in the 0.5% gel group (controlled studies), one in the vehicle group (skin tightness) and four in the long term study. Events in the 0.5% group included erythema and balance disorder. The numbers of non-Caucasians were too small to assess for trends.

Age

A total of 1,005 subjects 18 to 64 years participated in the Core Controlled Studies, and 105 subjects ≥ 65 years of age participated in these studies. The oldest ages reported were 87 years in the controlled studies and 81 years in the long-term study. The applicant analyzed adverse events in the Core Studies by categories of 18 to 64 years of age and ≥ 65 years, and 186 subjects and 14 subjects, reported adverse events in the respective categories. Adverse events were reported in similar proportions for the two categories in the 0.5% controlled group (33% of younger subjects and 32% of older subjects) and in the first 29 days of the long term study (30% of younger subjects and 26% of older subjects). In the vehicle group, 28% of subjects 18 to 64 years and 23% of subjects ≥ 65 years reported adverse events. In the Skin and Subcutaneous Tissue Disorders SOC (Core Studies), adverse events were reported by approximately 14% younger subjects and approximately 8% of geriatric subjects. All reports of erythema in the Core Controlled Studies were reported in the younger age group (irrespective of treatment group). All reports of flushing were reported in the younger age group. In the long-term study, 22 subjects (5.6%) in the younger group reported flushing compared to four subjects (7.4%) in the older group. All reports of skin burning sensation in the Core Studies occurred in the younger category of subjects.

7.5.4 Drug-Disease Interactions

Drug-disease interaction analyses were not done. Brimonidine tartrate gel has not been evaluated in subjects with renal or hepatic impairment.

7.5.5 Drug-Drug Interactions

The applicant did not conduct specific drug interaction studies.

Other rosacea therapies were permitted as concomitant medications in the long term trial, 18142. Those therapies included metronidazole, azelaic acid, and tetracycline and doxycycline. Under the applicant's analyses, as provided in the Summary of Clinical Safety, there was no apparent increase in adverse events in subjects receiving concomitant rosacea therapy compared to those receiving only 0.5% gel. However, conclusions that may be drawn from the analyses may be limited, as the applicant considered all concomitant therapies as a single group, i.e. "Concomitant Rosacea Medications" compared to "No Concomitant Rosacea Medications."

The Alphagan P (brimonidine tartrate ophthalmic solution) label discusses the potential for or possibility of interactions with antihypertensives/cardiac glycosides, CNS depressants, tricyclic antidepressants, and monoamine oxidase inhibitors. The label warns about the potentiation of syndromes associated with vascular insufficiency and use in patients with severe cardiovascular disease.

Per Amendment #1, the applicant excluded from the Phase 3 trials, subjects with less than 3 months stable dose treatment with tricyclic anti-depressants, cardiac glycosides, beta blockers or other antihypertensive agents. Additionally, the Phase 3 trials excluded subjects with Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depression. The label will reflect these restrictions and will include warnings regarding syndromes associated with vascular insufficiency and use in patients with severe cardiovascular disease (similar to Alphagan P label). Although these subjects were excluded from formal evaluation, the potential risk to patients with these afflictions or patients on any of those medications may be low, given the low systemic exposure from topically-applied brimonidine tartrate gel, 0.5% evidenced in the maximal use study.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The product is not an immune modulator. The following malignancies were reported in the long-term, open-label trial (single reports of each): basal cell carcinoma, breast cancer, squamous cell carcinoma of the lung, and squamous cell carcinoma of the skin. Mechanistically, there is no reason to suspect that exposure to brimonidine tartrate gel contributed to development to any of these malignancies.

7.6.2 Human Reproduction and Pregnancy Data

Per the Alphagan label, brimonidine tartrate is in Pregnancy Category B. Pregnant or lactating women with erythema of rosacea were excluded from participation in studies with brimonidine tartrate gel. Subjects who became pregnant were withdrawn immediately, and the pregnancy was followed to the final outcome.

Four pregnancies were reported during the clinical development program, and they are described in the following table.

Table 53 Pregnancy in the Brimonidine Tartrate Gel development program (Applicant Summary of Clinical Safety Table 64)

Study Number	Dose Group	Subject Number	Age	Study Completion Status	Treatment Duration	Pregnancy Outcome
RD.06.SRE.18123	0%, 0.07%, 0.18%, and 0.50% in patches	001-180	20	Pregnancy during induction phase; withdrawn from study	10 days/21 days	Follow up 3.5 months later showed no problems with pregnancy, then lost to follow-up
COL-118-ROSE-201 ^a	0.02%	118	24	Pregnancy despite oral contraception	8 days/29 days	Follow-up 1 month prior to due date, doing well
RD.06.SRE.18142	0.50%	8327-015	35	Pregnancy during treatment phase	79 days	Pregnancy went to full term and subject gave birth to a normal baby by Cesarean section
RD.06.SRE.18142	0.50%	8129-019	27	Pregnancy during treatment phase	374 days	Subject completed first trimester visit to obstetrician; outcome was to be monitored

^a Only COL-118-ROSE-201 considered pregnancy to be a TEAE/AE (see Listing 12, RD.06.SRE.18142). For other studies, pregnancy was not considered to be an AE but an important event to be monitored and as a reason for withdrawal.

Data Source: COL-118-ROSE-201, Listing 12; RD.06.SRE.18123, Section 10.1, RD.06.SRE.18142, Table 14.3.7.

The pregnancy for subject 8129-019 in study 18142 was ongoing at the conclusion of the study. Additional information about this subject was provided in the safety update: she delivered on (b) (6) by C-section “without issue.” Her hospital discharge information described an “absence of issue for the baby with normal apgar score and no neonatal illness.”

Proposed language for the Pregnancy section of the label is below:

“There are no adequate and well-controlled studies of MIRVASO Gel in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. MIRVASO Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Brimonidine tartrate was not teratogenic when given at oral doses up to 2.5 mg/kg/day in pregnant rats during gestation days 6 through 15 and 5 mg/kg/day in pregnant rabbits during gestation days 6 through 18.”

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant requested a full waiver of pediatric studies at the pre-NDA meeting on May 16, 2012, and the division agreed that the request was “reasonable.” The applicant provided the waiver request in the marketing application, along with the rationale for the request. The applicant’s rationale principally rested on the rare prevalence of rosacea in the pediatric population. The reviewer agrees that rosacea is considered to be rare in children.^{3,4}

The applicant convened a panel of pediatric dermatologists to consider the prevalence of rosacea in the adolescent population. The applicant reported the group’s consensus opinion as being that the “very small proportion” of post-pubertal pediatric patients who present with rosacea generally present solely with inflammatory lesions (papules, pustules), rather than persistent erythema. Further, rosacea patients in this age group may most often exhibit concomitant acne. Treatment would likely be primarily focused on the acneiform lesions, particularly given the attendant psychosocial burden in this age group.

Alphagan (brimonidine tartrate ophthalmic solution 0.2%) was evaluated in pediatric subjects with glaucoma, and that study is described in the pediatric use section of brimonidine tartrate ophthalmic solution products as below:

“Pediatric Use:

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.”

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant evaluated the potential for tachyphylaxis (see Section 7.3.5) and for rebound following discontinuation of treatment with brimonidine gel.

The applicant assessed the potential for rebound erythema by evaluating subjects at follow-up visits up to four weeks post-treatment in studies ROSE-201, 18161, 18140, and 18141. No treatment was applied during the four-week interval. Investigators and subjects conducted post-treatment assessments of erythema including the CEA and PSA.

The applicant concluded that there was no indication of a rebound effect in ROSE-201

4 weeks after treatment with 3 concentrations of brimonidine tartrate (the highest concentration being 0.20%) administered up to 3 times daily. However, ROSE-201 did not evaluate 0.5% brimonidine gel and evaluated different endpoints and assessment measures.

The Core Controlled Studies (18161, 18140 and 1841) all included post-treatment assessments at Weeks 6 and 8. (Study 18161 also included post treatment assessments at Day 30 and Week 5.) The applicant stated that the post-treatment assessments were intended to evaluate for the potential for a rebound effect. This reviewer did not find rebound expressly defined in any of the protocols. (For example, Gordon et al. proposed a definition of rebound for psoriasis as being “a (Psoriasis Area Severity Index) score of 125% of baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis occurring within 3 months of stopping therapy.”¹⁰)

Primary efficacy was determined by a two-grade composite success measure. The applicant assessed rebound by considering the outcomes at Weeks 6 and 8 (two and four weeks post treatment) for the individual elements of the two-grade composite measure separately. The applicant discussed rebound in terms of mean changes in CEA and PSA scores at those respective time points of the post-treatment follow-up period. The applicant reported that mean CEA and PSA scores continued to decrease post treatment relative to baseline, and concluded that “the propensity for rebound is low for subjects treated with (brimonidine gel) in the context of the low frequency of these reactions seen in the clinical studies.”

In Study 18161, the applicant reported that mean reductions in CEA scores ranged from 0.6 to 0.7 points, and the mean reductions in PSA scores ranged from 0.8 to 0.9 points relative to Day 1/Hour 0 across the post treatment follow-up visits. Although it is unclear to this reviewer whether mean decreases of less than one point really constitute meaningful changes. Tables 54 and 55 presents the numbers of subjects who experienced worsening of their facial erythema in the post-treatment period. The applicant concluded that these results suggest no evidence rebound erythema.

Table 54 Subjects with Clinician’s Erythema Assessment Score Worse than Baseline 18161 (Applicant Table 30 of study report)

Subjects with pre-dose CEA score increased (worsen) from Baseline (T0 on Day 1) ^a , n/N (%)	CD07805/47 Gel QD	Vehicle Gel QD
Day 29	1/51 (2.0)	2/53 (3.8)
Follow-up/Day 30	2/51 (3.9)	0/53
Follow-up/Week 5	0/50	1/53 (1.9)
Follow-up/Week 6	1/51 (2.0)	1/53 (1.9)
Follow-up/Week 8	0/51	2/53 (3.8)

^a CEA scores: 0=Clear, 1=Almost clear, 2=Mild erythema, 3=Moderate erythema, 4=Severe erythema

Table 55 Subjects with Patient Self Assessment-5 Score Worse than Baseline 18161 (Applicant Table 35 of study report)

Subjects with pre-dose PSA-5 score increased (worsen) from Baseline (T0 on Day 1) ^a , n/N (%)	CD07805/47 Gel 0.5% QD	Vehicle QD
Day 29	2/51 (3.9)	2/53 (3.8)
Follow-up/Day 30	5/51 (9.89)	1/53 (1.9)
Follow-up/Week 5	0/50	1/53 (1.9)
Follow-up/Week 6	1/51 (2.0)	1/53 (1.9)
Follow-up/Week 8	1/51 (2.0)	153 (1.9)

^a PSA-5 scores: 0=No redness, 1=Very mild redness, 2=Mild redness, 3=Moderate redness, 4=Severe redness

The results were generally similar between treatment groups for both the CEA and PSA, except at Day 30 for the PSA where approximately 10% of subjects in the 0.5% group reported worsening compared to 2% in the vehicle group. This may suggest that assessment for rebound should have included post-treatment evaluations within a narrower window relative to discontinuation of treatment, e.g. days after rather than only two and four weeks post-treatment assessments as with the pivotal trials.

For the Phase 3 pivotal studies, the applicant reported the mean decreases in CEA and PAS at the Week 6 and Week 8 follow-up relative to Day 1/Hour 0 (Summary of Clinical Efficacy):

- CEA in the 0.5% Gel group: mean decrease 0.3 points in 18140 and 0.5 points in 18141.
- PSA in the 0.5% Gel group: mean decrease 0.7 to 0.8 points in 18140 and 0.7 points in 18141.

The reviewer would consider mean decreases of 0.3 and 0.5 points for the CEA in studies 18140 and 18141 (above) to have little (perhaps no) clinical significance.

The numbers of subjects in the Phase 3 studies (studies 18140, 18141) who showed worsening CEA or PSA post-treatment relative to baseline are presented in Table 56

Table 56 Subjects with Worsening CEA or PSA during follow-up relative to Baseline; Studies 18140, 18141; ITT Population (Applicant Summary of Clinical Efficacy Table 40)

CEA and PSA, n (%)	18140		18141	
	CD07805/47 Gel 0.5% (N=129)	Vehicle Gel (N=131)	CD07805/47 Gel 0.5% (N=148)	Vehicle Gel (N=145)
Follow-up: Week 6				
1-grade CEA Increase	5 (4.0)	3 (2.4)	5 (3.6)	3 (2.1)
1-grade PSA Increase	3 (2.4)	4 (3.1)	6 (4.3)	3 (2.1)
Follow-up: Week 8				
1-grade CEA Increase	6 (4.7)	1 (0.8)	3 (2.1)	1 (0.7)
1-grade PSA Increase	2 (1.6)	1 (0.8)	3 (2.1)	4 (2.8)

There is an apparent difference in the perception of worsening of disease (relative to baseline) following discontinuation of treatment in the CEA (objective) assessment compared to the PSA (subjective) assessment. In both pivotal trials and at both the six and eight week follow-up visits (two and four weeks post treatment), a higher proportion of brimonidine-treated subjects had a post-treatment worsening of the CEA relative to baseline compared to subjects who were treated with vehicle. No consistent pattern was seen with the PSA results at the post treatment assessments. The applicant concluded that incidences of worsening post-treatment were similar between treatment groups in the Phase 3 trials, “which suggested that this response was indicative of the variability in the natural course of the disease” (Section 5.1 of Summary of Clinical Efficacy). However, this “variability” theory may not explain the consistency of the higher percentage of brimonidine-treated subjects showing a worsening of CEA in the post-treatment period.

Based on the available information, it appears that at least a small percentage (~3-4%) of subjects may have experienced some measure of rebound erythema. The reviewer notes also that some subjects who discontinued because of erythema were specifically said to have experienced rebound erythema (see discussion in Section 7.3.3). The reviewer considers that those reports may provide supportive information about the potential for rebound. The assessment of rebound effect may have more meaningful if the applicant had included additional assessments at earlier post-treatment time points. Post-treatment assessments earlier than two weeks may have allowed a more comprehensive assessment for rebound.

7.7 Additional Submissions / Safety Issues

The applicant submitted the four-month Safety Update on February 19, 2012. Two additional clinical trials were in progress as of the data cutoff date of January 15, 2013 for the Safety Update. The data from one of the additional trials GLI.04.SPR.US10219 (discussed below), which also evaluated the 0.5% gel formulation, were included, and

no safety data from the other ongoing study, RD.03.SPR.40174, were available at the time of the data cutoff date. Study 40174 was ongoing in Russia and Sweden and was a multicenter, randomized, double-blind, vehicle-controlled, parallel group study designed to demonstrate the efficacy and assess the safety of brimonidine tartrate 0.5% Gel applied topically once daily for 29 days in subjects with moderate to severe facial erythema of rosacea. Subjects are to be randomized in a 1:1 manner to receive either brimonidine tartrate 0.5% gel or vehicle Gel. It was initiated in December 2012.

Study GLI.04.SPR.US10219

This a recently completed multicenter, randomized, controlled, double-blind, crossover study designed to compare the efficacy and to assess the safety of brimonidine tartrate 0.5% gel applied topically once daily versus azelaic acid 15% gel (Finacea®) applied topically twice daily in subjects with moderate to severe facial erythema of rosacea. The regulatory intent of this trial for the U.S. jurisdiction is unclear.

Because the dose regimen for brimonidine tartrate gel was once daily, subjects who were treated with this product received it for the morning dose and vehicle gel for the evening dose during the same treatment period. The duration of each treatment period was 15 days, with a 3- to 7-day washout period between treatment periods. Randomization of approximately 70 subjects was planned; 70 subjects were treated with brimonidine and vehicle, and 68 of these subjects were also treated with azelaic acid.

The applicant submitted preliminary, unblinded safety data from this Phase 3b Study, which was conducted in the United States. No deaths, other serious adverse events, or pregnancies were reported. One subject discontinued due to severe erythema, and one subject discontinued for severe local adverse events of erythema and skin burning sensation. Erythema was reported in 15 subjects (21.4%) during brimonidine treatment and in two subjects (2.9%) in azelaic acid treatment. There was one report of flushing, and it was reported in the brimonidine group, as was the one report of pallor.

8 Postmarket Experience

The product is not marketed.

9 Appendices

9.1 Literature Review/References

1. Powell FC. Rosacea. *N Engl J Med*. 2005 Feb 24;352(8):793-803.
2. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46(4):584-587.
3. Kroshinsky D, Glick SA. Pediatric rosacea. *Dermatol Ther*. 2006 Jul-Aug(4):196-201.
4. Drolet B, Paller AS. Childhood rosacea. *Pediatr Dermatol*. 1992;9(1):22-26.
5. Lacz NL, Schwartz RA. Rosacea in the pediatric population. *Cutis*. 2004;74(2):99-103.
6. Kyriakis K, Palamaras I, Terzoudi S, et al. Epidemiologic aspects of rosacea. *J Am Acad Dermatol*. 2005 Nov;53(5):918-9.
7. ICH E1A Guideline for Industry: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life-Threatening Conditions.
8. Westfall TC, Westfall DP. Chapter 12. Adrenergic Agonists and Antagonists. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill;2011. <http://www.accessmedicine.com/content.aspx?aID=16661344>. Accessed May 2, 2013.
9. Catapres label
10. Gordon KB, Feldman SR, Koo JY, Menter A, Rolstad T, Krueger G. Definitions of measures of effect duration for psoriasis treatments. *Arch Dermatol*. 2005 Jan;141(1):82-4.

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.

9.3 Advisory Committee Meeting

Not applicable.

Clinical Review
 Brenda Carr, M.D.
 NDA 204708
 Mirvaso (brimonidine) gel, 0.33%

9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: 204708

Submission Date(s): October 25, 2012

Applicant: Galderma Research and Development

Product: brimonidine gel, 0.33% (Mirvaso)

Reviewer: Brenda Carr, M.D.

Date of Review: May 8, 2013

Covered Clinical Study (Name and/or Number): RD.06.SRE.181410 and
 RD.06.SRE.18141

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>five</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>five</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>none</u></p> <p>Significant payments of other sorts: <u>five</u></p> <p>Proprietary interest in the product tested held by investigator: <u>none</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>none</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information

Clinical Review
Brenda Carr, M.D.
NDA 204708
Mirvaso (brimonidine) gel, 0.33%

minimize potential bias provided:		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>none</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.² Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Yes; the applicant adequately disclosed financial interests/arrangements with clinical investigators.

Minimization of Potential Bias:

(b) (6)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The disclosed financial arrangements did not affect approvability of the application.

² See [web address].

(b) (4)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA CARR
06/24/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204708

Applicant: Galderma

Stamp Date: 10/25/12

Drug Name: brimonidine tartrate gel
NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			Narrative portion in the Summary of Clinical Safety (2.7.4) per agreement at pre-NDA meeting
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			Narrative portion in the Summary of Clinical Efficacy (2.7.3) per agreement at pre-NDA meeting
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Benefit-risk conclusions in Section 6 of Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2); the reference drug: Alphagan (brimonidine tartrate ophthalmic solution) 0.2%
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: RD.06.SRE.18144	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			Long-term safety study (qd use for up to 52 weeks) is RD.06.SRE.18142 449 enrolled; 335 completed ≥ 6 mos and 279 completed study
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	No specific discussion found
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?				Not found
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver requested
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			From clinical perspective
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			As above

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
34.	Are all datasets to support the critical safety analyses available and complete?	x			As above
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				defer
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA CARR
01/07/2013

JILL A LINDSTROM
01/08/2013