CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204708Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204708	Submission Date(s): 10/25/2012, 11/21/2012, 12/3/2012, 12/7/2012
Brand Name	Mirvaso® Topical Gel
Generic Name	Brimonidine Tartrate
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Galderma Research and Development Inc.
Submission Type; Code	Original NDA
Formulation; Strength(s)	Topical Gel, 0.5% (5 mg/g)
Indication	The topical treatment of facial erythema of rosacea in adults 18 years of age or older

Table of Contents

1 Executive Summary

This application is for Mirvaso® (Brimonidine Tartrate) Topical Gel, 0.5%[1]. The proposed indication for Mirvaso Topical Gel is topical treatment of facial erythema of rosacea in adults 18 years of age or older. It is intended to be applied a small pea-size amount once daily to each of the five areas of the face (i.e., forehead, chin, nose, each cheek) avoiding the eyes and lips. It should be applied smoothly and evenly across all application areas.

In the United States, brimonidine tartrate is commercially available as ophthalmic solutions in the following strengths: 0.1% (NDA 21770), 0.15% (NDA 21262 and NDA 21764), 0.2% (NDA 20613, discontinued but available as generics), 0.5% (NDA 20490, discontinued), or in combination with timolol maleate (Combigan® NDA 21398, brimonidine tartrate 0.2% plus timolol maleate 0.5%).

To support the NDA, the applicant has submitted one Clinical Pharmacology trial: a comparative bioavailability and pharmacokinetics (PK) trial to assess the systemic exposure of both brimonidine tartrate topical gel applied under maximal use conditions 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.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 204708 acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes.

1.2 Phase IV Commitments/Requirements

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Comparative bioavailability and maximal use PK trial

Trial 18143 was a comparative bioavailability and pharmacokinetics trial to assess the systemic exposure of both brimonidine tartrate topical gel applied across different concentrations and dose regimens [0.07 % twice daily (BID), 0.18 % once daily (QD) or twice daily (BID) and 0.5% once daily (QD)] under maximal use conditions (1 gram applied to the entire face) and brimonidine tartrate ophthalmic solution 0.2% administered as three doses (one drop into each eye every 8 hours) over 24 hours in subjects with moderate to severe facial erythema associated with rosacea. One hundred

[1] Review Note: Per United States Pharmacopeia (USP) Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations (the USP Salt Policy), which becomes official on May 1, 2013, the name and strength of the active moiety, instead of the salt, should be expressed. In this submission, Brimonidine Tartrate (the salt), 0.5%, referred in this review is the same as Brimonidine (active moiety), 0.33%, which will be reflected in the label.

two (102) subjects 18 years of age or older with Clinician's Erythema Assessment (CEA) score of ≥3 (Moderate) were enrolled, and 93 subjects completed the trial.

Brimonidine tartrate ophthalmic solution 0.2% was administered at Day 1 every 8 hours, and after a wash-out period of two days, brimonidine tartrate topical gel (0.07%, 0.18%, or 0.50%) were applied to the face for 29 days. Plasma brimonidine concentrations were tested at various timepoints throughout the trial. The PK parameters of brimonidine tartrate ophthalmic solution 0.2% and topical gel 0.5% (i.e., proposed commercial strength) are shown below.

		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 15th application)	Day 32 (after 29th application)
C_{max} (pg/mL)	Mean ±SD	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)	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)

The results of relative bioavailability of brimonidine tartrate topical gel, 0.5%, QD (Test) compared to ophthalmic route (Reference) based on AUC_{0-24h} and C_{max} are shown below:

	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 15th application)	370 (69%) N=20	71%	54%-92%
Test (Day 32, after 29th application)	313 (40%) N=15	63%	46%-86%

	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 15th application)	32 (95%) N=20	66%	47%-94%
Test (Day 32, after 29th application)	24 (62%) N=15	55%	38%-79%

The systemic exposure of brimonidine tartrate gel 0.5% QD was higher after 15th application than after 29th application. After 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%. Therefore, 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.

Thorough QTc Trial

The effects of brimonidine tartrate on prolonging QT intervals were evaluated by using a single supra-therapeutic dose (two drops of a 0.2% solution to each eye) by the ocular route. From the review of Interdisciplinary Review Team for QT Studies Consultation, it was concluded that no significant QTc prolongation effect of brimonidine tartrate was detected in this TQT study.

Pediatrics:

The applicant requested a waiver of pediatric trials citing that rosacea is not commonly reported in the pediatric population. The Division of Dermatology and Dental Products (DDDP) regarded this rationale reasonable, and accepted this waiver of pediatric trials.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for Brimonidine Tartrate Topical Gel, 0.5%?

Brimonidine tartrate topical gel, 0.5% is proposed for the topical treatment of facial erythema of rosacea in adults 18 years of age or older.

2.1.2 What is rosacea?

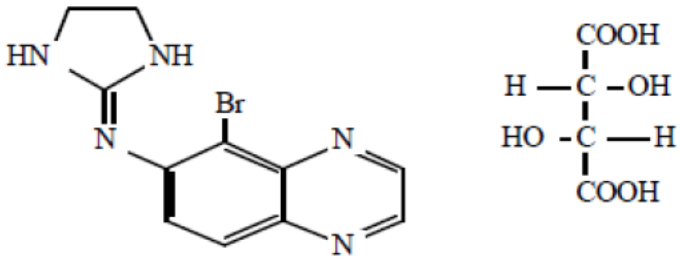
Rosacea is characterized by erythema of the central face that has persisted for months or more. The convex areas of the nose, cheeks, chin, and forehead are the characteristic distribution. The subtypes of rosacea were defined provisionally by the National Rosacea Society (NRS) Expert Committee in 2002 and include erythematotelangiectatic, papulopustular, phymatous, and ocular subtypes.

Because of prominent clinical variation among the rosacea subtypes, it has been hypothesized that etiologic and pathophysiologic differences may exist. Rosacea is unmasked or induced by chronic, repeated trigger exposure, in particular by triggers of flushing that may include hot or cold temperature, sunlight, wind, hot drinks, exercise, spicy food, alcohol, emotions, cosmetics, topical irritants, menopausal flushing, and medications that promote flushing. Facial prominence occurs because baseline facial blood flow is increased compared with other body sites, and the facial cutaneous vasculature is more superficial and comprised of larger and more numerous vessels when compared with other sites. Possible etiologies of rosacea include the exacerbation of the innate immune response, some dermal factors (matrix degeneration and endothelial damage), and sun damage, etc.

2.1.3 What are the highlights of the physicochemical properties of Brimonidine Tartrate?

Chemically, brimonidine tartrate is 5-Bromo-6-(2-imidazolin-2-ylamino) quinoxaline L-(+)-tartrate. Brimonidine tartrate has a molecular weight of 442.2 and appears as white to slightly yellowish powder.

The molecular formula of brimonidine tartrate is $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$. It has the following structural formula:



Formulation properties:
Brimonidine Tartrate 0.5% Gel is packaged in laminated plastic tubes with a [redacted] (b) (4) child resistant closure (supplied by [redacted] (b) (4)). Tube sizes proposed for registration are 30 g and 45 g. [redacted] (b) (4) For details of product composition see section 2.5.2.

Dosage and Route of Administration:
Apply a small pea-size amount once daily to each of the five areas of the face (i.e., forehead, chin, nose, each cheek). It should be applied smoothly and evenly across all application areas.

Mechanism of Action:
Mirvaso (Brimonidine tartrate topical gel, 0.5%) is an alpha-2 adrenergic agonist. The sponsor proposed that topical facial application of a highly selective an alpha-2-adrenergic agonist may reduce facial erythema through direct vasoconstriction.

2.2 General Clinical Pharmacology

2.2.1 How was the dose/duration selected for Brimonidine tartrate gel, 0.5%?

The proposed dosage is to apply a small pea-size amount once daily to each of the five areas of the face (i.e., forehead, chin, nose, each cheek). It should be applied smoothly and evenly across all application areas. In this current submission, the above dosing regimen was determined in the Phase 2 dose-finding trial RD.06.SRE.18144.

This trial was conducted to investigate the pharmacodynamics and safety of three concentrations 0.07%, 0.18%, and 0.50%, applied in subjects ≥18 years of age with moderate to severe erythematotelangiectatic rosacea. The pharmacodynamics measurements include PSA (patient's self assessment), CEA (clinician's erythema assessment), and Chromameter assessments, which were performed on the Treatment day at baseline (pre-dose, just prior to study drug application), and 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after study drug application.

Following a single application of brimonidine tartrate gel (1.0 g ±0.1 g), a dose-response relationship was observed for the pharmacodynamic variables. All three concentrations were shown to be more effective than vehicle gel at reducing facial erythema, with the largest effect observed with the 0.50% concentration, followed by the 0.18% and 0.07% concentrations. Safety and tolerability were comparable between the groups treated with brimonidine tartrate gel and vehicle. Therefore, the applicant decided to use the 0.5% gel as the to-be-marketed concentration.

2.2.2 What are the design features of the clinical pharmacology and clinical trials used to support Brimonidine tartrate gel, 0.5%?

The applicant has sponsored the following 13 clinical trials in support of the development of Brimonidine tartrate gel, 0.5%.

Clinical Pharmacology Trials:

Trial RD.06.SRE.18143: Maximal use PK trial in adult subjects with moderate to severe facial erythema of rosacea. N=20, age: 18-64.

Trial RD.06.SRE.18126: Assessment of relative bioavailability and safety in subjects with rosacea. N=20, age: 25-59. This PK trial was not reviewed, as Trial RD.06.SRE.18143 was regarded as the most relevant PK trial.

Trial RD.06.SRE.18144: Evaluation of dose response relationship and safety in subjects with rosacea. N=122, age: 18-74. The medical reviewer is reviewing this trial.

Phase I trials:

Trial RD.06.SRE.18123: Randomized, intra-individual comparison, evaluator-blind, single-center, vehicle-control and negative-control trial to assess sensitization potential of healthy subjects. N=247, age: 18-65. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18124: Randomized, intra-individual comparison, evaluator-blind, single-center, vehicle-control and negative-control trial to assess photosensitization/photoallergic potential of healthy subjects. N=57, age: 19-63. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18125: Randomized, intra-individual comparison, evaluator-blind, single-center, vehicle-control and negative-control trial to assess cumulative irritancy potential of healthy subjects. N=38, age: 18-64. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18137: Randomized, intra-individual comparison, evaluator-blind, single-center; active control and non-irradiated control to determine the static sun protection factor (SPF) value of vehicle gel of healthy subjects for 1 day. N=25, age: 26-65. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18189: Randomized, intra-individual comparison, evaluator-blind, single-center; active control and non-irradiated control to assess phototoxic (photoirritation) potential of healthy subjects administered with single application of 200 μL of each product (0.07%, 0.18%, 0.5%, and vehicle gel) to the back under occlusion for 1 day. N=35, age: 21-64. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18139: Randomized, double blind, 3-way crossover, single center; positive control and placebo control to assess effect on ventricular repolarization, PD relationship between QT/QTc interval duration and plasma concentration, and safety of healthy subjects. This reviewer has reviewed the PK portion of the result. N=60, age: 18-54.

Phase III trials:

Trial RD.06.SRE.18161: Randomized, double-blind, parallel-group, multicenter, vehicle-controlled trial to assess efficacy and safety of subjects with rosacea administered with 5 different dosage regimens of topical brimonidine tartrate gel 1 gram to the face for 29 days. (0.18% QD or BID, 0.5% QD, and Vehicle gel QD or BID). N=269, age: 18-74. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18140: Randomized, double-blind, parallel-group, multicenter, vehicle-controlled trial to assess efficacy and safety of subjects with rosacea administered with topical brimonidine tartrate 0.5% gel or vehicle gel 1 gram to the face once daily for 29 days. N=260, age: 18-87. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18141: Randomized, double-blind, parallel-group, multicenter, vehicle-controlled trial to assess efficacy and safety of subjects with rosacea administered with topical brimonidine tartrate 0.5% gel or vehicle gel 1 gram to the face once daily for 29 days. N=293, age: 19-78. The medical reviewer is reviewing this trial.

Trial RD.06.SRE.18142: Long-term, open label, multicenter, uncontrolled trial to assess long-term safety and efficacy of subjects with rosacea administered with topical brimonidine tartrate 0.5% gel 1 gram to the face once daily for 12 months. N=449, age: 19-81. The medical reviewer is reviewing this trial.

2.2.3 What trials have been conducted for bioavailability evaluation of the drug product, and what are the outcomes of these trials?

The systemic exposure of brimonidine tartrate topical gel, 0.5% was evaluated in trial 18143. Trial 18143 was a comparative bioavailability and pharmacokinetics trial to assess the systemic exposure of both brimonidine tartrate topical gel applied across different concentrations and dose regimens [0.07 % twice daily (BID), 0.18 % once daily (QD) or twice daily (BID) and 0.5% once daily (QD)] under maximal use conditions (1 gram applied to the entire face) and brimonidine tartrate ophthalmic solution 0.2% administered as three doses (one drop into each eye every 8 hours) over 24 hours in subjects with moderate to severe facial erythema associated with rosacea. One gram of brimonidine tartrate topical gel applied to the entire face was also used in all four Phase III trials.

One hundred and two (102) subjects 18 years of age or older with Clinician's Erythema Assessment (CEA) score of ≥3 (Moderate) were enrolled, and 93 subjects completed the trial. The brimonidine tartrate ophthalmic solution 0.2% used in this trial was a generic drug from Bausch & Lomb, as Alphagan® 0.2% ophthalmic solution has been discontinued (not due to safety reason).

Brimonidine tartrate ophthalmic solution 0.2% was administered at Day 1 every 8 hours, and after a wash-out period of two days, brimonidine tartrate topical gel (0.07%, 0.18%, 0.50%) were applied to the face for 29 days. PK sampling timepoints are based on the following flow chart (CD078514/47 is brimonidine tartrate gel):

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

ET=Early Termination

The PK parameters of both brimonidine tartrate ophthalmic solution 0.2% and brimonidine tartrate topical gel 0.5% (the to-be-marketed formulation) are listed in Table 1 (Compiled by this reviewer, values from applicant's PK report). Administration of Brimonidine tartrate 0.2% by ophthalmic route resulted in quantifiable exposure (≥ 10 pg/mL) in all 96 subjects receiving TID treatment, while there was 79% of the subjects receiving brimonidine tartrate 0.5% gel QD for 29 days resulted in quantifiable systemic exposure. In this submission, no elimination half-life was calculated in that the applicant determined there was a lack of distinct elimination phase of brimonidine tartrate topical gel.

Table 1: PK parameters of brimonidine tartrate ophthalmic solution 0.2% and topical gel 0.5% for Trial 18143

		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 15th application)	Day 32 (after 29th 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 AUC0-24hr calculated in this trial (i.e. 10 pg.hr/mL)

The Appendix (Section 4) in this review has the detail review of this trial. The mean brimonidine tartrate plasma profile after ocular administration of 0.2% TID of brimonidine ophthalmic solution is shown in Figure 2 in Appendix. The mean brimonidine tartrate plasma profiles after topical administration of 4 different regimens of topical gel at Day 4 (1st application), Day 18 (15th application), and Day 32 (29th application) are shown in Figure 3, Figure 4, Figure 5 in Appendix, respectively.

Mean accumulation ratios were calculated between 15th and 1st application, 29th and 1st application, and 29th and 15th application. The result for brimonidine tartrate topical gel, 0.5% is shown below in Table 2 (Compiled by this reviewer, values from applicant's PK report). 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 2: Mean AUC_{0-24hr} and C_{max} Accumulation Ratio

		15th / 1st application	29th / 1st application	29th / 15th application
Mean AUC_{0-24hr}[a]	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 C_{max}[b]	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)

The relative bioavailability of brimonidine tartrate topical gel, 0.5%, QD (Test) compared to ophthalmic route (Reference) is shown in Table 3 and Table 4 (calculated by this reviewer):

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

	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)	370 (69%) N=20	71%	54%-92%
Test (Day 32)	313 (40%) N=15	63%	46%-86%

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

	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)	32 (95%) N=20	66%	47%-94%
Test (Day 32)	24 (62%) N=15	55%	38%-79%

The systemic exposure of brimonidine tartrate gel 0.5% QD was higher at Day 18 than at Day 32. At Day 18, 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_{0-24} were below100%. Therefore, 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.

2.2.4 Does Brimonidine Tartrate Topical Gel, 0.5% prolong QT intervals?

The effects of brimonidine tartrate on prolonging QT intervals were evaluated in the Thorough QTc Trial 18139. Because of the low concentration obtained after topical administration of brimonidine tartrate topical gel, the applicant used brimonidine tartrate administered by the ocular route in a single supra-therapeutic dose (two drops of a 0.2% solution to each eye). This dose is 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.

The primary objective was 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 QTc interval corrected by QTcB, QTcF, and QTcI (subject-specific) at the Tmax using 12-lead electrocardiograms (ECGs). The treatments administered were shown below in Table 5.

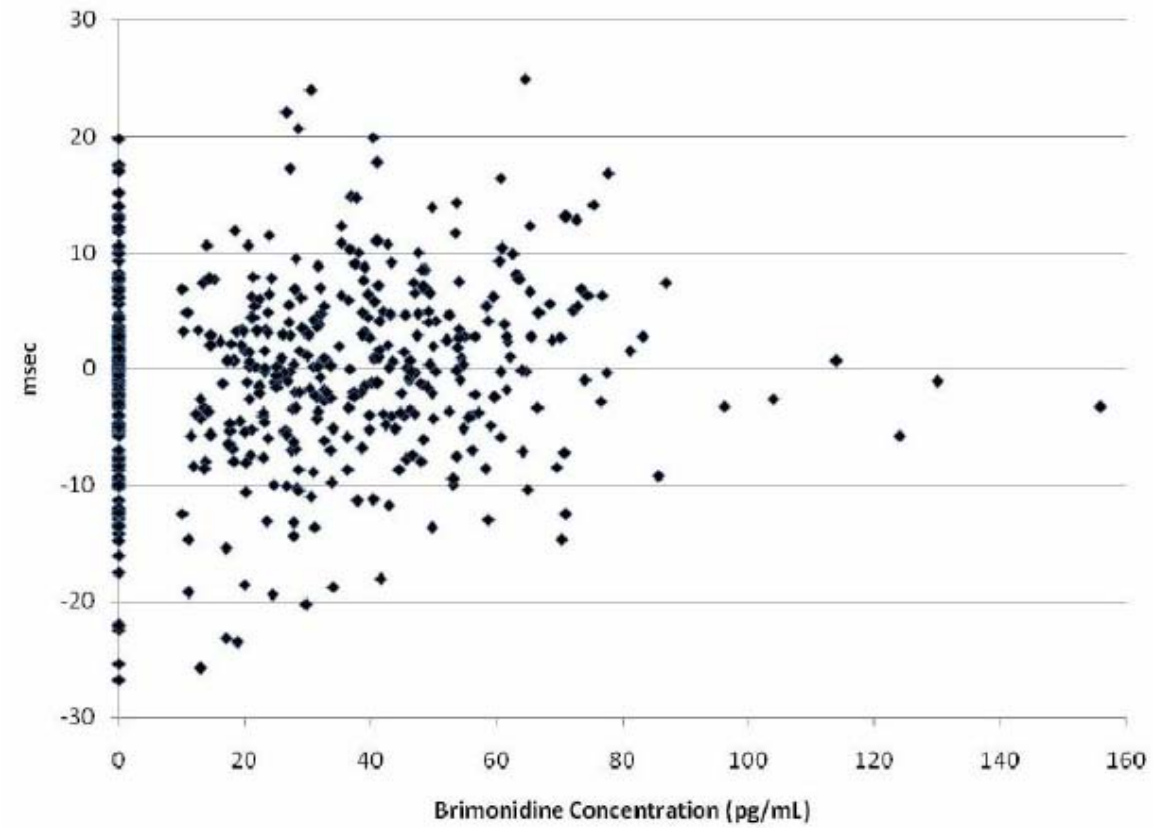
Table 5: Treatments Administered

	Brimonidine tartrate Ophthalmic Solution 0.2%	Brimonidine tartrate Placebo Advanced Eye Relief™	Moxifloxacin Oral Placebo	Moxifloxacin Oral 400 mg Tablet
Treatment A (Brimonidine tartrate Supra-Therapeutic Dose)	2 drops in each eye	None	One over-encapsulated placebo capsule	None
Treatment B (Placebo)	None	2 drops in each eye	One over-encapsulated placebo capsule	None
Treatment C (Moxifloxacin 400 mg)	None	2 drops in each eye	None	One over-encapsulated Moxifloxacin 400 mg capsule

All subjects were treated with each of the three treatments over 3 individual dosing periods. There was a 6-day washout period between dosing periods. The dosage administered of the eye drops was a total dose of two drops of 0.2% brimonidine or two drops of the Advanced Eye Relief™ Dry Eye Rejuvenation Lubricant Eye Drops. There was a 3 minute window of time between the administration of the first and second drop of ocular medications.

From the review of Interdisciplinary Review Team for QT Studies Consultation, Dr. Moh Jee Ng has concluded that "No significant QTc prolongation effect of brimonidine tartrate was detected in this TQT study". Dr. Ng has assessed the relationship between placebo-subtracted differences in changes from pre-dose baseline in QTcI intervals and log brimonidine plasma concentration, and the scatter plot is shown below in Figure 1. Dr. Ng concluded that it appears to be no trend between ΔΔQTcI and brimonidine concentrations.

Figure 1: Time-Matched ΔΔQTcI vs. Brimonidine Concentrations



Source: Applicant's TQT Clinial Study Report.

2.3 Intrinsic Factors

2.3.1 What is the systemic drug exposure in pediatrics?

In this submission, the applicant requested a waiver of pediatric trials citing that "it is generally recognized that rosacea is a very rare condition in infants and children less than 12 years of age, and is uncommon in adolescents (ages 12 to 17 years)". The applicant further added that "The incidence of stand-alone facial erythema of rosacea is even more exceptional in this population and the medical need to treat this pathology appears marginal". The Division of Dermatology and Dental Products (DDDP) has regarded this rationale reasonable, and accepted this waiver of pediatric trials.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (food, drugs, herbal products, smoking, alcohol use) influence the PK of Brimonidine Tartrate Topical Gel, 0.5%?

There were no specific drug interaction studies conducted with brimonidine tartrate topical gel, 0.5%. However, since brimonidine is an alpha-2 agonist, it may reduce blood pressure if used together with anti-hypertensives/cardiac glycosides. In addition, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Thirdly,

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension.

Other effects of extrinsic factors, such as herbal products, smoking, and alcohol use on the PK of Brimonidine Tartrate Topical Gel, 0.5% were not evaluated. Since this is a topical product, an effect of food is not anticipated.

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation identical to the one used in Phase 3 efficacy and safety trials?

The to-be-marketed formulation was used in the following 7 trials: two pivotal Phase 3 trials (RD.06.SRE.18140 and RD.06.SRE.18141), the Phase 3 safety uncontrolled efficacy trial RD.06.SRE.18142, the maximal use PK trial RD.06.SRE.18143, the Phase 2b dose-finding, efficacy and safety trial RD.06.SRE.18161, the photosensitization/photoallergic potential trial RD.06.SRE.18124, and the phototoxicity trial RD.06.SRE.18189. The rest of the trials used the gel formulation of brimonidine which has a higher concentration of methyparaben, except trial COL-118-ROSE-102 which utilized pilot formulations.

2.5.2 What is the final product composition?

Table 6 shows the components and composition of Brimonidine Tartrate Topical Gel, 0.5%.

Table 6: Composition of the Final Product of Brimonidine Tartrate Topical Gel, 0.5%

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

qs=Quantum satis (as much needed to achieve target).

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess drug concentrations?

Two bioanalytical methods used in two trials (Maximal use PK trial 18143 and Thorough QTc Trial 18139) were assessed by this reviewer.

Maximal use PK trial 18143:
The determination of brimonidine in human plasma samples was by using HPLC (High-performance liquid chromatography) with TIS-MS/MS (Turbo ion spray/Mass Spectrometry) detection.

Briefly, the lithium heparin human plasma used for the plasma samples preparation and unknown samples are centrifuged for at least 5 minutes at 3500 rpm before analysis. Brimonidine and the internal standard, Briminidine d4 D-tartrate, were extracted from human plasma using Ethyl Acetate. Vacuum was applied until samples appeared dry, and the eluent was evaporated to dryness under nitrogen at 37°C. The dry residue was reconstituted with the reconstitution phase, and centrifuge at 3000 rpm at room temperature for 5 min, then was submitted for analysis.

Thorough QTc Trial 18139:
The method employed supported liquid phase extraction and liquid chromatography with tandem mass spectrometry using Turbo IonSpray, in positive ion, multiple reaction monitoring mode.

In summary, the sodium heparin human plasma samples, calibration samples, and quality control samples were diluted by either water or control human plasma (NaH). Samples are then transferred to Isolute SLE+ 200 mg plate. Vacuum was applied and eluent was evaporated to dryness under nitrogen at 40°C. Samples were then reconstituted with 100 µL of 0.1 % formic acid (aq): Methanol (85:15 v/v) and mix well. Centrifuge at 3000 rpm at room temperature for 5 minutes. Finally samples were submitted for analysis.

2.6.2 Were the bioanalytical methods adequately validated?

Maximal use PK trial 18143:
The method for measuring brimonidine in human plasma by high-performance liquid chromatography (HPLC) with Turbo ion spray/Mass Spectrometry (TIS-MS/MS) detection was adequately validated in Galderma Research & Development, France. Brimonidine is reported to be stable in plasma when stored at -20 ºC for up to 428 days. The sample collection date was between 8/17/2010 and 12/16/2010, and the sample analysis date was between 9/17/2010 and 1/11/2011. The sample storage condition was at approximately -20 °C in polypropylene tubes during this time. The duration from the first sample collection to the last day of sample analysis was 147 days. The standard curve range was from 10 to 5000 pg/mL. Intra-day and Inter-day precision and accuracy was assessed at 4 quality control (QC) levels. Accuracy and precision at LLOQ was assessed using 6 replicates. A summary of precision and accuracy results is shown in Table 7.

Table 7: Precision and Accuracy Results of Brimonidine Assay Validation in Trial 18143

Standard Curve Range	10 to 5000 pg/mL using 100µL of plasma
Lower Limit of Quantitation (LLOQ)	10 pg/mL
Average Recovery of Drug	88.6%
Intra-Batch Accuracy	105.1% (range: 100.5-109.9%)
Inter-Batch Accuracy	99.0 – 108.8%
Intra-Batch Precision Range	2.3 – 11.7%
Inter-Batch Precision Range	3.3 – 8.1%

Thorough QTc Trial 18139:

The method for measuring brimonidine in human plasma by Liquid chromatography – tandem mass spectrometry using Turbo IonSpray, in positive ion, multiple reaction monitoring mode was adequately validated in (b) (4) . Brimonidine is reported to be stable in plasma when stored at -20 ºC for up to 169 days. The trial was initiated on December 4, 2009, and the last day of sample analysis was on February 8, 2010. The plasma samples were isolated and frozen (-20°C) pending analysis. The duration from the trial initiation to the last day of sample analysis was 66 days. The standard curve range was from 10 to 1000 pg/mL. Intra-run precision and accuracy was assessed at 5 quality control (QC) levels, and inter-run precision and accuracy was assessed at 5 QC levels. Accuracy and precision at LLOQ was assessed using 6 replicates. A summary of precision and accuracy results is shown in Table 8.

Table 8: Precision and Accuracy Results of Brimonidine Assay Validation in Trial 18139

Standard Curve Range	10 pg/mL to 1000 pg/mL
Lower Limit of Quantitation (LLOQ)	10 pg/mL
Average Recovery of Drug [a]	84.6% (87.2% if excluding 1 outlier at 10,000 pg/mL)
Intra-Run Accuracy	98.52% (range: 93.6-103.0%)
Inter-Run Accuracy [a]	0.03-25 ng/mL: 104-112.3% 0.01 ng/mL (LLOQ): 94.5%
Intra-Run Precision Range	0.8 – 5.9%
Inter-Run Precision Range [a]	0.03-25 ng/mL: 9.1-12.7% 0.01 ng/mL (LLOQ):19.4%

[a]: values were determined in the bioanalytical method validation report RDS.03.VPR.34214 (YCV/002), December 2009 (complete validation report, validated concentration range 0.01-25 ng/mL). Other validation values were taken from the partial validation report, RDS.06.SRE.18139 (YCV/006), May 2010 (validated concentration range: 10-1000 pg/mL).

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5.1 and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

Alpha-2 agonists, as a class, may reduce blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives and/or cardiac glycosides is advised.

7.~~1~~ 2 CNS Depressants

Although specific drug-drug interactions studies have not been conducted with MIRVASO Gel, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

7.~~2~~ 3 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

12.3 Pharmacokinetics

Absorption

The absorption of brimonidine from MIRVASO Gel was evaluated in a clinical (b) (4) trial in 24 adult subjects with facial erythema associated with rosacea. All enrolled subjects received (b) (4) once daily topical application of MIRVASO Gel 1 gram to the entire face for 29 days. (b) (4) Pharmacokinetic (PK) assessments were performed on Day 1, Day 15, and Day 29. The mean plasma maximum concentration (C_{max}) and area under the concentration-time curve (AUC) were highest on Day 15, with C_{max} and AUC values (± standard deviation) of (b) (4) 46 ± 62 pg/mL and 417 ± 264 pg.hr/mL respectively. The systemic drug exposure was slightly lower on Day 29 indicating no further drug accumulation.

(b) (4)

(b) (4)

(b) (4)

Metabolism

Brimonidine is extensively metabolized by the liver.

Excretion

Urinary excretion is the major route of elimination of brimonidine and its metabolites.

4 Appendix

4.1 Individual Trial Reviews

Note: Brimonidine tartrate gel is referred as CD078514/47 gel in this section.

Trial No. 18143

Title: 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.

Trial Initiation/Completion Dates: 8/5/2010 to 12/16/2010

Objectives:

- To evaluate the safety of CD07805/47 gel (0.07%, 0.18%, and 0.50%) applied to the face of male and female subjects with moderate to severe facial erythema associated with rosacea.
- To assess the pharmacokinetics (PK) of CD07805/47 gel under maximal use conditions with once or twice daily application (1 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 4 weeks treatment to the systemic exposure of brimonidine tartrate ophthalmic solution 0.2% after 1 day treatment (1 drop to each eye every 8 hours over a 24-hour period, according to the current label of the ophthalmic solution). The study consisted of 4 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

Trial Centers: A total of 5 investigational centers enrolled subjects in this US study. One additional investigational center screened subjects for this study.

Design of Trial:

Trial Population Demographics: One hundred two (102) subjects with moderate to severe facial erythema associated with rosacea.

Age range: 18-64 years (96.1%), 65 and above (3.9%); **Race:** Caucasian (97.1%), Asian (2%), other (1%); **Gender:** 40 Male (39.2%), 62 Female (60.8%); **Weight:** mean=163.8 lb, SD=27.14.

Diagnosis and main criteria for inclusion:

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

Clinician's Erythema Assessment (CEA) scoring

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

(b) (4) **Products:**

Brimonidine tartrate (CD07805/47) gel 0.07%
Brimonidine tartrate (CD07805/47) gel 0.18%
Brimonidine tartrate (CD07805/47) gel 0.5%
Brimonidine tartrate ophthalmic solution 0.2% (Bausch & Lomb)

Dosing Regimen, Mode of Administration and Treatment Duration:

Brimonidine tartrate ophthalmic solution 0.2% was administered by a qualified person at first study visit (Day 01) TID (every 8 hours) as reported by the approved product label. Then, after a wash-out period of two days CD07805/47 topical gel (0.07%, 0.18%, 0.50%) were applied by a qualified person on face during four weeks (29 days). A total of 102 subjects, with a mean age of 41.6 years were randomized in four groups as follows:

CD07805/47 topical gel 0.5% QD: 24 subjects
CD07805/47 topical gel 0.18% BID: 26 subjects
CD07805/47 topical gel 0.18% QD: 25 subjects
CD07805/47 topical gel 0.07% BID: 27 subjects

The quantity of drug product applied was 1g on a full face (estimated 400 to 500 cm^2, 3% of body surface area) which corresponds to an average of 2 mg/cm^2 of drug product; therefore, representing the maximal use condition in subjects with moderate to severe facial erythema associated with rosacea.

Pharmacokinetic Sampling:

An amount of 6 mL of blood samples were collected according to the following flow chart:

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

ET=Early Termination

Analytical Methods:
See Question-Based-Review Section 2.6.1.

Table 9: Analytical Method Validation

Assay Method	High-performance liquid chromatography (HPLC) with Turbo ion spray/Mass Spectrometry (TIS-MS/MS) detection
Analytical Site	Galderma Research & Development, France
Compound	CD07805 (Sodium Heparin as anticoagulant)
Standard Curve Range	10 to 5000 pg/mL using 100µL of plasma
Lower Limit of Quantitation (LLOQ)	10 pg/mL
Average Recovery of Drug	88.6%
Intra-Batch Accuracy	105.1% (range: 100.5-109.9%)
Inter-Batch Accuracy	99.0 – 108.8%
Intra-Batch Precision Range	2.3 – 11.7%
Inter-Batch Precision Range	3.3 – 8.1%
Freeze-Thaw Stability	5 cycles
Bench-Top Stability	24 hours (room temperature)
Processed Stability	35 days (approximately 4°C) 24 hours (room temperature) in the working solutions
Long Term Stability	14 months and 23 days (428 days) (-20°C) *The sample collection date was between 8/17/2010 and 12/16/2010, and the sample analysis date was between 9/17/2010 and 1/11/2011.The sample storage condition was at approximately at -20 °C in polypropylene tubes during this time. The duration from the first sample collection to the last day of sample analysis was 147 days.*
Dilution Integrity	Up to 100-fold
Recovery	85.6% (at 30 pg/mL), 88.4% (at 1000 pg/mL), 92.0% (at 4000 pg/mL) Internal standard: 87.0% (at 1000 pg/mL)
Selectivity/Matrix Effect	The ratio of peak areas for CD07805 obtained after spiking in blank human plasma before extraction to those obtained for standard solutions is 89.8% (at 30 pg/mL), 85.8% (at 1000 pg/mL), 90.3% (at 4000 pg/mL). The ratio for internal standard is 85.5% (at 1000 pg/mL)
Reviewer's comments	***Method acceptable***

Pharmacokinetic Analysis:

- Brimonidine tartrate ophthalmic solution: C_{max}, T_{max}, and AUC_{0-24h}
- CD07805/47 gel: C_{max}, C_{trough}, T_{max}, AUC_{0-t}, AUC_{0-tau}, AUC_{0-24h}, AUC_{0-inf}, kel, and $t_{½}$
- Accumulation ratios (based on AUC_{0-24h} and C_{max}) if sufficient plasma concentrations were above the limit of quantification
- Relative bioavailability was to be calculated based on AUC ratios (Ratio of AUC_{0-24hr} of topical gel to ophthalmic solution corrected by the dose ratio) and C_{max} ratios (Ratio of Cmax of facial gel to ophthalmic solution corrected by the dose ratio).

Statistical Methods:

Descriptive statistics for the plasma concentrations by each PK sampling time for brimonidine tartrate ophthalmic solution 0.2% and CD07805/47 gels (0.5% QD, 0.18% QD and BID, 0.07% BID), and descriptive summaries for the PK parameters for each treatment by PK sampling day.

When applicable, the PK parameters from topical treatment were to be examined for treatment effect and time effect by analysis of covariance (ANCOVA) using PROC MIXED procedure in SAS including the corresponding PK value from the ophthalmic solution as a covariate, and subject, time, treatment, and time*treatment as factors in the model.

For each PK parameter and each gel treatment, the estimate and its 90% confidence interval (CI) of each pairwise difference between time points (Day 32 vs Day 4, Day 32 vs Day 18, Day 18 vs Day 4) were to be constructed. Estimates of the accumulation ratios with 90% CI were to be obtained to determine the time to steady state with each gel treatment.

In addition, the estimates of the ratios of geometric means between ophthalmic solution and each gel treatment were to be provided with 90% CI. The primary time point for this analysis was Day 32, but earlier time points were to be examined if steady state was reached earlier.

Similarly, the 90% CIs for the ratios of geometric means between any two gel treatments for AUC_{0-24h} and C_{max} on Days 4, 18 and 32, and for C_{trough} on Days 5, 10, 18 and 32 were to be provided, when applicable.

Pharmacokinetic Results:

A total of 93 subjects completed the study with 9 subjects discontinued the study prematurely. Among the 9 subjects who discontinued, 4 were due to subject requests and 5 were due to adverse events.

Some concentration data were excluded from calculation of PK parameters. The excluded data points included subjects with missed dose affecting PK profile (i.e. during PK visits) and outlier concentration values. In addition, all PK profiles of subject #8319-100 were

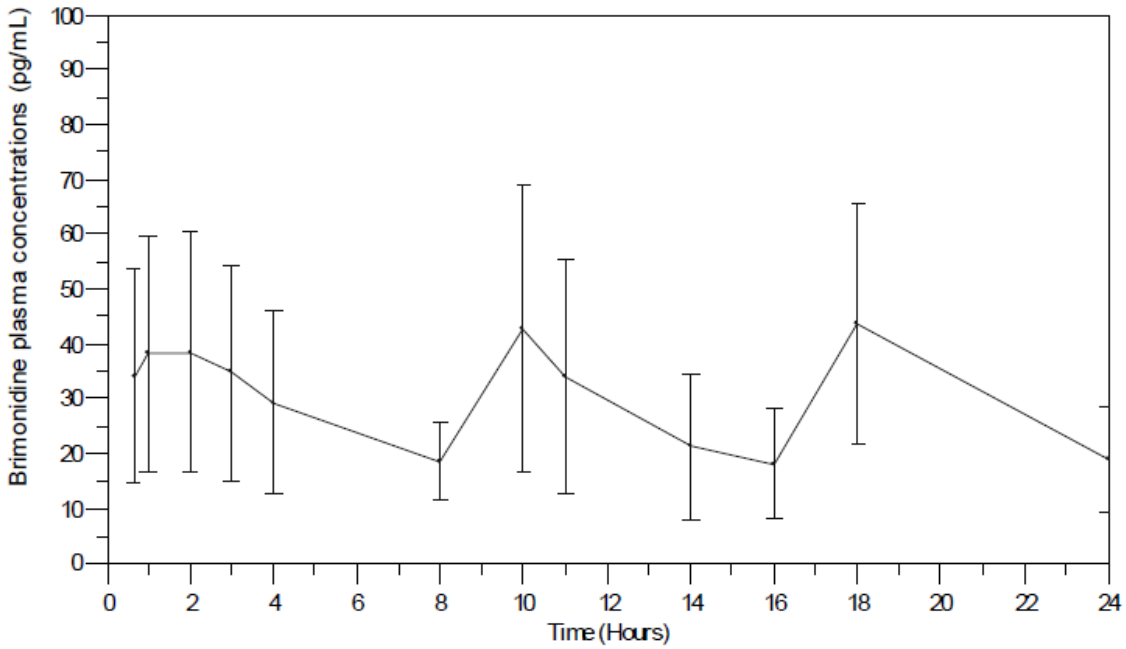
excluded because several outlier points were detected and subject missed application at Day 18.

The exclusion of the concentration data from calculation of PK parameters were reviewed and regarded as appropriate by this reviewer.

Brimonidine Ophthalmic Solution 0.2% TID

Administration of Brimonidine tartrate 0.2% by ophthalmic route resulted in quantifiable exposure (≥ 10 pg/mL) in all 96 subjects receiving TID treatment and included in the PK analysis. The mean C_{max} and $AUC_{0\text{-}24hr}$ on Study Day 1 of Brimonidine tartrate 0.2% ophthalmic solution were 54 ± 28 pg/mL (range: 16-134 pg/mL) and 568 ± 277 pg.hr/mL (range: 124-1490 pg.hr/mL), respectively. The mean±SD brimonidine plasma profile after ocular administration of 0.2% TID of brimonidine ophthalmic solution is shown in Figure 2.

Figure 2: Mean ± SD Brimonidine plasma profile after ocular administration (dose regimen: TID)



CD07805/47 Gel

Daily topical application of CD07805/47 Gel for 29 days resulted in quantifiable (≥ 10 pg/mL) systemic exposure in 22%, 48%, 71% and 79% of subjects receiving CD07805/47 Gel 0.07% BID, 0.18 % QD, 0.18% BID or 0.5% QD, respectively. The summary of mean PK parameters is shown below in Table 10, Table 11, and Table 12 for Days 4, 18, and 32-35, respectively.

Table 10: Overall CD07805 mean PK parameters at Day 4 (First topical application)

	C_{max} [(a)] (pg/mL)	T_{max} (h)	AUC_{0-6hr} (pg.hr/mL)	AUC_{0-t} (pg.hr/mL)	AUC_{0-24hr} [(a)] (pg.hr/mL)
CD07805/47 Gel 0.07% BID					
Mean ± SD	10.3 ± 1.0	13.0 ± 15.6	42.5 ± 24.8	135.2 ± 156.0	20.0 ± 46.2
Min - Max	10.0 - 14.9	2.0 - 24.0	24.9 - 60.0	24.9 - 245.5	10.0 - 245.5
CV	10%	120%	58%	115%	231%
N (N quantifiable)	26 (2)	2	2	2	26 (2)
CD07805/47 Gel 0.18%-BID					
Mean ± SD	13.5 ± 4.8	14.1 ± 4.6	59.9 ± 0.7	198.4 ± 89.8	157.1 ± 122.1
Min - Max	10.0 - 26.7	9.0 - 24.0	58.5 - 61.2	90.5 - 413.0	10 - 413.0
CV	36%	33%	1%	45%	78%
N (N quantifiable)	23 (16)	16	16	16	23 (16)
CD07805/47 Gel 0.18%-QD					
Mean ± SD	13.1 ± 6.7	11.5 ± 7.0	73.3 ± 19.7	163.4 ± 76.5	72.3 ± 107.4
Min - Max	10.0 - 32.5	2.0 - 23.9	60.0 - 115.9	67.3 - 261.5	10 - 353.5
CV	51%	61%	27%	47%	149%
N (N quantifiable)	25 (8)	8	8	8	25 (8)
CD07805/47 Gel 0.5%-QD					
Mean ± SD	19.4 ± 11.7	12.5 ± 4.7	71.8 ± 28.7	334.3 ± 182.2	262.1 ± 209.4
Min - Max	10.0 - 52.0	5.1 - 24.0	60.0 - 177.9	90.6 - 732.9	10 - 732.9
CV	60%	38%	40%	54%	80%
N (N quantifiable)	23 (17)	17	17	17	23 (17)

[(a)] Note: 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 study (i.e. 10 pg.hr/mL)

Figure 3: Mean CD07805 plasma profiles sorted by treatment group (Day 4)

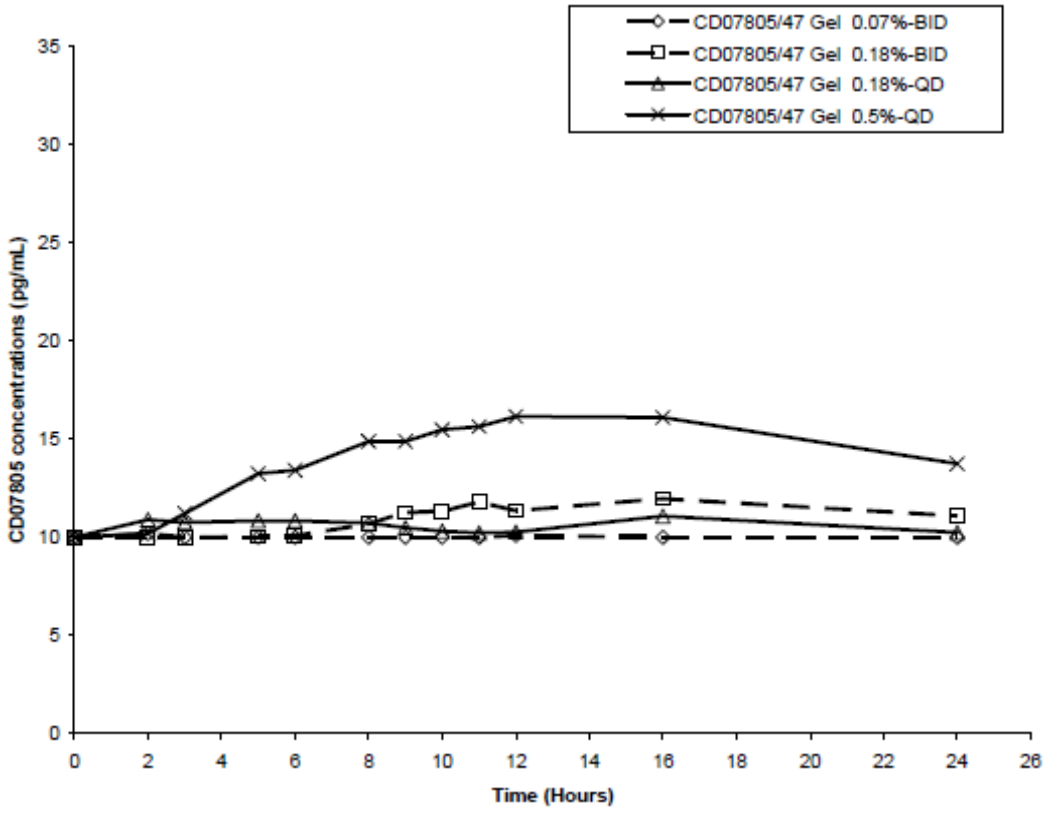


Table 11: Overall CD07805 mean PK parameters at Day 18 (15th application)

	C_{max} [(a)] (pg/mL)	T_{max} (hr)	$AUC_{0\text{-}6hr}$ (pg.hr/mL)	$AUC_{0\text{-}t}$ (pg.hr/mL)	$AUC_{0\text{-}24hr}$ [(a)] (pg.hr/mL)
CD07805/47 Gel 0.07%-BID					
Mean ± SD	10.1 ± 0.5	16.0 ± 0.0	60.3 ± 0.7	162.2 ± 1.8	33.6 ± 65.3
Min - Max	10.0 - 12.0	16.0 - 16.0	59.5 - 60.8	160.5 - 164.1	10 - 212.2
CV	5%	0%	1%	1%	194%
N (N quantifiable)	25 (3)	3	3	3	25 (3)
CD07805/47 Gel 0.18%-BID					
Mean ± SD	21.2 ± 24.3	10.9 ± 6.4	69.6 ± 13.5	273.1 ± 170.7	176.4 ± 198.1
Min - Max	10.0 - 110.5	0.0 - 23.7	59.3 - 104.6	111.1 - 742.9	10 - 742.9
CV	115%	59%	19%	62%	112%
N (N quantifiable)	23 (13)	13	13	13	23 (13)
CD07805/47 Gel 0.18%-QD					
Mean ± SD	12.7 ± 5.5	11.8 ± 6.5	74.5 ± 29.8	205.2 ± 79.5	77.3 ± 108.6
Min - Max	10.0 - 29.0	5.0 - 24.0	59.8 - 142.9	80.2 - 322.5	10 - 322.5
CV	43%	55%	40%	39%	141%
N (N quantifiable)	25 (8)	8	8	8	25 (8)
CD07805/47 Gel 0.5%-QD					
Mean ± SD	46.2 ± 61.5	9.3 ± 5.2	112.1 ± 70.1	426.8 ± 261.8	417.3 ± 263.6
Min - Max	10.0 - 254.6	2.0 - 24.0	60.0 - 320.8	83.3 - 1077.4	10 - 1077.4
CV	133%	56%	63%	61%	63%
N (N quantifiable)	21 (20)	20	20	20	21 (20)

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

Figure 4: Mean CD07805 plasma profiles sorted by treatment group (Day 18)

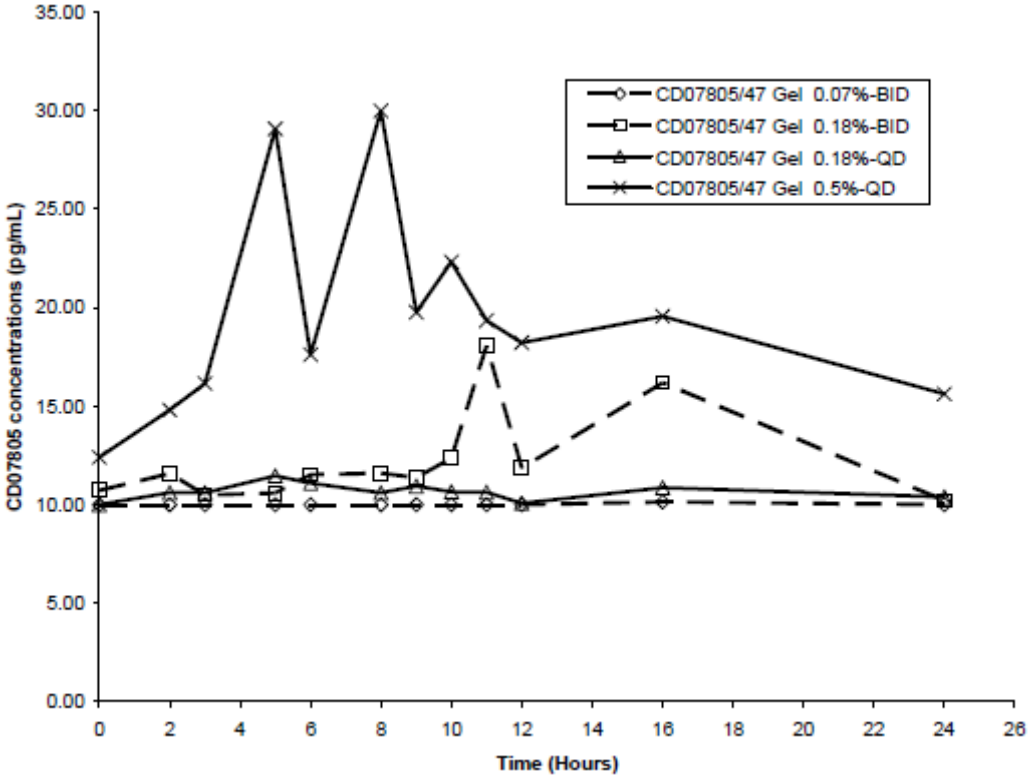
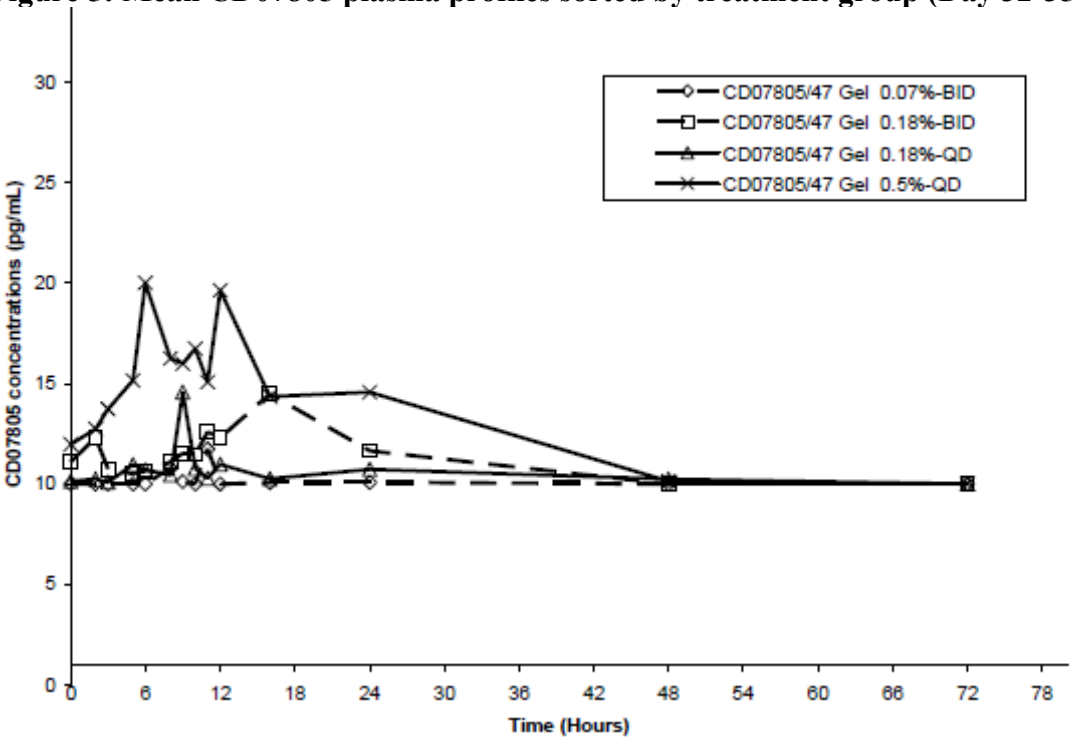


Table 12: Overall CD07805 mean PK parameters at Day 32-35 (29th application)

	C_{max} [(a)] (pg/mL)	T_{max} (hr)	$AUC_{0\text{-}6hr}$ (pg.hr/mL)	$AUC_{0\text{-}t}$ (pg.hr/mL)	$AUC_{0\text{-}24hr}$ [(a)] (pg.hr/mL)
CD07805/47 Gel 0.07%-BID					
Mean ± SD	12.7 ± 8.9	11.8 ± 9.0	60.2 ± 0.5	172.6 ± 51.7	42.3 ± 73.6
Min - Max	10.0 - 49.5	0.0 - 24.0	59.5 - 60.8	129.7 - 247.3	10.0 - 247.3
CV	70%	76%	1%	30%	174%
N (N quantifiable)	23 (5)	5	4	4	23 (5)
CD07805/47 Gel 0.18%-BID					
Mean ± SD	17.6 ± 10.2	12.7 ± 6.4	68.9 ± 15.4	246.8 ± 129.2	193.3 ± 155.0
Min - Max	10.0 - 49.6	0.0 - 24.0	59.0 - 115.1	93.0 - 469.3	10.0 - 469.3
CV	58%	50%	22%	52%	80%
N (N quantifiable)	21 (15)	15	15	15	21 (15)
CD07805/47 Gel 0.18%-QD					
Mean ± SD	16.6 ± 20.2	9.5 ± 5.8	61.6 ± 6.0	227.0 ± 287.8	93.2 ± 116.9
Min - Max	10.0 - 111.2	3.0 - 23.6	50.2 - 73.4	50.2 - 1097.0	10.0 - 380.8
CV	122%	61%	10%	127%	125%
N (N quantifiable)	25 (12)	12	12	12	25 (12)
CD07805/47 Gel 0.5%-QD					
Mean ± SD	25.5 ± 24.3	9.7 ± 7.0	91.0 ± 39.4	379.3 ± 282.8	290.0 ± 241.8
Min - Max	10.0 - 117.9	0.0 - 24.0	60.0 - 186.4	81.3 - 1086.6	10.0 - 949.1
CV	95%	72%	43%	75%	83%
N (N quantifiable)	19 (15)	15	15	15	19 (15)

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

Figure 5: Mean CD07805 plasma profiles sorted by treatment group (Day 32-35)



Several trough concentrations were determined and summarized in the table below. At Day 4, the trough concentrations before the first topical application of CD07805 gel were below the limit of quantification. This indicates the elimination of Brimonidine Ophthalmic Solution after two days of wash-out period.

Table 13: Mean trough concentrations (C_{trough})

	Day	Mean ± SD pg/mL	Min – Max	N (N C_{trough} quantifiable)
CD07805/47 Gel 0.07% BID	D04	BLQ	-	- -
	D05	12.0	-	- (1)*
	D10	BLQ	-	- -
	D18	BLQ	-	- -
	D19	BLQ	-	- -
	D24	10.4 ± 1.8	10.0 - 19.1	25 (2)
	D32	10.1	-	- (1)*
CD07805/47 Gel 0.18% QD	D04	BLQ	-	- -
	D05	14.7	-	- (1)*
	D10	12.4 ± 7.4	10.0 - 41.6	24 (4)
	D18	BLQ	-	- -
	D19	10.3 ± 1.0	10.0 - 13.7	23 (3)
	D24	10.0	-	- (1)*
	D32	10.0 ± 0.1	10.0 - 10.5	24 (2)
CD07805/47 Gel 0.18% BID	D04	BLQ	-	- -
	D05	11.0 ± 3.5	10.0 - 26.7	23 (5)
	D10	10.3 ± 1.0	10.0 - 14.6	22 (4)
	D18	10.7 ± 2.0	10.0 - 17.8	23 (3)
	D19	13.3 ± 14.1	10.0 - 76.6	22 (5)
	D24	11.3 ± 2.9	10.0 - 19.7	22 (6)
	D32	11.1 ± 2.6	10.0 - 20.6	21 (5)
CD07805/47 Gel 0.5% QD	D04	BLQ	-	- -
	D05	13.3 ± 4.8	10.0 - 24.4	23 (11)
	D10	12.3 ± 4.1	10.0 - 26.3	22 (4)
	D18	12.4 ± 5.6	10.0 - 29.6	21 (7)
	D19	15.1 ± 7.9	10.0 - 39.0	21 (14)
	D24	13.9 ± 7.0	10.0 - 33.7	20 (8)
	D32	12.0 ± 4.7	10.0 - 25.9	19 (5)

*As there is only one quantifiable C_{trough} value, no statistical description were reported.
BLQ: Below the limit of quantification (i.e < 10 pg/mL)

Reviewer's Comment: In this submission, elimination half-life was not calculated because the applicant stated that there was a lack of distinct elimination phase. Alphagan® 0.2% ophthalmic solution has been discontinued, and this trial used the generic brimonidine tartrate ophthalmic solution 0.2% from Bausch & Lomb (listed as Reference Listed Drug in Orange Book)

Mean accumulation ratios between Day 18 and Day 4, Day 32 and Day 4, and Days 32 and 18 are summarized in the table below.

Table 14: Mean $AUC_{0\text{-}24hr}$ Accumulation Ratio

GROUP	R1 Day 18/Day 4	R2 Day 32/Day 4	R3 Day 32/Day 18
CD07805/47 Gel 0.07% BID			
Mean	N.R.	5.3	1.0
Min – Max	N.R.	N.R.	N.R.
N	N.R.	1	1
CD07805/47 Gel 0.18% QD			
Mean	1.1 ± 0.5	1.1 ± 0.3	1.1 ± 0.7
Min – Max	0.4 - 1.8	0.8 - 1.6	0.4 - 2.5
N	5	5	8
CD07805/47 Gel 0.18% BID			
Mean	1.8 ± 1.4	1.3 ± 0.4	1.1 ± 0.7
Min – Max	0.6 - 4.9	0.4 - 1.8	0.4 - 2.9
N	10	12	11
CD07805/47 Gel 0.5% QD			
Mean	1.4 ± 0.6	1.2 ± 0.8	0.9 ± 0.3
Min – Max	0.7 - 3.1	0.3 - 3.6	0.4 - 1.7
N	16	12	15

Note: Unquantifiable AUC were not used for calculation of accumulation ratios;
N.R.: Not Reportable

Table 15: Mean C_{max} Accumulation Ratio

GROUP	R1 Day 18/Day 4	R2 Day 32/Day 4	R3 Day 32/Day 18
CD07805/47 Gel 0.07% BID			
Mean	1.0 ± 0.1	1.2 ± 0.8	1.3 ± 0.9
Min – Max	0.7 - 1.2	0.8 – 5.0	0.8 – 5.0
N	25	23	23
CD07805/47 Gel 0.18% QD			
Mean	1.0 ± 0.2	1.2 ± 0.7	1.3 ± 0.9
Min – Max	0.7 - 1.5	0.4 - 3.5	0.5 - 5.4
N	25	25	25
CD07805/47 Gel 0.18% BID			
Mean	1.7 ± 1.9	1.3 ± 0.7	1.2 ± 0.5
Min – Max	0.4 - 8.7	0.4 - 3.4	0.3 - 2.4
N	23	21	21
CD07805/47 Gel 0.5% QD			
Mean	2.8 ± 4.5	1.4 ± 1.4	0.8 ± 0.6
Min – Max	0.0 - 19.4	0.0 - 6.3	0.2 - 2.8
N	21	21	20

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

Reviewer's Comment: After the last dose on Day 32, the accumulation ratio of Day 32/Day 4 for C_{max} ranged from 1.2 to 1.4, and for $AUC_{0\text{-}24hr}$ ranged from 1.1 to 1.3 (Except for 0.07% BID in which only 1 subject had available $AUC_{0\text{-}24h}$ value on Day 4 and Day 32 , the mean $AUC_{0\text{-}24h}$ accumulation ratio was 5.3). It appears that after 28 days of Brimonidine gel applied topically, there was almost no to a small degree of accumulation. On the other hand, the accumulation ratio of Day 18/Day 4 for C_{max}

ranged from 1.0 to 2.8, and for $AUC_{0\text{-}24hr}$ ranged from 1.1 to 1.8, although the variability was high. It appears that there was some degree of accumulation after 15 days of Brimonidine gel applied topically.

Relative bioavailability of CD07805/47 Gel was evaluated in comparison to the ophthalmic route using both $AUC_{0\text{-}24hr}$ and C_{max}. The two tables below show the amounts of CD07805 administered by topical and ophthalmic routes at different doses and dose regimens and the mean relative bioavailability for each treatment group.

Table 16: Quantity of active compound administrated by both topical and ophthalmic routes

Treatment		CD07805 (mg/g)	Daily dose (Number)	Quantity of formulation /application (g)	Daily Quantity of formulation applied (g)	Quantity of active compound per day (mg) [(a)]
0.07 % BID	Topical	0.7	2	1	2	1.4
0.18 % QD	Topical	1.8	1	1	1	1.8
0.18 % BID	Topical	1.8	2	1	2	3.6
0.5 % QD	Topical	5	1	1	1	5
0.2 % TID	Ocular	2	6	0.0307[(b)]	0.1842	0.368

(a) assuming than one drop is 30.7 mg (calculated by a mock dose experimentation, see report in Appendix II.

(b) assuming a volumetric density of 1

Table 17: Relative topical bioavailability (reference route: Ophthalmic route)

GROUP	Relative Bioavailability ($AUC_{0\text{-}24h}$)	Relative Bioavailability (C_{max})
CD07805/47 Gel 0.07% BID Mean Min – Max N	 9 ± 6% 3% - 15% 4	 7 ± 2% 6% - 10% 4
CD07805/47 Gel 0.18% QD Mean Min – Max N	 6 ± 5% 2% - 18% 12	 9 ± 12% 3% - 46% 12
CD07805/47 Gel 0.18% BID Mean Min – Max N	 8 ± 4% 2% - 16% 14	 5 ± 2% 2% - 9% 14
CD07805/47 Gel 0.5% QD Mean Min – Max N	 5 ± 3% 1% - 12% 14	 4 ± 2% 1% - 8% 14

Only the quantifiable data (C_{max} and $AUC_{0\text{-}24hr}$) were used

Reviewer's Comments: The sponsor's calculation of relative bioavailability was based on $AUC_{0\text{-}24h}$ and C_{max} of topical gel from Day 32 to ophthalmic solution from Day 1 corrected by the dose ratio. Compared to ophthalmic route, topical administration of Brimonidine tartrate topical gel has lower bioavailability if using the same dose. The mean relative bioavailability by both $AUC_{0\text{-}24h}$ and C_{max} were similar among the four treatment groups. However, since the proposed dose for this submission is 0.5% QD of the topical gel, the most relevant relative bioavailability should be the systemic exposure

of 0.5% topical gel compared to 0.2% ophthalmic solution under their respective conditions of use (i.e., route of administration, dose, and dosing frequency) without dose corrections. The table below is calculated by this reviewer using Phoenix® WinNonlin® 32.

Table 18: CD07805/47 Gel 0.5% QD relative bioavailability in reference to ophthalmic route without dose correction

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

	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)	32 (95%) N=20	66%	47%-94%
Test (Day 32)	24 (62%) N=15	55%	38%-79%

The systemic exposure of CD07805/47 gel 0.5% QD was higher at Day 18 than at Day 32, therefore the relative bioavailability in reference to ophthalmic solution 0.2% TID was higher in both $AUC_{0\text{-}24h}$ and C_{max} at Day 18 than at Day 32. At Day 18, the mean relative bioavailability of $AUC_{0\text{-}24h}$ and C_{max} were 71% and 66%, respectively. The 90% confidence intervals for the relative bioavailability of both C_{max} and $AUC_{0\text{-}24}$ were below100%. Therefore, the systemic exposure of once daily topical use of brimonidine tartrate topical gel, 0.5%, was less than the exposure of brimonidine tartrate ophthalmic solution 0.2% TID.

Applicant's Safety Conclusions:
Adverse events (AEs) were reported in 63.7% of subjects during the study. During the ophthalmic treatment period, 22.5% of all 102 subjects had at least 1 AE, and 12.7% of all 102 patients had drug-related AEs. During the gel treatment period, 50.0% to 59.3% of subjects in all four of the CD07805/47 gel groups had at least 1 AE, and the incidence of drug-related AEs ranged from 12.5% of subjects in the CD07805/47 gel 0.5% QD group to 24.0% of subjects in the CD07805/47 gel 0.18% QD group.

Two subjects were reported to have serious adverse events (SAEs), with 1 subject had hypotension and 1 subject had chest pain. Both SAE occurred within the ophthalmic

treatment period. Four severe AEs were reported in 4 subjects: 2 subjects during the ophthalmic treatment period (migraine in 1 subject and hypotension in 1 subject) and 2 subjects during treatment with CD07805/47 gel 0.07% BID (headache in 1 subject and nausea in 1 subject). For the to-be-marketed dose (CD07805/47 gel 0.5%), the most common AEs were headache (12.5%), dizziness (8.3%), and nasopharyngitis (8.3%).

Reviewer's Comments: This data is currently being reviewed by the medical reviewer.

Table 19: Demographics

Variable	CD07805/47 Gel				Total N=102	p-value
	0.5% QD N=24	0.18% BID N=26	0.18% QD N=25	0.07% BID N=27		
Gender, n (%)						
Male	13 (54.2)	10 (38.5)	6 (24.0)	11 (40.7)	40 (39.2)	0.198
Female	11 (45.8)	16 (61.5)	19 (76.0)	16 (59.3)	62 (60.8)	
Total	24 (100.0)	26 (100.0)	25 (100.0)	27 (100.0)	102 (100.0)	
Age (Years), n (%)						
n	24	26	25	27	102	0.402
Mean	40.4	41.1	39.4	45.0	41.6	
SD	15.15	12.78	11.21	11.07	12.60	
18 - 64	23 (95.8)	24 (92.3)	25 (100.0)	26 (96.3)	98 (96.1)	0.575
65 and above	1 (4.2)	2 (7.7)	0	1 (3.7)	4 (3.9)	
Total	24 (100.0)	26 (100.0)	25 (100.0)	27 (100.0)	102 (100.0)	
Race, n (%)						
Caucasian	24 (100.0)	25 (96.2)	24 (96.0)	26 (96.3)	99 (97.1)	0.555
Asian	0	1 (3.8)	0	1 (3.7)	2 (2.0)	
Other	0	0	1 (4.0)	0	1 (1.0)	
Total	24 (100.0)	26 (100.0)	25 (100.0)	27 (100.0)	102 (100.0)	
Ethnicity, n (%)						
Hispanic or Latino	4 (16.7)	4 (15.4)	4 (16.0)	4 (14.8)	16 (15.7)	0.998
Not Hispanic or Latino	20 (83.3)	22 (84.6)	21 (84.0)	23 (85.2)	86 (84.3)	
Total	24 (100.0)	26 (100.0)	25 (100.0)	27 (100.0)	102 (100.0)	

P-values for nominal categorical variables were based on the CMH general association statistic.
P-values for ordinal categorical variables were based on the CMH row mean difference statistic, RIDIT transformed score.
P-values for continuous variables were based on one-way ANOVA model with terms for treatment.

Applicant's Conclusion:
Ophthalmic instillation of Brimonidine tartrate 0.2% ophthalmic solution resulted in quantifiable exposure (≥10 pg/mL) in all 96 subjects who received all 3 doses. The mean C_{max} (±SD) was 54±28 pg/mL and the mean $AUC_{0\text{-}24h}$ (±SD) was 568±277 pg.h/mL.

For daily topical application of Brimonidine tartrate gel for 29 days, quantifiable (≥10 pg/mL) systemic exposure was found in 22%, 48%, 71%, and 79% of subjects receiving Brimonidine tartrate 0.07% gel BID, 0.18% gel QD, 0.18% gel BID, and 0.5% gel QD, respectively. For the intended to-be-marketed formulation (Brimonidine tartrate 0.5% gel), the highest mean C_{max} (±SD) and the mean $AUC_{0\text{-}24h}$ (±SD) were observed at Day 18 (after 15th application), as 46±62 pg/mL and 417±264 pg.h/mL, respectively. The

C_{max} for 1 day and after 29 days of topical application of Brimonidine tartrate 0.5% was 19±12 pg/mL and 25±24 pg/mL, respectively, and the AUC_{0-24h} for 1 day and after 29 days of topical application of Brimonidine tartrate 0.5% was 262±209 pg.h/mL and 290±242 pg.h/mL, respectively.

Reviewer's Comments:
The applicant's conclusion is acceptable.

Trial No. 18139

Title: 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.

Trial Initiation/Completion Dates: 11/8/2009 to 12/21/2009

Objectives:

Primary objectives:

- 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 QTc interval corrected by QTcB, QTcF, and QTcI (subject-specific) at the T_{max} using 12-lead electrocardiograms (ECGs).

Secondary objectives:

- To determine if there was a pharmacodynamic relationship between the duration of the QT/QTc intervals and the plasma concentration of brimonidine.

Safety objectives:

- All subjects who received study drug and had at least one follow-up assessment were included in the safety analyses. The safety data, including adverse events (AEs), laboratory data, vital signs, ECGs, changes in physical examination, and, if appropriate, reasons for withdrawal from study, was listed and/or descriptively summarized by study drug.

Trial Center:

(b) (4)

Design of Trial:

The treatments administered were shown in the table below:

	Brimonidine tartrate Ophthalmic Solution 0.2%	Brimonidine tartrate Placebo Advanced Eye Relief™	Moxifloxacin Oral Placebo	Moxifloxacin Oral 400 mg Tablet
Treatment A (Brimonidine tartrate Supra-Therapeutic Dose)	2 drops in each eye	None	One over-encapsulated placebo capsule	None
Treatment B (Placebo)	None	2 drops in each eye	One over-encapsulated placebo capsule	None
Treatment C (Moxifloxacin 400 mg)	None	2 drops in each eye	None	One over-encapsulated Moxifloxacin 400 mg capsule

All subjects were treated with each of the three treatments over 3 individual dosing periods. There was a 6-day washout period between dosing periods. The dosage administered of the eye drops was a total dose of two drops of 0.2% brimonidine or two drops of the Advanced Eye Relief™ Dry Eye Rejuvenation Lubricant Eye Drops. There was a 3 minute window of time between the administration of the first and second drop of ocular medications. Blood samples for the analysis of brimonidine tartrate blood concentrations were obtained following the ECG 10 minute acquisition windows at the following times:

- Pre-dosing: -5 min (for brimonidine tartrate and moxifloxacin)
- Post-dosing: 42 min, 1 hr 12 min, 2 hr and 12 min, 3 hr and 12 min, 4 hr and 12 min, 6 hr and 12 min, and 8 hr and 12 min. (for brimonidine tartrate and moxifloxacin)
- Post-dosing: 10 hr and 12 min, 12 hr and 12 min, and 23 hr and 12 min. (for brimonidine tartrate only)

The PK parameters of C_{max}, T_{max}, and AUC_{0-t} were calculated for brimonidine tartrate using actual sample collection times. In addition, Kel, $T_{1/2}$, and AUC_{0-inf} were also calculated.

This trial is reviewed by the medical reviewer, Dr. Brenda Carr, and the Interdisciplinary Review Team for QT Studies (IRT-QT). This reviewer will discuss the PK results in this trial only.

Analytical Methods:
See Question-Based-Review Section 2.6.1.

Table 20: Analytical Method Validation

Assay Method	Liquid chromatography – tandem mass spectrometry using Turbo IonSpray, in positive ion, multiple reaction monitoring mode
Analytical Site	(b) (4)
Compound	Brimonidine in human plasma (sodium heparin)
Standard Curve Range	10 pg/mL to 1000 pg/mL
Lower Limit of Quantitation (LLOQ)	10 pg.mL-1
Average Recovery of Drug [a]	84.6% (87.2% if excluding 1 outlier at 10,000 pg/mL)
Intra-Run Accuracy	98.52% (range: 93.6-103.0%)
Inter-Run Accuracy [a]	0.03-25 ng/mL: 104-112.3% 0.01 ng/mL (LLOQ): 94.5%
Intra-Run Precision Range	0.8 – 5.9%
Inter-Run Precision Range [a]	0.03-25 ng/mL: 9.1-12.7% 0.01 ng/mL (LLOQ):19.4%
Freeze-Thaw Stability	5 cycles
Bench-Top Stability	24 hours (room temperature)
Processed Stability	35 days (approximately 4°C), 24 hours (room

	temperature) in the working solutions
Long Term Stability	169 days (-20°C) *The trial was initiated on December 4, 2009, and the last day of sample analysis was on February 8, 2010. The plasma samples were isolated and frozen (-20°C) pending analysis. The duration from the trial initiation to the last day of sample analysis was 66 days.*
Recovery	88.4% (at 30 pg/mL), 79.5% (at 10,000 pg/mL, 87.3% if excludeing 1 outlier), 85.8% (at 18,000 pg/mL) [a]
Selectivity	The precision and mean bias of the observed concentrations of brimonidine analyzed in lipaemic and haemolysed plasma at the second lowest calibration standard level (0.025 ng/mL) were within 15% and ±15%, respectively.
Reviewer's comments	***Method acceptable***

[a]: values were determined in the bioanalytical method validation report RDS.03.VPR.34214 (YCV/002), December 2009 (complete validation report, validated concentration range 0.01-25 ng/mL). Other validation values were taken from the partial validation report, RDS.06.SRE.18139 (YCV/006), May 2010 (validated concentration range: 10-1000 pg/mL).

Pharmacokinetic Results:

A total of 60 subjects were enrolled with age ranged from 18 to 54 years in this trial, and 57 completed all three treatment periods (three subjects missed one dose of study medication). The dose of brimonidine tartrate of this trial was calculated to be approximately 0.244 mg of Brimonidine tartrate. The sponsor determined that 33 subjects out of 60 lacked a distinct elimination phase, and therefore the estimation of $T_{1/2}$ and Kel were not performed for these 33 subjects. Mean C_{max} and AUC_{0-t} were 54±24 pg/mL and 250±25 pg.hr/mL, respectively, for brimonidine. The summary of pharmacokinetic parameters for Brimonidine is shown in Table 21.

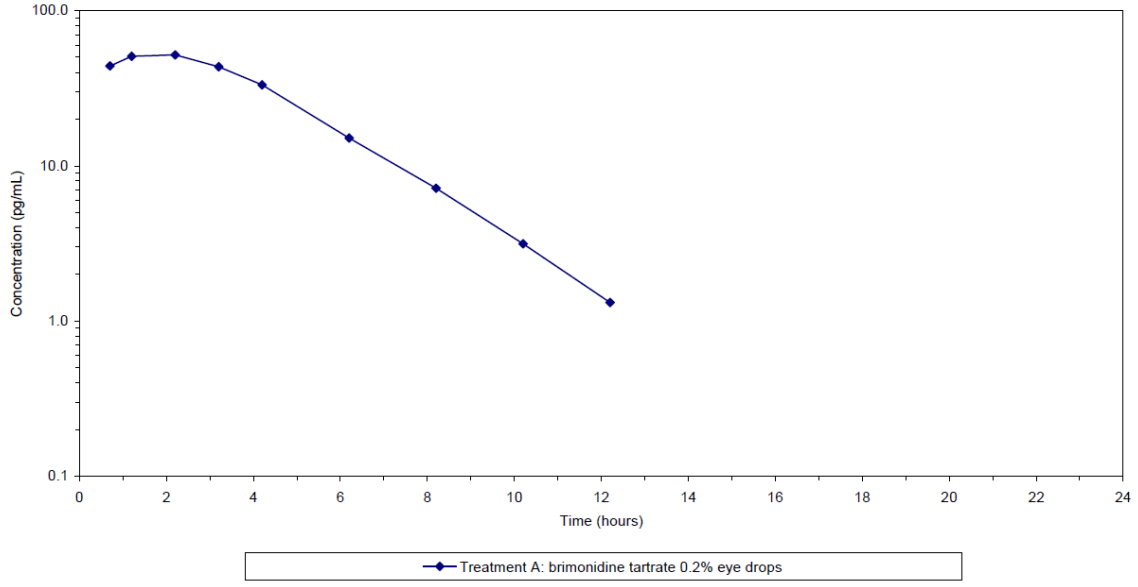
Table 21: Summary of Brimonidine Tartrate (two drops of a 0.2% solution to each eye) pharmacokinetic parameters

Parameters	N	
$AUC_{0\text{-}t}$ (pg.hr/mL) Mean ± SD Min-Max CV (%)	60	 250 ± 125 75 – 627 50%
$AUC_{0\text{-}inf}$ (pg.hr/mL) Mean ± SD Min-Max CV (%)	27	 346 ± 109 185 – 654 32%
C_{max} (pg/mL) Mean ± SD Min-Max CV (%)	60	 54 ± 24 22 – 156 44%
T_{max} Mean ± SD Min-Max CV (%)	60	 1.7 ± 0.6 0.7 – 3.2 34%
Kel (h^{-1}) Mean ± SD Min-Max CV (%)	27	 0.35 ± 0.09 0.15 – 0.53 25%
$T_{1/2}$ (h) Mean ± SD Min-Max CV (%)	27	 2.2 ± 0.7 1.3 – 4.6 31%

$AUC_{(0\text{-}t)}$: AUC calculated from 0 to the last quantifiable point (23.20 hr)

The mean plasma concentration-time profile of brimonidine from 0-23.3 hours is shown in Figure 6**.**

Figure 6: Mean Plasma Concentration of Brimonidine dosed at two drops of a 0.2% solution to each eye (0 - 23.2 Hours), N=60.



Reviewer's comments: According to the label of 0.2% Alphagan® (brimonidine tartrate ophthalmic solution), after ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. This is consistent with the T_{max} and $T_{1/2}$ estimated in this trial. The applicant's rationale for using 0.2% brimonidine tartrate ophthalmic solution instead of using 0.5% brimonidine tartrate topical gel was due to the poor absorption after dermal administration of topical gel. The regimen of two drops in each eye of 0.2% ophthalmic solution was chosen to obtain the supratherapeutic level of exposure.

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 trial18143, 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.

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

/s/

AN-CHI LU
04/25/2013

DOANH C TRAN
04/25/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 204708 **Applicant: Galderma Research & Development** **Stamp Date: 10/25/2012**

Drug Name: Brimonidine Tartrate Gel, 0.5% **NDA/BLA Type: Original**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?		X		
Criteria for Assessing Quality of an NDA					
	Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X			PK trial RD.06.SRE.18143: in 5.3.3.2.25.1.1, pp.xpt and pc.xpt. Thorough QTc Trial 18139: in 5.3.5.4.25.1.1, pp.xpt and pc.xpt
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?		X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Sponsor requested waiver of pediatric studies.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
13	On its face, is the clinical pharmacology and	X			

	biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?				
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes___

If the NDA/BLA is not fileable from the clinical pharmacology 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 Pharmacologist Date

Team Leader/Supervisor Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**204708**	**Brand Name**	**Mirvaso**
OCP Division	**Division of Clinical Pharmacology 3**	**Generic Name**	**Brimonidine Tartrate**
Medical Division	**Division of Dermatology and Dental Product**	**Drug Class**	**Alpha adrenergic agonist**
OCP Primary Reviewer	**An-Chi Lu, M.S., Pharm.D.**	**Indication(s)**	**Topical treatment of facial erythema of rosacea in adults 18 years of age or older**
OCP Secondary Reviewer	**Doanh Tran, R.Ph., Ph.D**	**Dosage Form**	**Gel**
		Dosing Regimen	**Apply a small pea-size amount once daily to each of the five areas of the face (i.e., forehead, chin, nose, each cheek).**
Date of Submission	**10/25/2012**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**6/11/2013**	**Sponsor**	**Galderma Research and Development**
PDUFA Due Date	**8/25/2012**	**Priority Classification**	**Standard**
Division Due Date	**6/11/2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		PK trial COL-118-BAPK-101 Thorough QTc Trial 18139
multiple dose:				
Patients-				
single dose:	X	1		PK trial RD.06.SRE.18126
multiple dose:	X	1		PK trial RD.06.SRE.18143
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2		Phase 2a dose-finding trial RD.06.SRE.18144 and Phase 2b dose-finding efficacy and safety trial RD.06.SRE.18161
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	3		Two phase 3 pivotal trials RD.06.SRE.18140 and RD.06.SRE.18141. One Phase 3 safety uncontrolled efficacy trial RD.06.SRE.18142.
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• **Systemic exposure to Brimonidine Tartrate Topical Gel**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memorandum

Clinical Pharmacology Review

NDA: 204708
Compound: Brimonidine Tartrate Topical Gel, 0.5% (5 mg/g)
Sponsor: Galderma Research and Development

Date: 12/3/2012
Reviewer: An-Chi Lu

Background:
Galderma is submitting this New Drug Application (NDA) for Brimonidine Tartrate 0.5% Gel under 505(b)(2) of the Federal Food, Drug, and Cosmetics (FD&C) Act. Each gram contains 5 mg (0.5%) of brimonidine tartrate in a white to light yellow opaque aqueous gel. The applicant intends to rely for approval based on FDA findings of safety for Alphagan® (brimonidine tartrate ophthalmic solution) 0.2%.

The proposed new drug product, Brimonidine Tartrate Topical Gel, 0.5%, is indicated for the topical treatment of facial erythema of rosacea in adults 18 years of age or older. The proposed dosage and administration is to apply a small pea-size amount once daily to each of the five areas of the face (i.e., forehead, chin, nose, each cheek).

Clinical development program:
The clinical development program for Brimonidine Tartrate Gel included clinical trials conducted by the Applicant and clinical trials conducted by a previous Sponsor (CollaGenex Pharmaceuticals, Inc [hereafter referred to as CollaGenex]). CollaGenex had named the drug product COL-118 Gel.

The clinical development program for Brimonidine Tartrate Gel included a total of 18 clinical trials conducted in adult subjects: 13 clinical trials were conducted by the Applicant and 5 clinical trials were conducted by a previous Sponsor (CollaGenex Pharmaceuticals). A total of 10 of the 18 clinical trials were conducted in subjects with rosacea, and Brimonidine Tartrate 0.5% Gel (the proposed to-be marketed concentration) was evaluated in 6 of the 10 trials in subjects with rosacea.

A total of 3 pharmacokinetics (PK), relative bioavailability trials were conducted: 2 single-day crossover trials (COL-118-BAPK-101 [healthy subjects] and RD.06.SRE.18126 [subjects with rosacea]) and 1 multiple-dose trial under maximal use conditions in subjects with rosacea (RD.06.SRE.18143). Among the 3 relative bioavailability trials, Study 18143 is regarded by the Applicant as the most relevant because the trial was conducted in subjects with rosacea, included the intended to-be-marketed formulation, used the more sensitive analytical method (limit of quantification [LOQ]=10 pg/mL), and evaluated repeated dosing of Brimonidine Tartrate Gel (29 days). The Applicant conducted thorough QTc Trial 18139 in healthy subjects using ophthalmic instillation of Bausch & Lomb brimonidine tartrate 0.2% ophthalmic solution. A dose-

finding trial RD.06.SRE.18144 was conducted to investigate the pharmacodynamics and safety of three concentrations 0.07%, 0.18%, and 0.50%, applied in subjects with moderate to severe erythematotelangiectatic rosacea.

Maximal use PK trial RD.06.SRE.18143
Subjects with moderate to severe facial erythema of rosacea were treated for a single day with ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution (One drop of ophthalmic solution instilled in each eye every 8 hours for 24 hours) and, following a 2-day washout period, for 29 days with Brimonidine Tartrate Gel under maximal use conditions (1 g of gel applied to the entire face). A total of 102 subjects were randomized on Day 1 to receive Brimonidine Tartrate Gel 0.07% Gel twice daily (BID), 0.18% Gel QD or BID, or 0.5% QD during Days 4 to 32. Complete 24-hour PK profiles were obtained on Day 1 (ophthalmic solution instillation), Day 4 (first day of gel application), Day 18 (15th day of gel application), and Day 32 (29th day of gel application). After the last application of gel, a 72-hour PK profile was obtained to characterize the systemic exposure after 4 weeks of treatment. In addition, residual concentrations (C_{trouph}) were assessed at Days 10 and 24.

Ophthalmic instillation of brimonidine tartrate 0.2% ophthalmic solution resulted in quantifiable exposure (≥10 pg/mL) in all 96 subjects who received all 3 doses (Section 2.7.2.2.3.2.3). The mean Cmax (±SD) was 54±28 pg/mL and the mean AUC0-24h (±SD) was 568±277 pg.h/mL.

For daily topical application of Brimonidine Tartrate Gel for 29 days, quantifiable (≥10 pg/mL) systemic exposure was found in 22%, 48%, 71%, and 79% of subjects receiving Brimonidine Tartrate 0.07% Gel BID, 0.18% Gel QD, 0.18% Gel BID, and 0.5% Gel QD, respectively. For the intended to-be-marketed formulation (Brimonidine Tartrate 0.5% Gel), the highest mean C_{max} (±SD) and the mean AUC_{0-24h} (±SD) were observed at Day 15, as 46±62 pg/mL was 417±264 pg.h/mL, respectively. The C_{max} for 1 day and after 29 days of topical application of Brimonidine Tartrate 0.5% was 19±12 pg/mL and 25±24 pg/mL, respectively, and the AUC_{0-24h} for 1 day and after 29 days of topical application of Brimonidine Tartrate 0.5% was 262±209 pg.h/mL and 290±242 pg.h/mL, respectively.

Overall, systemic exposure after topical application of Brimonidine Tartrate 0.5% Gel was 1.2 times lower (based on C_{max}) or 1.4 times lower (based on AUC_{0-24h}) at Day 15 in comparison to a single day of 3 ocular instillations of brimonidine tartrate 0.2% ophthalmic solution.

Thorough QTc Trial 18139:
The thorough QTc trial was conducted in healthy subjects using ophthalmic instillation of Bausch & Lomb brimonidine tartrate 0.2% ophthalmic solution. It was to evaluate the effect of a supra-therapeutic dose of brimonidine tartrate ophthalmic solution (2 drops instilled in each eye with 3 minutes time interval between administrations of each drop) on ventricular repolarization compared to a positive control (oral moxifloxacin) and to placebo. It was also to determine whether a pharmacodynamics relationship existed

between QTc interval duration and plasma concentrations of brimonidine (PK/PD relationship).

In this trial, the sponsor reported that brimonidine tartrate did not show any potential to delay cardiac repolarization. Compared to the systemic exposures observed under maximal use conditions for the highest tested dose (Brimonidine Tartrate 0.5% Gel) in trial 18143 at Day 15 and Day 1, the brimonidine mean maximal systemic concentration (C_{max}) obtained in this thorough QTc trial was 1.2-times and 2.8-times higher, respectively.

Phase 2a dose-finding trial RD.06.SRE.18144:
This trial was conducted to investigate the pharmacodynamics and safety of three concentrations 0.07%, 0.18%, and 0.50%, applied in subjects with moderate to severe erythematotelangiectatic rosacea. Following a single application of CD07805/47 gel, a dose-response relationship was observed for the pharmacodynamic variables. The highest tested concentration (0.50%) showed the strongest observable effect.

Specific population:
Pediatric: The applicant requested a waiver of pediatric studies citing the scarcity of reported cases of rosacea in the pediatric population, and the unfavorable safety profile of brimonidine tartrate in young children.

Clinical vs. to-be-marketed formulation:
The to-be-marketed formulation was used in the following 7 trials: two pivotal Phase 3 trials (RD.06.SRE.18140 and RD.06.SRE.18141), the Phase 3 safety uncontrolled efficacy trial RD.06.SRE.18142, the maximal use PK trial RD.06.SRE.18143, the Phase 2b dose-finding, efficacy and safety trial RD.06.SRE.18161, the photosensitization/photoallergic potential trial RD.06.SRE.18124, and the phototoxicity trial RD.06.SRE.18189. The rest of the trials used the gel formulation of brimonidine which has a higher concentration of methyparaben, except trial COL-118-ROSE-102 which utilized the pilot formulations.

Method validation:
Brimonidine assay:
The method validation report and bioanalysis report for trial RD.06.SRE.18143, the Thorough QTc Trial 18139, the PK trial COL-118-BAPK-101, and RD.06.SRE.18126 are available for review. Adequate storage condition and long-term stability data are available for review.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 204708 is fileable.

Comments for sponsor:
None.

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

/s/

AN-CHI LU
12/04/2012

DOANH C TRAN
12/04/2012