CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208552Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208552
Link to EDR	\\CDSESUB1\evsprod\NDA208552\208552.enx (SDN 1, eCTD 0000)
Submission Type	Original NDA (Standard); 505(b)(1)
Applicant	Allergan, Inc.
Submission Date	March 23, 2016
PDUFA Goal Date	January 23, 2017
Brand Name	RHOFADE™
Generic Name	Oxymetazoline Hydrochloride Cream, 1.0% w/w
Dosage Form and Strength	Cream, 1.0%
Route of Administration	Topical
Proposed Indication	Topical treatment of persistent facial erythema associated with rosacea in adults
Proposed Dosage Regimen	Apply a pea-sized amount once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin, avoiding the eyes and lips.
Primary reviewer	Yanhui Lu, PhD
Secondary reviewer	Jie Wang, PhD
Division Director	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Dermatology and Dental Products/ODEIII

Table of Contents:

1 Executive Summary

The Applicant submitted the current NDA seeking for the approval for RHOFADE, oxymetazoline hydrochloride (HCl) cream, 1.0% (w/w) [equivalent to 0.88% (w/w) free base oxymetazoline], for the treatment of persistent facial erythema associated with rosacea in adults. Oxymetazoline is an alpha1A adrenoceptor agonist. Oxymetazoline is currently available in the United States as over-the-counter treatments for nasal congestion (e.g. nasal spray 0.05%) and for temporary relief of ocular redness (e.g. ophthalmic solution/drops 0.025%).

The overall clinical development program comprised two identical Phase 3 studies (199201-004 and 199201-005), one Phase 2 dose ranging study (199201-002), nine Phase 1/2 studies, and a long-term safety study (199201-006). All clinical studies used the same cream formulation with varying oxymetazoline HCl concentrations/strengths ranging from 0.01% to 1.5%. The to-be-marketed strength of 1.0% was used in the pivotal Phase 3 clinical studies. The Phase 2 Study 199201-002 characterized the full pharmacokinetic (PK) profiles of oxymetazoline HCl cream, 1.0% following single dose (Day 1) and multiple dose (Day 28) administrations.

The efficacy and safety of oxymetazoline HCl Cream, 1.0% were supported by the two pivotal Phase 3 studies. The Phase 2 dose-ranging study provided supportive evidence of effectiveness and supported the selection of oxymetazoline HCl cream, 1.0% daily dosing for Phase 3 studies. The recommended dosage and administration of RHOFADE will be to apply a pea-sized amount once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin, avoiding the eyes and lips.

The clinical pharmacology program had four clinical studies that evaluated the PK of oxymetazoline following topical application in subjects with moderate to severe erythema associated with rosacea. In addition, the Applicant conducted *in vitro* studies to evaluate the metabolism and explore the drug interaction potential of oxymetazoline. The Appendix of this review provides the Individual Study Summary of the clinical pharmacology studies. The primary focus of this Question-Based Review is on the assessment of the ADME properties of oxymetazoline that supported the clinical pharmacology information in the product labeling for RHOFADE.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 finds NDA 208552 acceptable and recommends approval of this NDA from a Clinical Pharmacology perspective.

1.2 Post-Marketing Commitments/Requirements

None

1.3 Summary of Clinical Pharmacology Findings

1.3.1. Pharmacokinetics

Following single dose and multiple doses topical administration of oxymetazoline HCl cream 0.5%, 1.0%, or 1.5%, daily (QD) or twice a day (BID) in subjects with moderate to severe facial erythema associated with rosacea, plasma oxymetazoline was measurable in most of the subjects. **Table 1.3.1** provides a summary of the PK parameters of oxymetazoline in Study 199201-002.

Table 1.3.1. PK parameters of oxymetazoline following topical administration of oxymetazoline HCl cream in subjects with moderate to severe facial erythema associated with rosacea in Study 199201-002. N represents the number of evaluable subjects in calculating $AUC_{0\text{-}24hr}$. Approximately a pea-sized amount of oxymetazoline cream 0.5%, 1.0%, 1.5%, or vehicle was applied QD or BID to cover the entire face of the subjects for 28 consecutive days. Plasma oxymetazoline concentrations over a 24 hours period were measured on Days 1 and 28. The mean weight of the 1.0% cream for each dose applied on Days 1, 2, 14, and 28 in the QD group ranged from 0.31 g to 0.37 g. The mean total weight of the two doses of 1.0% cream applied in the BID group on Days 1, 14, and 28 ranged from 0.70 g to 0.73 g. (*Source of data: Table 3, Summary of Clinical Pharmacology Studies; CSR 199201-002 Amd 1*)

Regimen	Strength	Day	T_{max} (hr)	C_{max} (pg/mL)	$AUC_{0\text{-}6hr}$ (pg.hr/mL)	$AUC_{0\text{-}24hr}$ (pg.hr/mL)
QD	0.5%	1 (N=37)	12	35.0±56.7	N/A	467±558
		28 (N=38)	6	41.5±30.0	N/A	590±518
	1.0%	1 (N=43)	12	60.5±53.9	N/A	895±798
		28 (N=41)	10	66.4±67.1	N/A	1050±992
	1.5%	1 (N=43)	10	68.5±54.6	N/A	1090±794
		28 (N=43)	8	98.0±79.5	N/A	1680±1430
BID	0.5%	1 (N=43)	6	20.6±11.1	49.9±40.8	563±357
		28 (N=40)	6	39.0±29.7	168±129	752±581
	1.0%	1 (N=45)	6	56.9±68.9	155±154	1400±1220
		28 (N=40)	4	68.8±61.1	311±252	1530±922
	1.5%	1 (N=45)	6	62.6±65.7	183±152	1740±942
		28 (N=40)	6	115±111	563±609	2660±2170

1.3.2. Metabolism and drug interactions

The following is a summary of oxymetazoline metabolism and drug interaction findings:

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

1.3.3. Pediatric studies

The Agency has agreed to the Applicant's full waiver request of the requirement to conduct studies in pediatric patients from 0 to 17 years of age (see *Advice Letter dated 07/18/2014*). Refer to the Agreed Initial Pediatric Study Plan under IND 107983.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is RHOFADE?

RHOFADE is a topical white to off-white cream. RHOFADE cream contains 1.0% (w/w) oxymetazoline HCl which is equivalent to 0.88% (w/w) oxymetazoline free base. Oxymetazoline is an alpha1A adrenoceptor agonist and acts as a vasoconstrictor.

2.1.2 What is the to-be-marketed formulation/product of RHOFADE?

The formulation composition of RHOFADE is presented in **Table 2.1.2**.

Table 2.1.2. The formulation composition of RHOFADE (oxymetazoline hydrochloride) cream, 1.0%.

Component	Function	Quality Standard	Concentration (% w/w)
Oxymetazoline HCl	Active	USP	1.0
Methylparaben	(b) (4)	NF	(b) (4)
Propylparaben		NF	
Phenoxyethanol		NF	
Sodium citrate dihydrate	(b) (4)	USP	
Citric acid anhydrous		USP	
Disodium edetate dihydrate		USP	
Butylated hydroxytoluene		NF	
Anhydrous lanolin		USP	
Medium chain triglycerides		NF	
Diisopropyl adipate		Non-compendial	
Oleyl alcohol		NF	
Polyethylene glycol 300		NF	
(b) (4) (PEG-6 stearate (and) Glycol stearate (and) PEG-32 stearate)		Non-compendial[a]	
Cetostearyl alcohol		NF	
(b) (4) (Ceteareth-6 (and) Stearyl alcohol)		Non-compendial	
(b) (4) (Ceteareth-25)		Non-compendial	
Purified water		USP	
			(b) (4)

2.1.3 What are the proposed indication and dosing regimen for RHOFADE?

The proposed indication is for the topical treatment of persistent facial erythema associated with rosacea in adults. The proposed dosing regimen is to apply a pea-sized amount once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin, avoiding the eyes and lips. RHOFADE is not for oral, ophthalmic or intravaginal use. Wash hands after application.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and pivotal clinical trials used to support the NDA for RHOFADE?

Clinical Pharmacology Studies:

The Clinical Pharmacology program of the NDA contains 4 clinical studies:

- **Phase 2 dose-ranging Study 199201-002**. Study 199201-002 provided PK data for oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% administered QD or BID for 28 days in subjects with moderate to severe facial erythema associated with rosacea. This study provided the PK information for the to-be-marketed formulation of oxymetazoline HCl cream, 1.0%. The dose-response results supported the selection of the 1.0% strength and the QD dosing regimen for Phase 3.
- **Relative bioavailability Studies V-101-ROSE-201 and V-101-ROSE-205**. Studies V-101-ROSE-201 and V-101-ROSE-205 compared the PK of oxymetazoline HCl cream (0.15% and 0.5%, respectively) to Afrin® nasal spray (0.05%).
- **Dermal tolerability Study 199201-001**. Study 199201-001 provided PK data for oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% applied BID in a split-face manner.

The Appendix of this review provides the individual study summary of these clinical pharmacology studies.

Phase 3 Efficacy and Safety Studies:

- **Pivotal Studies 199201-004 and 199201-005**. The two pivotal Phase 3 studies had identical study design that assessed the safety and efficacy of RHOADE (oxymetazoline HCl cream, 1.0%) for the treatment of persistent facial erythema associated with rosacea.
- **A long-term safety Study 199201-006**. Study 199201-006 was an open-label study to evaluate the long-term safety.

2.2.2 Have the Phase 3 pivotal trials demonstrated evidence of effectiveness? Do the Phase 2 dose-response results support the dose selection for Phase 3?

Yes. The overall Phase 3 efficacy results have demonstrated that oxymetazoline HCl cream, 1.0% is effective for the treatment of adult patients with persistent facial erythema associated with rosacea. The dose-response relationship for efficacy as observed in Phase 2 study provided supportive evidence of effectiveness and supported the dose selection for Phase 3.

Phase 3 efficacy results

Both pivotal Studies 199201-004 and 199201-005 demonstrated statistically significant treatment effect of oxymetazoline HCl cream, 1.0% compared with vehicle control (Table 2.2.2). In the Phase 3 studies, subjects applied oxymetazoline HCl cream, 1.0% or vehicle once daily for 29 days. Primary efficacy variables of 5-point Clinician Erythema Assessment (CEA) and 5-point Subject Self-Assessment for Rosacea Facial Redness (SSA) were measured over a 12-hour period at equally-spaced time-points (hours 3, 6, 9, and 12) post-dose on Days 1, 15, and 29. The primary efficacy endpoint was defined as the proportion of subjects with at least a 2-grade reduction in erythema (improvement) from baseline (pre-dose on Day 1) on both the CEA and SSA measured at hours 3, 6, 9, and 12 on Day 29.

Table 2.2.2. Proportion of subjects achieved at least 2-grade reduction on both primary efficacy endpoints CEA and SSA in Phase 3 Studies 199201-004 and 199201-005. $p<0.05$ between oxymetazoline HCl cream, 1.0% and vehicle across time-points of 3, 6, 9, and 12 hours on Day 29. CEA, Clinician Erythema Assessment; SSA, Subject Self-Assessment. *(Source of data: Table 16, Summary of Clinical Efficacy)*

Time (Hour)	Study 199201-004		Study 199201-005	
	oxymetazoline HCl cream, 1.0% (N = 222)	Vehicle Cream (N = 218)	oxymetazoline HCl cream, 1.0% (N = 224)	Vehicle Cream (N = 221)
3	12%	6%	14%	7%
6	16%	8%	13%	5%
9	18%	6%	16%	9%
12	15%	6%	12%	6%

Phase 2 dose-response results

The overall dose-response results supported the selection of oxymetazoline HCl cream, 1.0% daily dosing for Phase 3 testing which further supported the recommendation of the HCl cream, 1.0% daily dosing for the treatment of persistent facial erythema associated with rosacea. Study 199201-002 evaluated the safety and efficacy of oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% compared with placebo administered QD or BID (the same-day second dose was applied 6 to 10 hours after the first dose) for 28 days. The primary efficacy results on Day 28 (Figure 2.2.2) showed that:

- The BID dosing regimen did not provide improvement in treatment effect compared to QD dosing regimen;
- The higher strength of oxymetazoline HCl cream, 1.5% did not result in greater clinical response rates than oxymetazoline HCl cream, 1.0%. Oxymetazoline HCl cream, 1.0% showed the best efficacy results among the QD treatment groups.

  Overall, oxymetazoline HCl cream, 1.0% with the QD dosing regimen demonstrated acceptable safety and tolerability in both Phase 2 and Phase 3 studies (data not shown).

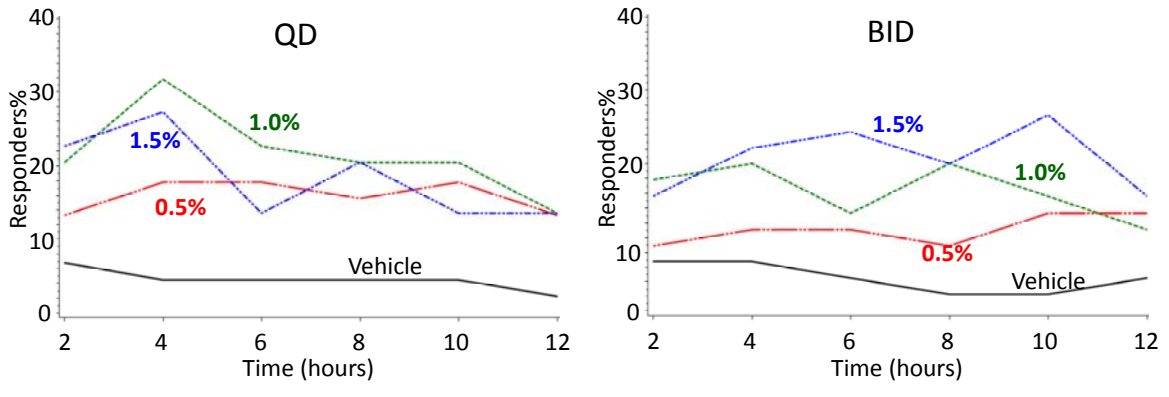


Figure 2.2.2. Proportion of subjects achieved 2-grade reduction on both primary efficacy endpoints CEA and SSA on Day 28 in Phase 2 Study 199201-002. *(Source of data: Figures 11-1 and*

11-2, CSR 199201-002)

2.2.3 What are the PK characteristics of the to-be-marketed oxymetazoline HCl cream 1.0% under maximal use conditions?

Study 199201-002 provided PK data for oxymetazoline HCl cream 0.5%, 1.0%, and 1.5% administered QD or BID for 28 days in subjects with moderate to severe facial erythema associated with rosacea under maximal use conditions. The PK results are shown in Table 1.3.1 (*Section 1.3.1*). The PK profiles for the oxymetazoline HCl cream, 1.0% QD treatment group are shown in Figure 2.2.3 and the results are further described below.

A total of 43 subjects completed the study in the 1.0% QD group. The median weight of study medication applied was 0.3 g per day. Oxymetazoline was measurable in most of the subjects. Following the first dose of oxymetazoline HCl cream 1.0%, the mean (± SD) C_{max} and $AUC_{0\text{-}24hr}$ was 60.5 (± 53.9) pg/mL and 895 (± 798) pg*hr/mL, respectively. After 28 consecutive days of once daily application, the mean (± SD) C_{max} and $AUC_{0\text{-}24hr}$ was 66.4 (± 67.1) pg/mL and 1050 (± 992) pg*hr/mL, respectively. Plasma concentrations of oxymetazoline were below the LLOQ of 10 pg/mL in all subjects on Day 35 (a week after the last dose applied on Day 28). Based on the trough plasma concentrations on Days 2 (24 hours after the dose on Day 1), 14, 28, and 29 (24 hours after the dose on Day 28), the systemic concentrations of oxymetazoline appear to have reached steady state by Day 2.

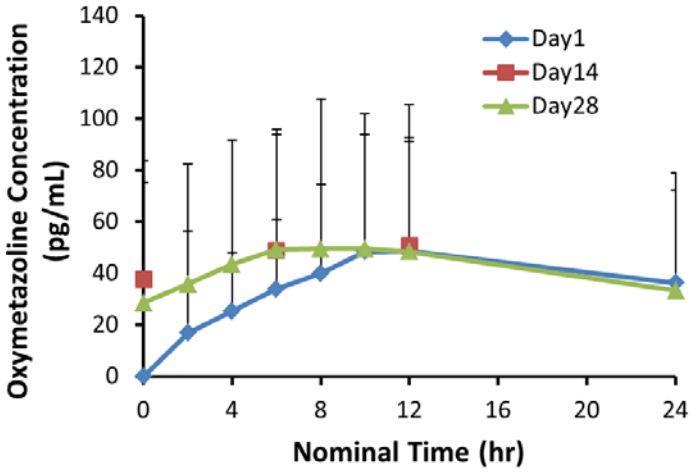


Figure 2.2.3. Plasma oxymetazoline concentration-time profiles following once daily application of oxymetazoline HCl Cream, 1.0% in Study 199201-002. Mean (+SD) plasma oxymetazoline concentrations on Day 1 (Blue diamond), Day 14 (dark red square), and Day 28 (green triangle) are presented. (*Source of Data: reviewer's plots*).

2.2.4 What information is submitted to assess or waive TQT trial?

At the time of End of Phase 2 meeting, the Applicant requested whether a thorough QT/QTc (TQT) study for RHOFADE could be waived. After review of the available data, the Agency agreed that a TQT study was not needed for RHOFADE for the treatment of erythema in patients with rosacea (*see Agency Advice Letter dated 03/05/2014*).

2.2.5 What are protein binding properties of oxymetazoline?

Oxymetazoline plasma protein binding was assessed *in vitro* using ultracentrifugation over the tested oxymetazoline concentration range of 1.8-439 ng/mL. The results showed the following:

- The fraction of protein bound oxymetazoline were 56.7-57.5% and 36.0-49.1%, respectively, in fresh Na_2EDTA human plasma and frozen K_2EDTA human plasma.
- The fraction of protein bound oxymetazoline was 23.5-26.1% in 600 µM human serum albumin and 20.5-31.2% in 25 µM human alpha1-acid glycoprotein.
- The fractions of protein bound oxymetazoline were concentration independent within the tested oxymetazoline concentration range of 1.8-439 ng/mL.

Additionally, the fraction of protein bound oxymetazoline was 4.3-25.0% in 50 mcg/mL synthetic melanin within the tested oxymetazoline concentration range of 1.29-5000 ng/mL.

2.2.6 What are the metabolites of oxymetazoline?

In vitro studies using incubation of [^{14}C]-oxymetazoline with human liver microsomes showed that oxymetazoline was metabolized and generated mono-oxygenated and dehydrogenated products of oxymetazoline. The percentage of parent drug oxymetazoline remaining was 95.9% after 120 minute incubation with human liver microsomes.

2.3 Drug Interactions

2.3.1 What are the effects of concomitant use of CYP2C19 inhibitors on the pharmacokinetics of RHOFADE?

An exploratory *post-hoc* analysis did not indicate an increase in oxymetazoline exposure in subjects who experienced co-administration of oral moderate CYP2C19 inhibitors in Study 199201-002.

In Study 199201-002, 17 subjects in the oxymetazoline HCl cream, 1.0% once daily dosing group had concomitant oral moderate CYP2C19 inhibitors (e.g., esomeprazole, fluoxetine, and omeprazole). The applicant compared dose-normalized steady-state $AUC_{0\text{-}24hr}$ of oxymetazoline in these 17 subjects with the 103 subjects who did not receive the concomitant CYP2C19 inhibitors. The results did not indicate an increase in oxymetazoline exposure associated with co-administration of oral moderate CYP2C19 inhibitors (Figure 2.3.1).

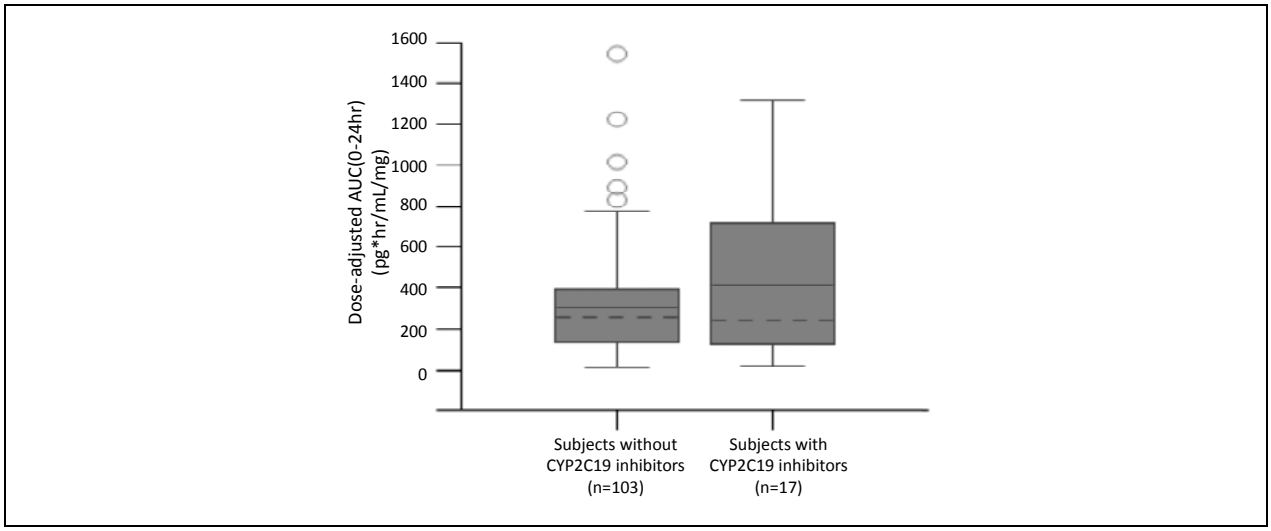


Figure 2.3.1. Dose adjusted oxymetazoline $AUC_{0\text{-}24hr}$ in subjects with and without concomitantly administered CYP2C19 inhibitors in Study 199201-002. (*Source of data: Figure 2, Summary of Clinical Pharmacology*)

2.3.2 Does RHOFADE inhibit CYP enzyme activity?

No, available *in vitro* study results did not suggest that RHOFADE has inhibitory effect on CYP enzyme activity.

The Applicant conducted *in vitro* studies using human liver microsomes to evaluate the inhibitory effect of oxymetazoline on CYP enzymes activity at oxymetazoline concentrations up to 100 nM (450-fold higher than the observed mean oxymetazoline C_{max} of 66.4 pg/mL or 0.26 nM in Study 199201-002). The results did not show significant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 activity (Table 2.3.2).

Enzyme	Substrate	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		30-minute preincubation with NADPH		Potential for metabolism-dependent inhibition [c]
		IC_{50} (nM) [a]	Inhibition observed at 100 nM (%) [b]	IC_{50} (nM) [a]	Inhibition observed at 100 nM (%) [b]	IC_{50} (nM) [a]	Inhibition observed at 100 nM (%) [b]	
CYP1A2	Phenacetin	> 100	NA	> 100	NA	> 100	1.1	No
CYP2B6	Efavirenz	> 100	NA	> 100	NA	> 100	NA	No
CYP2C8	Amodiaquine	> 100	NA	> 100	1.2	> 100	0.80	No
CYP2C9	Diclofenac	> 100	NA	> 100	NA	> 100	NA	No
CYP2C19	*S*-Mephenytoin	> 100	NA	> 100	NA	> 100	4.4	No
CYP2D6	Dextromethorphan	> 100	6.6	> 100	3.9	> 100	7.1	No
CYP3A4/5	Testosterone	> 100	NA	> 100	NA	> 100	NA	No
CYP3A4/5	Midazolam	> 100	NA	> 100	2.1	> 100	4.9	No

Table 2.3.2. Summary of in vitro evaluation of oxymetazoline as an inhibitor of CYP enzymes. (*Source of data: Table 3, PK report for Protocol XT135125*)

2.3.3 Does RHOFADE cause induction of CYP enzyme expression?

No, available *in vitro* study results did not suggest that RHOFADE causes induction of CYP enzyme expression.

The Applicant conducted *in vitro* studies to investigate the effects of treating primary cultures of cryopreserved human hepatocytes with oxymetazoline on the expression of CYP enzymes. The results showed the following:

- Positive control CYP inducers omeprazole, phenobarbital, and rifampin resulted in 27.6- to 69.9-fold, 10.2- to 22.4-fold, and 10.2- to 42.0-fold increases in CYP1A2, CYP2B6, and CYP3A4 mRNA levels, respectively (Figure 2.3.3).
- Oxymetazoline did not cause increase in CYP1A2, CYP2B6, or CYP3A4 mRNA expression (Figure 2.3.3).

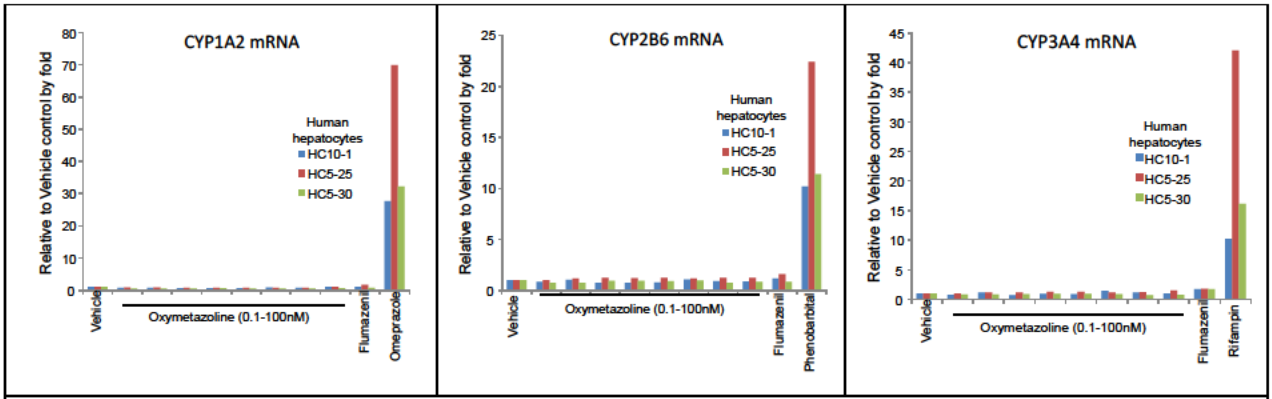


Figure 2.3.3. Effect of treating primary cultures of cryopreserved human hepatocytes with oxymetazoline on the expression of CYP enzymes in vitro. Three cryopreserved preparations of cultured human hepatocytes from three separate livers were treated once daily for three consecutive days with vehicle control dimethyl sulfoxide (DMSO, 0.1% v/v), negative control flumazenil (25 µM), oxymetazoline (0.1, 1, 2.5, 5, 10, 25, 50, and 100 nM) or one of three known human CYP inducers, namely, omeprazole (50 µM), phenobarbital (750 µM) and rifampin (20 µM) as positive control. The CYP1A2, CYP2B6, and CYP3A4 mRNA levels were analyzed by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). (*Source of data: reviewer's plot based on study report for XT133138*)

2.4 Biopharmaceutics and Bioanalytical Methods

2.4.1 What bioanalytical assays were used for measurement of the active moieties in the clinical studies to characterize the PK of oxymetazoline? Was the bioanalytical method validated? Briefly describe the performance of the bioanalytical methods.

The plasma oxymetazoline concentrations were measured using a high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS). The LC-MS/MS assays detected total drug concentrations. The LC-MS/MS assays have been validated to support the clinical PK studies of oxymetazoline. A brief summary of the assays associated with the clinical PK studies is shown in Table 2.4.1.a. The assay validation results are summarized in Table 2.4.1.b.

Table 2.4.1.a. Bioanalytical methods and validation reports associated with the clinical studies for characterization of the PK of oxymetazoline. *Note: Oxymetazoline had a company code AGN-199201 during the drug development.* (*Source of data: Table 1, Summary of Biopharmaceutics and Associated analytical methods*)

Validation Report Number	Clinical Study Number	Matrix	Bioanalytical Method	Assay Range (pg/mL)		Analyte	Validated	Stability
				Lower LOQ	Upper LOQ			
8223793 8223793-A1	V-101-ROSE-201 V-101-ROSE-205	Plasma	LC-MS/MS	25	2500	AGN-199201	Yes	249 days (-10°C to -30°C)
AN12001-BM AN12001-BM-A1	199201-001 199201-002	Plasma	LC-MS/MS	10	1000	AGN-199201	Yes	109 days (-60°C to -80°C)

Table 2.4.1.b. The assay validation results of the LC-MS/MS bioanalytical method used for measuring plasma oxymetazoline concentrations in clinical studies 199201-001 and 199201-002.
*Storage stability: Upon the Agency's Information Request, in the review cycle the Applicant submitted a Final Report Addendum No.2 (AN12001-BM-A2) which established a long-term stability of oxymetazoline in human plasma at conditions of both -10 to -30°C and -60 to -80°C for 578 days

(comparing to the 109 days reported in Table 2.4.1.a). [§]The precision and accuracy was calculated by the reviewer.

Parameter	Assay validation results
Matrix	K_2EDTA Plasma
Standard curve Assay range	10-1000 pg/mL
Intra-run precision[§]	0.3% to 8.0%
Intra-run accuracy[§]	-4.0% to 8.4%
Inter-run precision[§]	1.9% to 6.2%
Inter-run accuracy[§]	-2.3% to 3.1%
Freeze/thaw matrix stability	5 cycles at -10 to -30°C; 5 cycles at -60 to -80°C
Room temperature stability	24 hours
Processed-sample viability	287 hours at 2 to 8°C
Long term stability*	578 Days at -10 to -30°C; 578 Days at -60 to -80°C
Incurred sample reanalysis (ISR)	Three hundred and twenty-eight study samples (approximately 6.3% of the total samples, at least two samples per subject) were selected for ISR. The results showed that 93% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).

2.5 Specific populations

2.5.1 Pediatric subjects

The safety and effectiveness of RHOFADE in pediatric subjects have not been evaluated. The Applicant requested a full waiver of the requirement to conduct studies in pediatric patients from 0 to 17 years of age. The Agency has agreed to the Applicant's request according to the agreed initial pediatric study plan (Agreed iPSP) under IND 107983 (*Advice Letter dated 07/18/2014*). It is noted that the number of pediatric subjects with rosacea is too small and to conduct pediatric studies with RHOFADE is impractical.

3 Detailed Labeling Recommendations

The following changes are recommendations for sections 12 of the label for RHOFADE Cream, 1.0% at the time of completion of this review. Deletions are noted as ~~strikethrough~~ and additions are noted as double underlines.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption

(b) (4)

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

Distribution

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

Metabolism

In vitro studies using human (b) (4) liver microsomes showed that oxymetazoline was minimally metabolized, generating (b) (4) mono-(b) (4) oxygenated, and dehydrogenated products of oxymetazoline. The percentage of parent drug oxymetazoline remaining was 95.9% after 120 minute incubation with human liver microsomes. (b) (4)

Excretion

(b) (4)

(b) (4)

The excretion of oxymetazoline has not been characterized.

Drug Interaction

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

4 Appendix: Individual Study Summary

4.1 Study 199201-002

Title: Oxymetazoline HCl Cream for the Treatment of Erythema Associated with Rosacea

Studied period:

Study Initiation Date (First Patient Enrolled): 20 December 2012

Study Completion Date (Last Patient Completed): 03 June 2013

Objectives:

To evaluate the safety and efficacy of oxymetazoline cream 0.5%, 1.0%, and 1.5%, once daily (QD) and twice-daily (BID) topical application compared to vehicle for 28 consecutive days for the treatment of patients with moderate to severe facial erythema associated with rosacea.

Study design:

This was a multicenter, randomized, double-blind, parallel-group, vehicle-controlled study. There were 8 study visits: screening (days -30 to -2), randomization (day 1), treatment period visits (days 2, 14, and 28), follow-up (days 29 and 35), and exit (day 56). Eligible patients were randomized to receive 1 of 8 treatment groups as shown below in a 1:1:1:1:1:1:1:1 ratio for 28 consecutive days.

- Group 1 Oxymetazoline HCl, 0.5% QD
- Group 2 Oxymetazoline HCl, 1.0% QD
- Group 3 Oxymetazoline HCl, 1.5% QD
- Group 4 Vehicle QD
- Group 5 Oxymetazoline HCl, 0.5% BID
- Group 6 Oxymetazoline HCl, 1.0% BID
- Group 7 Oxymetazoline HCl, 1.5% BID
- Group 8 Vehicle BID

PK samplings:

PK blood samples were collected into tubes containing K_2EDTA to prepare plasma samples at the following time-points:

- Days 1 and 28: Pre-dose, 2, 4, 6 (before evening dose for BID groups), 8, 10, and 12 hours after the morning dose ;
- Day 14: Pre-dose, 6 (before evening dose for BID groups) and 12 hours after morning dose.
- Days 2, 29, and 35 (a week after the last dose administration): Pre-dose.

The plasma samples were stored at -20°C or below until analyzed.

Number of subjects (planned and analyzed):

Approximately 360 patients were planned to be enrolled at approximately 15 sites in the United States. A total of 357 patients were enrolled and randomized into the study. A majority of patients (95.2%, 339 out of 356) completed the study. Patient allocation to each treatment group and their subsequent disposition is summarized in **Table 4.1.1**.

Table 4.1.1. Patient allocation and their subsequent disposition in Study 199201-002. Oxy, oxymetazoline HCl. (*Source of data: Table 10-1, CSR 199201-002 Amendment 1*)

Dosing Groups	Disposition	Oxy 0.5%	Oxy 1.0%	Oxy 1.5%	Total Oxy	Vehicle	Total
QD	Enrolled	45	44	44	133	44	177
	Completed	42	43	44	129	42	171
BID	Enrolled	45	45	45	135	44	179
	Completed	44	40	42	126	42	168

Main criteria for inclusion:

Male or female patients 18 years of age or older with moderate to severe facial erythema associated with rosacea defined as a grade of ≥ 3 on the Clinician Erythema Assessment (CEA) scale with photonumeric guide as assessed by the investigator and either "more redness than I prefer" or "completely unacceptable redness" on the Subject Self-Assessment (SSA) scale as assessed by the patient, and stable facial erythema associated with rosacea with minimal variation from day to day and within each day, in the opinion of the patient.

Test product, dose and mode of administration, batch number:

The patients were to apply approximately a pea size amount (approximately 0.5 grams) of study medication (oxymetazoline cream 0.5%, 1.0%, 1.5%, or vehicle) onto the erythematous area of the face, gently spreading the study medication to thinly cover the entire face, once or twice daily, based on the randomization assignment, for 28 consecutive days. Patients were instructed to wash their hands before and after each application of study medication. Patients assigned to the QD groups (group 1, 2, 3, or 4) were to apply study medication in the morning each day. Patients assigned to the BID groups (group 5, 6, 7, or 8) were to apply study medication in the morning and a second dose approximately 6 to 10 hours later. On days 1, 2 (morning dose only), 14, and 28, all patients were instructed to apply the study medication at the clinic. Patients in the BID dosing groups applied the second dose 6 hours after the morning dose.

The formulation and batch numbers of the medications used in this study are shown in the **Table 4.1.2** below.

Table 4.1.2. Formulation and batch numbers of the cream products used in Study 199201-002. (*Source of data: section 9.4.2 of CSR 199201-002 Amendment 1*)

Medication	Formulation No.	Batch No.
Oxymetazoline HCl, 0.5%	11007X	EHC-C
Oxymetazoline HCl, 1.0%	11008X	EHD-C
Oxymetazoline HCl, 1.5%	11009X	EHE-C
Vehicle	11006X	EHB-C

Bioanalytical methods:

The plasma samples were analyzed using a validated high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantitation (LLOQ) of 10 pg/mL. See more details in section 2.4.1 of this review.

Results:

Treatment: weight of formulation applied

The weight of medication applied at clinical sites is shown in **Table 4.1.3**. Across the once-daily groups, the mean weight of study medication applied ranged from 0.33 to 0.37 g. Across the twice-daily groups, the mean weight of study medication (the sum of two BID doses within a day) applied on days 1, 14, and 28 were 0.81 g, 0.68 g, and 0.67 g, respectively.

Table 4.1.3. Exposure to study treatment measured as weight of medication applied at the clinic in Study 199201-002. Data are presented as mean ± SD (number of subjects measured). (*Source of data: Table 14.3-1.3 of CSR 199201-002 Amendment 1*)

	Day	Vehicle	0.5%	1.0%	1.5%	All Groups
QD	1	0.33 ± 0.15 (43)	0.4 ± 0.2 (45)	0.37 ± 0.17 (44)	0.33 ± 0.15 (42)	0.37 ± 0.18 (131)
	2	0.31 ± 0.2 (43)	0.31 ± 0.13 (45)	0.35 ± 0.23 (44)	0.36 ± 0.19 (44)	0.34 ± 0.19 (133)
	14	0.39 ± 0.38 (42)	0.36 ± 0.18 (42)	0.32 ± 0.16 (43)	0.32 ± 0.15 (44)	0.34 ± 0.16 (129)
	28	0.34 ± 0.3 (42)	0.34 ± 0.15 (41)	0.31 ± 0.16 (43)	0.34 ± 0.16 (43)	0.33 ± 0.15 (127)
BID	1	0.72 ± 0.35 (44)	0.92 ± 1.08 (44)	0.73 ± 0.36 (44)	0.78 ± 0.86 (44)	0.81 ± 0.82 (132)
	2[a]	0.31 ± 0.17 (43)	0.36 ± 0.25 (45)	0.29 ± 0.12 (45)	0.33 ± 0.18 (44)	0.33 ± 0.19 (134)
	14	0.7 ± 0.32 (40)	0.7 ± 0.51 (42)	0.72 ± 0.38 (39)	0.64 ± 0.25 (40)	0.69 ± 0.4 (121)
	28	1.35 ± 4.46 (42)	0.67 ± 0.37 (42)	0.7 ± 0.3 (40)	0.64 ± 0.3 (40)	0.67 ± 0.32 (122)

[a]Weight of study medication applied for the first dose only.

Demographics:

The modified intent-to-treat (mITT) population was used for PK analysis. The age and gender information from all treatment groups is shown in **Table 4.1.4.** The mean age of the patients was 50.0 years (range 19 to 79 years). There were more females than males (80.1% versus 19.9%), and the majority of the population was Caucasian (91.3%).

Table 4.1.4. Demographics of subjects (mITT population) in Study 199201-002 (*Source of data: Table 14.1-2.1 of CSR 199201-002 Amendment 1*).

Dosing groups	N	Age, yrs (Mean (SD))	No. of Male/Female
Vehicle QD	44	50.2 (11.3)	6/38
Oxymetazoline HCl, 0.5% QD	45	49.6 (10.4)	10/35
Oxymetazoline HCl, 1.0% QD	44	51.3 (12.1)	9/35
Oxymetazoline HCl, 1.5% QD	44	51.2 (11.0)	11/33
Vehicle BID	44	53.0 (13.2)	11/33
Oxymetazoline HCl, 0.5% BID	45	48.1 (10.6)	4/41
Oxymetazoline HCl, 1.0% BID	45	51.0 (10.8)	11/34
Oxymetazoline HCl, 1.5% BID	45	45.9 (12.8)	9/36

Oxymetazoline pharmacokinetics:

Oxymetazoline was measurable in most of the subjects. The plasma oxymetazoline concentration-time profiles are shown in **Figure 4.1.1**. The PK parameters of oxymetazoline are summarized in **Table 4.1.5**. The PK results showed the following:

- Following the first dose of oxymetazoline HCl cream 1.0%, the mean (± SD) C_{max} and $AUC_{0\text{-}24hr}$ was 60.5 (± 53.9) pg/mL and 895 (± 798) pg*hr/mL, respectively.
- After 28 consecutive days of once daily applications, the mean (± SD) C_{max} and $AUC_{0\text{-}24hr}$ was 66.4 (± 67.1) pg/mL and 1050 (± 992) pg*hr/mL, respectively.
- For both QD and BID dosing regimen, systemic exposure ($AUC_{0\text{-}24hr}$) of oxymetazoline increased as the dose strength increased from 0.5% to 1.5% on Day 28.
- Oxymetazoline $AUC_{0\text{-}24hr}$ accumulated approximately 2-fold (QD groups) or less than 2-fold (BID groups) following 28 days of treatment.
- Based on the values of trough level concentrations on Days 2 (24 hours after the dose on Day 1), 14, 28, and 29 (24 hours after the dose on Day 28), the systemic concentrations of oxymetazoline appear to have reached steady state by Day 2 for both QD and BID applications (**Figure 4.1.2**).
- Plasma concentrations of oxymetazoline were below the LLOQ (10 pg/mL) in a majority of the subjects on Day 35 (7 days after the last dose applied on Day 28).

Table 4.1.5. PK parameters (mean ± SD) of oxymetazoline following 28 consecutive days of once daily (QD) or twice daily (BID) applications of 0.5%, 1.0%, or 1.5% oxymetazoline HCl cream in Study 199201-002. [a]T_{max} is presented as median (range). Note: On Days 1, 14, and 28, subjects in the BID groups applied the second dose 6 hours after the first dose; and on other days, the subjects were instructed to apply the cream in the morning and a second dose approximately 6 to 10 hours later. T_{max}, C_{max}, and $AUC_{0\text{-}6hr}$ in the BID group were calculated using data prior to administration of the second dose on that day. (*Source of data: Table 3, Summary of Clinical Pharmacology Studies; CSR 199201-002 Amd 1*)

Regimen	Strength	Day	T_{max} (hr)[a]	C_{max} (pg/mL)	$AUC_{0\text{-}6hr}$ (pg.hr/mL)	$AUC_{0\text{-}24hr}$ (pg.hr/mL)
QD	0.5%	1	12 (4, 24)	35.0±56.7	N/A	467±558
		28	6 (0, 24)	41.5±30.0	N/A	590±518
	1.0%	1	12 (2, 24)	60.5±53.9	N/A	895±798
		28	10 (0, 24)	66.4±67.1	N/A	1050±992
	1.5%	1	10 (4, 24)	68.5±54.6	N/A	1090±794
		28	8 (0, 24)	98.0±79.5	N/A	1680±1430
BID	0.5%	1	6 (2, 6)	20.6±11.1	49.9±40.8	563±357
		28	6 (0, 6)	39.0±29.7	168±129	752±581
	1.0%	1	6 (4, 6)	56.9±68.9	155±154	1400±1220
		28	4 (0, 6)	68.8±61.1	311±252	1530±922
	1.5%	1	6 (4, 6)	62.6±65.7	183±152	1740±942
		28	6 (0, 6)	115±111	563±609	2660±2170

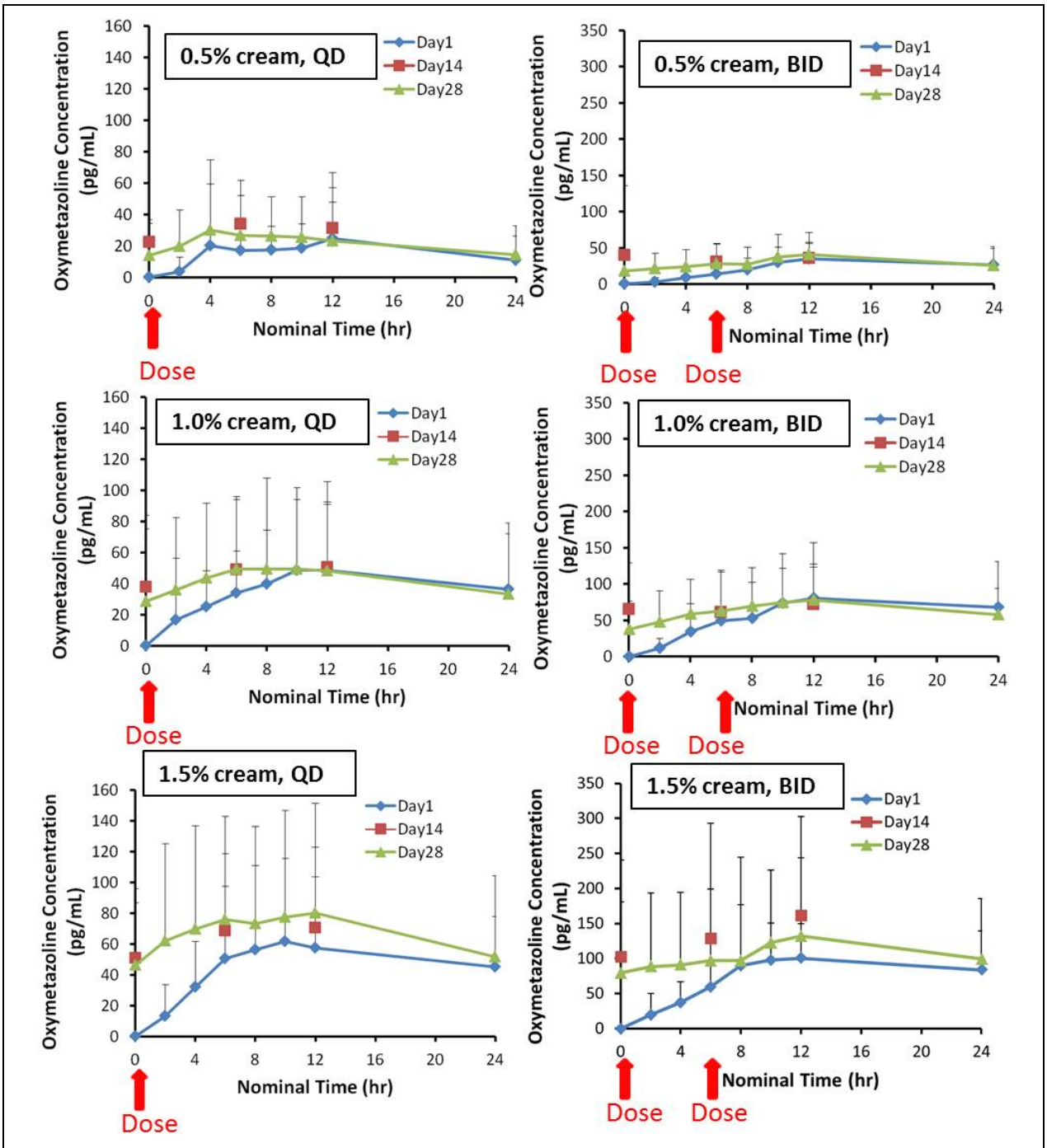


Figure 4.1.1. Plasma oxymetazoline concentration-time profiles following 28 consecutive days of once daily (QD, left panel) or twice daily (BID, right panel) applications of 0.5%, 1.0%, or 1.5% oxymetazoline HCl cream in Study 199201-002. Mean (+SD) data from Day 1 (Blue diamond), Day 14 (dark red square), and Day 28 (green triangle) are presented (data were plotted by the reviewer using PK analysis dataset provided by the Applicant). On Days 1, 14, and 28, subjects in the BID groups applied the second dose 6 hours after the first dose; and on other days, the subjects were instructed to apply the cream in the morning and a second dose approximately 6 to 10 hours later.

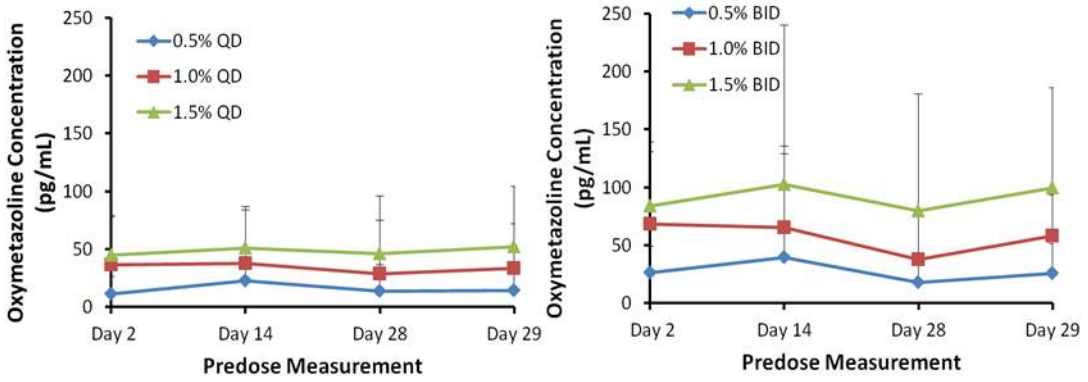


Figure 4.1.2. Pre-dose plasma oxymetazoline concentrations following 28 consecutive days of once daily (QD, left panel) or twice daily (BID, right panel) applications of 0.5%, 1.0%, or 1.5% oxymetazoline HCl cream in Study 199201-002. Mean (+SD) data from strengths of 0.5% (Blue diamond), 1.0% (dark red square), and 1.5% (green triangle) are presented (data were plotted by the reviewer using PK analysis dataset provided by the Applicant).

Drug-drug interaction potential evaluation: impact of CYP2C19 inhibitors

A subset of 17 subjects in the oxymetazoline QD dosing groups were on concomitant medications categorized as moderate CYP2C19 inhibitors, such as esomeprazole, fluoxetine, and omeprazole. The dose-adjusted $AUC_{0\text{-}24hr}$ values on Day 28 in these 17 patients who received once-daily treatment with topical oxymetazoline HCl cream concomitantly with oral moderate CYP2C19 inhibitors were within the range of the $AUC_{0\text{-}24hr}$ values observed in those patients who did not receive concomitant CYP2C19 inhibitors (**Figure 2.3.1**).

4.2 Study V-101-ROSE-201

Reviewer's note: *Oxymetazoline had a company code of V-101 previously. The oxymetazoline topical cream was referred to as V-101 (Oxymetazoline) Cream. This study evaluated the topical cream at 0.15% which is lower than the to-be-marketed strength of 1.0% for RHOFADE.*

Title: A Single-center, Two-way Crossover Relative Bioavailability Study of V-101 Cream 0.15% Administered Topically and Oxymetazoline HCl Solution (Afrin®) 0.05% Administered Intranasally to Subjects with Moderate to Severe Erythematous Rosacea.

Studied period:

Study Initiation (First Subject Enrolled): 5 May 2010
Study Completion (Last Subject Completed): 9 June 2010

Objectives:

To assess the relative bioavailability of V-101 cream 0.15% and oxymetazoline nasal spray 0.05% under conditions of maximum use, to evaluate the safety of V-101 cream 0.15% administered topically to the face, and to evaluate the correlation of the SSA scale with the CEA scale and chromameter readings in male and female subjects with moderate to severe erythematous rosacea.

Study design:

Single-center, double-blind, randomized, two-way crossover study. After screening, enrolled subjects had 2 treatment visits to receive Treatment A or B, separated by a washout period of 7 to 21 days.

- Treatment A: one 0.5 g facial application of V-101 cream 0.15% (0.75 mg oxymetazoline) plus 3 sprays of control (normal saline) nasal spray (0.1 mL/spray) in each nostril
- Treatment B: one 0.5 g facial application of vehicle cream plus 3 sprays of oxymetazoline nasal spray 0.05% in each nostril

Number of subjects (planned and analyzed):

Approximately 20 adult subjects with moderate to severe erythematous rosacea (10 per treatment sequence) were planned and 22 were randomized; and 19 (86%) received both treatments and completed the study.

Diagnosis and main criteria for inclusion:

Diagnosis: Erythematous rosacea

Main Inclusion Criteria: Males and females age ≥ 18 years in good general health with a clinical diagnosis of stable erythematous rosacea, SSA and CEA scores of > 3, ≤ 3 inflammatory lesions (papules and/or pustules) within the treatment area.

Test product, dose and mode of administration, batch number:

V-101 (oxymetazoline) cream 0.15% (lot B10021) was applied topically to the face by a site staff member at a dose of 0.5 g after the subject received the assigned nasal spray.

Duration of treatment:

The study included 2 treatments separated by a washout period of 7 to 21 days. Treatment A was V-101 cream 0.15% and control saline nasal spray. Treatment B was vehicle cream and oxymetazoline nasal spray 0.05%.

Reference therapy, dose and mode of administration, batch number:

Vehicle cream (lot b10020) was applied topically to the face by a site staff member at a dose of 0.5 g after the subject received the assigned nasal spray. Oxymetazoline nasal spray 0.05% (Afrin® Original Pump Mist) or control nasal spray (Ocean® Premium Saline Nasal Spray) were administered by the subject as 3 sprays to each nostril before the assigned cream was applied.

PK evaluation:

Pharmacokinetics and relative bioavailability were to be evaluated based on quantitation of oxymetazoline levels from blood samples collected in sodium heparin containing tubes at each treatment visit pre-dose and at 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose.

Bioanalytical methods:

Oxymetazoline in human plasma treated with sodium heparin anticoagulant was measured using a high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection following solid-phase extraction. A summary of results are shown in **Table 4.2.1**.

Table 4.2.1. Summary of performance of the plasma oxymetazoline assay used in Study V-101-ROSE-201. [§]The precision and accuracy was calculated by the reviewer.

Parameter	Oxymetazoline
Assay range	25.0-2500 pg/mL
Intra-run precision[§]	0.5% to 8.2% for quality controls; 7.0% to 16.8% for LLOQ
Intra-run accuracy[§]	-14.6% to 10.3%
Inter-run precision[§]	1.0% to 4.3%
Inter-run accuracy[§]	-3.0% to 2.7%
Freeze/thaw matrix stability	4 cycles at -10 to -30°C
Room temperature stability	28 hours
Reinjection reproducibility	125 hours at 2 to 8°C
Long term stability	249 Days at -10 to -30°C

Results:

Demographics: All subjects were Caucasian and the majority (86%) were female. Age ranged from 18 to 62 years with an average of 43 years.

Oxymetazoline pharmacokinetics:

All oxymetazoline concentration values following treatment with V-101 cream 0.15% and control nasal spray were below the LLOQ of 25 pg/mL, except for a single value in one subject at 6 hours post-dose with a concentration value of 98.6 pg/mL.

Following treatment with the vehicle cream and oxymetazoline nasal spray 0.05%, oxymetazoline was measurable. The plasma oxymetazoline concentration-time profile is shown in **Figure 4.2.1**. The PK parameters of oxymetazoline are summarized in **Table 4.2.2**.

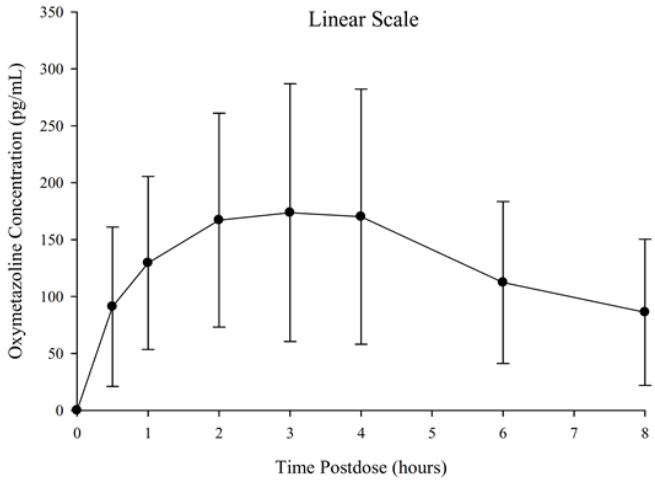


Figure 4.2.1. Mean (±SD) plasma concentration-time profiles for oxymetazoline following administration of V-101 cream vehicle plus Oxymetazoline Nasal Spray 0.05% (Treatment B) in study V-101-ROSE-201. *(Source of data: Figure 1, Final Pharmacokinetic Report of V-101-ROSE-201)*

Table 4.2.2. Summary of the mean (SD) PK parameters of oxymetazoline following administration of V-101 cream vehicle plus Oxymetazoline Nasal Spray 0.05% (Treatment

B) in study V-101-ROSE-201 *(Source of data: Table 1, Final Pharmacokinetic Report of V-101-ROSE-201)*.

C_{max} (pg/mL)	N	T_{max}[a] (hr)	N	AUC_{0-t} (pg*hr/mL)	N	$AUC_{0-\infty}$ (pg*hr/mL)	N	λ_Z (1/hr)	N	$t_{½}$ (hr)	N
206 (106)	19	3.17 (1.15, 6.00)	19	1098 (584)	19	1414 (667)	6	0.227 (0.074)	6	3.27 (0.78)	6

[a] Median (Min, Max).
N = Number of observations.
Notes: Treatment B: One 0.5 g topical facial application of V−101 cream vehicle plus 3 sprays (0.1 mL/spray) of Afrin Pump Mist Original (0.05% oxymetazoline) nasal spray (50 µg oxymetazoline/spray) in each nostril (total of 0.6 mL/0.3 mg oxymetazoline).
PK parameters for Treatment A could not be calculated since most concentration values were BLQ.

4.3 Study V-101-ROSE-205

Reviewer's note: *The oxymetazoline had a company code of V-101 previously. The oxymetazoline topical cream was referred to as V-101 (Oxymetazoline) Cream. This study evaluated the topical cream at 0.50% which is lower than the to-be-marketed strength of 1.0% for RHOFADE.*

Title: A Single-center, Two-way Crossover Relative Bioavailability Study of V-101 (Oxymetazoline) Cream 0.50% Administered Topically and Oxymetazoline HCl Solution (Afrin®) 0.05% Administered Intra-nasally to Subjects with Moderate to Severe Erythematous Rosacea.

Studied period:

Study Initiation (First Subject Enrolled): 12 April 2011

Study Completion (Last Subject Completed): 12 May 2011

Objectives: To assess the relative bioavailability of V-101 cream 0.50% and oxymetazoline nasal spray 0.05% under conditions of maximum use and to evaluate the safety of V-101 cream 0.50% administered topically to the face in male and female subjects with moderate to severe erythematous rosacea under maximum use conditions.

Study design: This is a double-blind, randomized, 2-way crossover study. Enrolled subjects had 2 treatment visits to receive Treatment A or B, separated by a washout period of 6 to 21 days.

- Treatment A: one 0.5 g facial application of V-101 cream 0.50% (2.5 mg oxymetazoline) plus 3 sprays of control (normal saline) nasal spray (0.1 mL/spray) in each nostril
- Treatment B: one 0.5 g facial application of vehicle cream plus 3 sprays of oxymetazoline nasal spray 0.05% in each nostril (50 µg oxymetazoline/spray × 6 sprays = 0.3 mg oxymetazoline)

Number of subjects (planned and analyzed): Approximately 28 adult subjects with moderate to severe erythematous rosacea (14 per treatment sequence) were planned. A total of 28 subjects were randomized. All subjects (100%) received both treatments and completed the study.

Diagnosis and main criteria for inclusion:

Diagnosis: Moderate to severe erythematous rosacea

Main Inclusion Criteria: Males and females age ≥ 18 years in good general health with a clinical diagnosis of erythematous rosacea, SSA and CEA scores of ≥ 3, ≤ 3 inflammatory lesions (papules and/or pustules) within the treatment area.

Test product, dose and mode of administration, batch number:

V-101 (oxymetazoline) cream 0.50% (lot B10013) was applied topically to the face by a site staff member at a dose of 0.5 g after the subject administered the assigned nasal spray.

Duration of treatment:

The study included 2 treatments separated by a washout period of 6 to 21 days. Treatment A was V-101 cream 0.50% and control saline nasal spray. Treatment B was vehicle cream and oxymetazoline nasal spray 0.05%.

Reference therapy, dose and mode of administration, batch number:

Vehicle cream (lot B10020) was applied topically to the face by a site staff member at a dose of 0.5 g after the subject administered the assigned nasal spray.

Oxymetazoline nasal spray 0.05% (Afrin® Original Pump Mist) or control nasal spray (Ocean® Premium Saline Nasal Spray) was administered by the subject as 3 sprays to each nostril before the assigned cream was applied.

PK evaluation:

Pharmacokinetics and relative bioavailability were to be evaluated based on quantitation of oxymetazoline levels from blood samples collected at each treatment visit at 0 (just prior to the study medication dose), 1, 2, 3, 4, 6, 9, and 12 hours post-dose.

Bioanalytical methods:

The bioanalytical method used in study V-101-ROSE-201 was used to analyze the PK samples in this study. Forty-five study samples (approximately 10% of the total samples, 1-3 samples per subject) were selected for incurred sample reanalysis. The results showed that 98% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value). Storage stability in a freezer set to maintain -10 to -30°C for 249 days was established. This duration provided sufficient stability for the storage of the study samples. See more details about the method validation in **Table 4.2.1**.

Results:

Demographics: All subjects were Caucasian and the majority (68%) were female. Age ranged from 22 to 63 years with an average of 42.7 years.

Oxymetazoline pharmacokinetics:

The plasma oxymetazoline concentration-time profile is shown in **Figure 4.3.1**. The PK parameters of oxymetazoline are summarized in **Table 4.3.1**. The PK results showed the following:

- The majority of oxymetazoline concentrations following treatment with V-101 cream 0.50% and control nasal spray were below the LLOQ of 25 pg/mL.

- The mean C_{max} (n=14) and AUC_{0-t} (N = 3) following treatment with V-101 cream 0.50% and control nasal spray were 34.7 pg/mL and 295 pg·hr/mL respectively.
- Following treatment with vehicle cream and oxymetazoline nasal spray 0.05%, the mean(±SD) C_{max}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$ of oxymetazoline were 245 (±109) pg/mL, 1741(±846) pg*hr/mL, and 1859 (±871) pg*hr/mL, respectively.

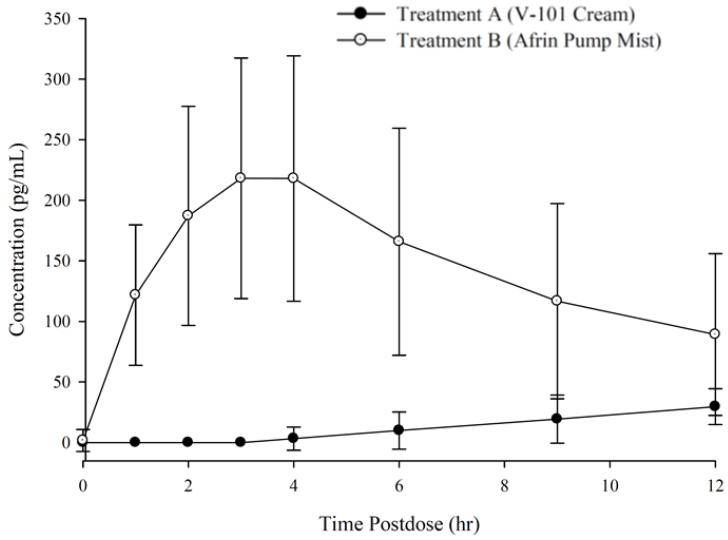


Figure 4.3.1. Figure 6. Mean (±SD) plasma concentration-time profiles for oxymetazoline in Treatments A (V-101 Cream, 0.50%) and B (Oxymetazoline Nasal Spray 0.05%) in study V-101-ROSE-205. *(Source of data: Figure 1, Final Pharmacokinetic Report of V-101-ROSE-205)*

Table 4.3.1. Summary of the PK parameters of oxymetazoline in Treatments A (V-101 Cream, 0.50%) and B (Oxymetazoline Nasal Spray 0.05%) in study V-101-ROSE-205 *(Source of data: Table 1, Final Pharmacokinetic Report of V-101-ROSE-205)*.

Dose	Amount Applied (Dose of Oxy)	Route	Mean (SD) Pharmacokinetic Parameter			
			C_{max} (pg/mL)	T_{max}[a] (hr)	$AUC_{0-tlast}$ (pg•hr/mL)	$T_{1/2}$ (hr)
Oxymetazoline HCl cream 0.5% applied topically	0.5 g (2.5 mg)	Dermal	34.7[b] (9.8)	12.0 (6.00, 12.1)	295[c] (81)	NC
Oxymetazoline HCl solution 0.05% (Afrin) administered as a nasal spray	0.6 mL[d] (0.3 mg)	Intranasal	245 (109)	3.00 (1.00, 6.02)	1741 (846)	4.99 (1.00)

$AUC_{0-tlast}$ = area under the concentration-time curve from time 0 to last observation, C_{max} = maximum observed plasma concentration, NC = not calculable, Oxy = oxymetazoline, SD = standard deviation, $T_{1/2}$ = half-life, T_{max} = time to maximum observed plasma concentration

[a] Presented as median (minimum, maximum)

[b] Based on data from 14 of 28 patients

[c] Based on data from 3 of 28 patients as other samples were below limit of quantification

[d] Patients were administered 3 sprays (0.1 mL/spray) into each nostril

4.4 Study 199201-001

Title: Dermal Tolerability and Safety of Oxymetazoline Cream for the Treatment of Erythema Associated with Rosacea.

Studied period:

Study Initiation Date (First Patient Enrolled): 07 May 2012
Study Completion Date (Last Patient Completed): 28 June 2012

Objectives:

To evaluate the dermal tolerability, safety, and efficacy of oxymetazoline 0.5%, 1.0%, and 1.5% cream in patients with erythema associated with rosacea.

Study design:

A multicenter, randomized, double-blind, vehicle-controlled, parallel-group, split-face study investigating the dermal tolerability, safety, and efficacy of oxymetazoline hydrochloride cream (0.5, 1.0, and 1.5%) administered twice daily for 5 consecutive days in patients with erythema associated with rosacea. On day 1, the two doses were to be applied approximately 12 hours apart; on day 2, 3, and 4, the two doses were applied 8 hours apart; and on day 5, the second dose was applied approximately 6 hours after the first dose.

Patients were randomly assigned to 1 of 10 treatment groups as shown below to receive treatment with 0.5, 1.0 or 1.5% oxymetazoline hydrochloride cream or vehicle in a 2:2:2:2:2:2:1:1:1:1 ratio. Patients in treatment groups 1 to 6 applied a different treatment to each side of the face and patients in treatment groups 7 to 10 applied the same treatment to each side of the face.

1) Oxymetazoline 1.0% + oxymetazoline 0.5% - 8 patients
2) Oxymetazoline 1.5% + oxymetazoline 1.0% - 8 patients
3) Oxymetazoline 1.5% + oxymetazoline 0.5% - 8 patients
4) Oxymetazoline 0.5% + vehicle – 8 patients
5) Oxymetazoline 1.0% + vehicle – 8 patients
6) Oxymetazoline 1.5% + vehicle – 8 patients
7) Oxymetazoline 0.5% + oxymetazoline 0.5% - 4 patients
8) Oxymetazoline 1.0% + oxymetazoline 1.0% - 4 patients
9) Oxymetazoline 1.5% + oxymetazoline 1.5% - 4 patients
10) Vehicle + vehicle – 4 patients

Number of subjects (planned and analyzed):

Sixty four adult subjects were planned and 64 adults were enrolled in 2 centers. All 64 patients completed the study. As the study utilized a split-face design, a total of 32 sides of faces were treated with oxymetazoline hydrochloride 0.5% cream, 32 with oxymetazoline HCl 1.0% cream, 32 with oxymetazoline HCl 1.5% cream and 32 with vehicle, resulting in a total of 128 facial sides (left and right side of the face) treated and evaluated.

Diagnosis and main criteria for inclusion:

Patients were eligible for the study if the following criteria were met:

- Male or female, aged 18 years or older

- Stable erythema with rosacea with minimal day to day variation
- Moderate to severe, bilaterally symmetrical facial erythema defined as CEA and SSA grades of 3 or higher

Test product, dose and mode of administration, batch number:

Oxymetazoline HCl cream; 0.5, 1.0 or 1.5%; administered as a thin film to the face. Each patient received treatment for 5 days. The formulation numbers were 11007X (0.5%), 11008X (1.0%), 11009X (1.5%); and the batch numbers were 0.5% - B11180, 1.0% - B11182, 1.5% - B11184.

Duration of treatment:!

The total duration of study participation for each patient was approximately 41 days and each patient received treatment for 5 days.

Reference therapy, dose and mode of administration, batch number:

Placebo (vehicle) was administered as a thin film to the face. The formulation number was 11006X and the batch number was B11178.

PK analysis:

Blood samples were collected for determination of plasma concentrations of oxymetazoline prior to and 12 hours (before the second dose) after the first dose on Day 1; and prior to and at 6 hours (before the second dose) and 12 hours post the first dose on Day 5.

Bioanalytical methods:

The bioanalytical method used in Study 199201-002 was used to analyze the PK samples in this study. Thirty two study samples (approximately 10% of the total samples, 2 samples per subject) were selected for incurred sample reanalysis. The results showed that 100% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value). The established long term stability supported the storage of the study samples. See more details about the method in section 2.5.1 of this review.

Results:

Demographics: The mean age of the 64 patients was 49.2 years (range 23 to 75 years). There were more females than males (76.6% versus 23.4%), and the majority of the population was Caucasian (96.9%). The mean weight was 89.71 kg (range 59.0 to 144.8 kg).

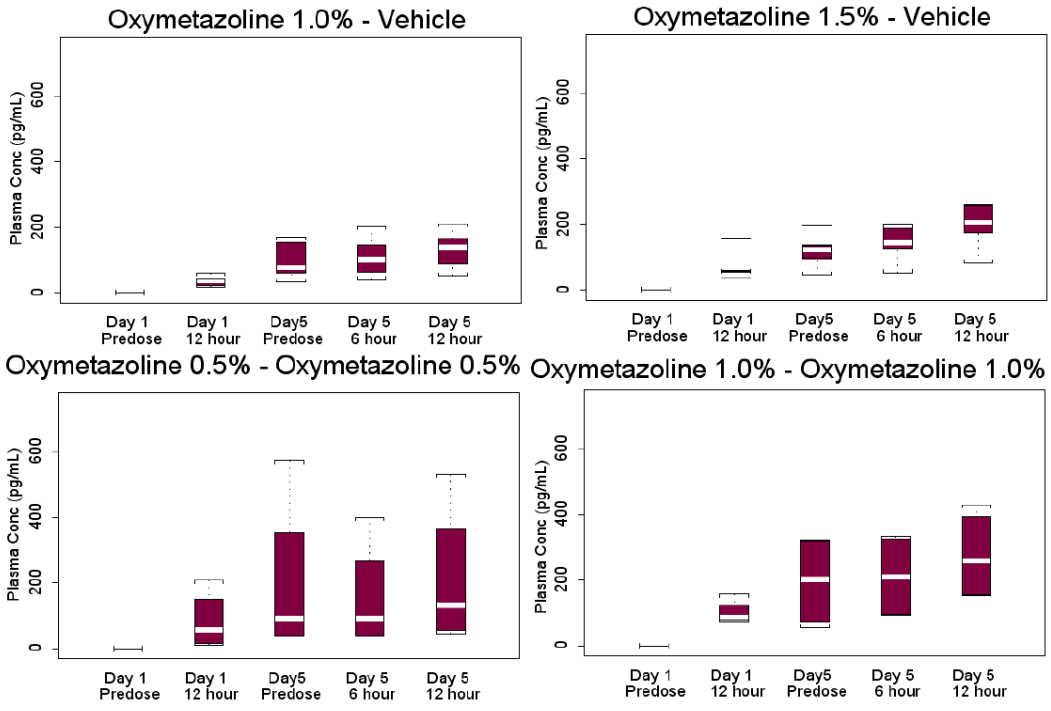
Oxymetazoline pharmacokinetics: The concentrations of oxymetazoline are summarized in **Table 4.4.1**. Boxplots of the oxymetazoline concentrations are shown in **Figure 4.4.1**. The PK results showed the following:

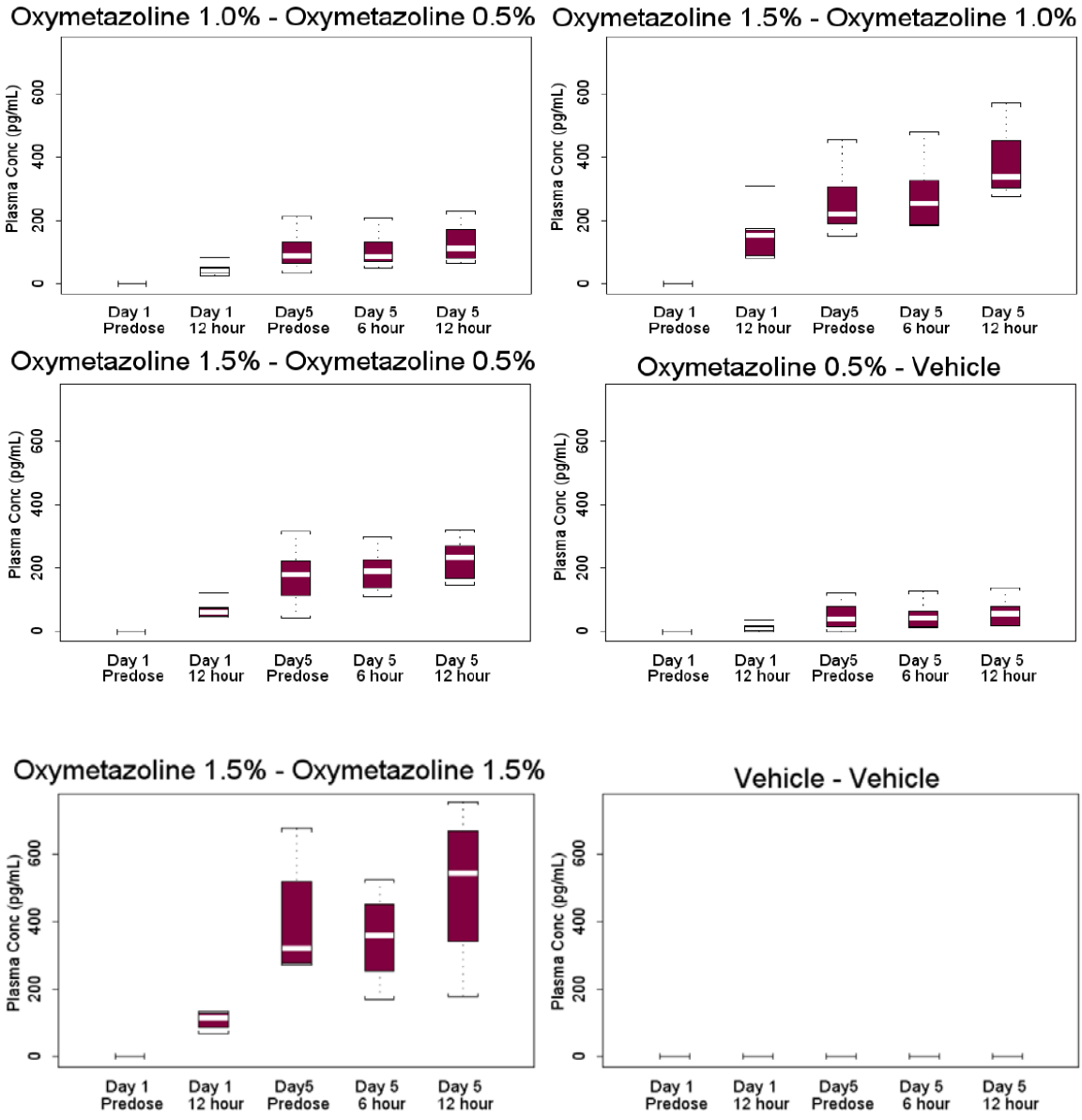
- The highest mean plasma concentrations measured for patients who received 0.5% or 1.0% oxymetazoline cream to both sides of their face were 210 pg/mL and 274 pg/mL, respectively. These were observed on day 5, and were comparable to the maximum observed concentrations after a single administration of Afrin® nasal spray in Study V-101-ROSE-205 (245 pg/mL).
- Following administration of 1.5% oxymetazoline cream to both sides of the face, the mean maximum plasma concentration was 506 pg/mL (on day 5), which was approximately 2-fold higher than that observed with a single administration of Afrin nasal spray in the previous Study V-101-ROSE-205 (245 pg/mL).

Table 4.4.1. Plasma oxymetazoline concentrations following topical dermal administration of Oxymetazoline HCl Cream twice-daily for 5 days in subjects with facial erythema associated with rosacea in study 199201-001. Data are presented as Mean ± SD. Abbreviation: BLQ = below the limit of quantitation (LLOQ = 10 pg/mL). [a]Treatment groups presented as percent (%) oxymetazoline cream applied to each side of the face.; [b]Samples were collected prior to second dose. [c]N=6 for day 1 at 12 hour and N=7 for day 5 predose due to BLQs. [d]N=7 for all day 5 samples due to a missed day 5 visit by one subject. *(Source of data: Table 7-2, Pharmacokinetic Report of Study 199201-001)*.

		Day 1 concentrations (pg/mL)		Day 5 concentrations (pg/mL)		
Treatment[a]	**N**	**Predose**	**12 hr postdose**	**Predose**	**6 hr postdose[b]**	**12 hr postdose**
0.5%/vehicle	8[c]	BLQ	13.1±11.6	49.2±46.6	48.3±39.3	58.2±42
1.0%/vehicle	8	BLQ	35.3±14.5	97.7±53.1	108±55	131±54
0.5%/0.5%	4	BLQ	82.1±90.6	196±255	154±170	210±223
1.5%/vehicle	8	BLQ	67.3±36.9	119±43	146±48	204±61
0.5%/1.0%	8	BLQ	44.7±17.7	101±60	105±53	128±59
1.0%/1.0%	4	BLQ	99.1±38.7	195±144	211±132	274±141
1.5%/0.5%	8	BLQ	67.1±24.7	174±85	191±63	226±62
1.0%/1.5%	8[d]	BLQ	152±74	251±102	285±103	387±104
1.5%/1.5%	4	BLQ	108±29	398±190	353±147	506±241

Figure 4.4.1. Boxplots of oxymetazoline concentrations following twice-daily topical dermal administration of Oxymetazoline HCl Cream for 5 days in subjects with facial erythema associated with rosacea stratified by treatment group *(Source of data: Figure 8-1, Pharmacokinetic Report of Study 199201-001)*.




Oxymetazoline 1.0% - Oxymetazoline 0.5%
Oxymetazoline 1.5% - Oxymetazoline 1.0%
Oxymetazoline 1.5% - Oxymetazoline 0.5%
Oxymetazoline 0.5% - Vehicle
Oxymetazoline 1.5% - Oxymetazoline 1.5%
Vehicle - Vehicle
Plasma Conc (pg/mL)
0
200
400
600
Day 1 Predose
Day 1 12 hour
Day5 Predose
Day 5 6 hour
Day 5 12 hour

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/s/

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