Office of Clinical Pharmacology Review

NDA Number	217064
Link to EDR	\\CDSESUB1\evsprod\NDA217064\0001
Submission Date	November 23, 2022
Submission Type	NDA 505(b)(2); Standard
Brand Name	Ryzumvi
Generic Name	Phentolamine Ophthalmic solution (0.75%)
Dosage Form and Regimen	Ophthalmic Solution: 2 drops in each eye in adults and children 12 years and older, and 1 drop in each eye in children 3 to 11 years of age, as appropriate, at the completion of the ophthalmic examination or surgical procedure requiring eye dilation.
Route of Administration	Ocular
Proposed Indication	Treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof.
Applicant	Ocuphire Pharma LLC
Associated IND	IND 070499
OCP Review Team	Sanjida Mahjabeen, Ph.D.; Ping Ji, Ph.D.

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1 EXECUTIVE SUMMARY

Phentolamine is a non-selective alpha-1 and alpha-2 adrenergic antagonist. The Applicant (Occuphire Pharma LLC) has submitted the 505(b)(2) new drug application (NDA) seeking marketing approval for Ryzumvi (Phentolamine ophthalmic solution, 0.75%) for the treatment of pharmacologically induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof. The proposed dosing regimen is to 2 drops in each eye in adults and children 12 years and older, and 1 drop in each eye in children 3 to 11 years of age, as appropriate, at the completion of the ophthalmic examination or surgical procedure requiring eye dilation.

The Applicant relies on the Agency's previous findings of nonclinical systemic safety, clinical pharmacology, and systemic clinical safety for the approved listed drugs (LDs), Regitine® (NDA 008278) and OraVerse® (NDA 022159), in addition to Applicant-conducted studies, and information available in the published literature. The clinical development program for phentolamine ophthalmic solution 0.75% in support of this application included 4 clinical studies, including one Phase 2 study MIRA-1, two pivotal Phase 3 studies (OPI-NYXRM-301 (MIRA-2), OPI-NYXRM-302 (MIRA-3)), and one pediatric Study OPI-NYXRM-303 (MIRA-4). PK of phentolamine ophthalmic solution 0.75% was assessed in a subset of adult participants in Study OPI-NYXRM-302 (MIRA-3).

The focus of this review is to evaluate the systemic exposure of phentolamine ophthalmic solution (0.75%) from the Study OPI-NYXRM-302 (MIRA-3).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of NDA 217064 and finds the application acceptable to support approval from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness for phentolamine ophthalmic solution (0.75%) is from the 2 adequate and well-controlled Phase 3 studies which are MIRA-2 and MIRA-3 (both included adult subjects and pediatric subjects of 12-17 years of age). The supportive evidence of effectiveness of phentolamine ophthalmic solution (0.75%) was also assessed in adults subjects in MIRA-1 study and pediatric subjects of 3-11 years of age in Study MIRA-4.

General dosing instructions	The recommended dosing regimen is 2 drops in each eye in adults and children 12 years and older, and 1 drop in each eye in children 3 to 11 years of age, as appropriate, at the completion of the ophthalmic examination or surgical procedure requiring eye dilation.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing regimen for pediatric patients of 3 to 11 years of age: 1 drop in each eye. The proposed dosing regimen for pediatric patients of 12 years and above and adults: 2 drops in each eye.
Labeling	See Section 2.4
Bridge between the to-be- marketed and clinical trial formulations	Not applicable. The to-be-marketed formulation was used in 2 pivotal clinical efficacy studies (MIRA-2, MIRA-3); and two other key supportive studies: MIRA-1 and MIRA-4 study.

1.2 Post Marketing Requirement

None

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Phentolamine is a non-selective alpha-1 and alpha-2 adrenergic antagonist.

Phentolamine systemic exposure was evaluated in the Phase 3 study (MIRA-3) following topical ocular administration of a total of 3 drops, each of 0.03 mL, of Phentolamine Ophthalmic Solution 0.75%. The peak concentration levels are achieved between 15 minutes and 1 hour after dosing with the median value of 0.45 ng/mL. The mean (CV%) $AUC_{0\text{-}3h}$ was determined to be 1.2 (62.37%) ng.h/mL.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The recommended dosing regimen is 2 drops in each eye in adults and children 12 years and older, and 1 drop in each eye in children 3 to 11 years of age, as appropriate, at the completion of the ophthalmic examination or surgical procedure requiring eye dilation.

2.2.2 Therapeutic Individualization

Therapeutic individualization is not applicable for proposed drug product.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

We recommend the Applicant removes their statement related to (b) (4) from the clinical pharmacology section (12.3 Pharmacokinetics). Below is the recommendation for the above-mentioned section (12.3) in the proposed label:

"Phentolamine systemic exposure was evaluated in a Phase 3 trial (MIRA-3) following topical ocular administration of a total of 3 drops, each of 0.03 mL, of Phentolamine Ophthalmic Solution 0.75%. The peak concentration levels are achieved between 15 minutes and 1 hour after dosing with the median value of 0.45 ng/mL. (b) (4)

(b) (4)

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Ryzumvi is a preservative free ophthalmic solution containing phentolamine 0.75% w/v. A summary of key clinical pharmacology-related discussions and correspondence with the Applicant are listed in Table 1.

Table 1: Summary of Key Clinical Pharmacology-related and Communication/Meetings with the Applicant

IND 070499 Type C (November 6, 2012)	Discussed the proposed indication of treatment of symptoms associated with night vision disturbance
IND 070499 Type B/EOP2 (May 11, 2020)	Discussed the PK assessment
IND 070499 Type B/EOP2 (June 24, 2021)	Adequacy of stability study plan and data for registration finished product batch
IND 070499 EOP2 Meeting (December 10, 2021)	The Applicant provided Initial Pediatric Study Plan (IPSP). The proposed plan reflected the inclusion of pediatric subjects in MIRA-2 and MIRA-3 study. In addition, the Applicant proposed to conduct a clinical study in children of 3 to 11 years of age (MIRA-4 study). The Applicant requested a waiver for 0 to 3 based on safety concerns. The plan was reviewed and agreed by the clinical review division.
IND 070499 Type B/EOP2 (March 4, 2022)	The Agency agreed with the PK analysis plan.
IND 070499 Pre-NDA Type B/EOP2 (July 20, 2022)	The Applicant requested for the Agency's concurrence on clinical development program. The Agency agreed that the Applicant fulfilled requirement for clinical pharmacology program by conducting: PK characterization study with to be marketed formulation, and pediatric efficacy study to determine the pediatric dose.
IND 070499 Pre-NDA Type B/EOP2 (February 24, 2023)	The Applicant requested the review of proprietary name for the product, "Ryzumvi" on October 3, 2022. As of 02/24/23, the proprietary name was granted to the Applicant.

Source: Reviewer's summary based on meeting minutes (DARRTS; IND070499, NDA217064)

3.2 General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology data of phentolamine from Phentolamine ophthalmic solution, 0.75% (Study MIRA-3, NDA217064), the approved listed drugs, Regitine® (NDA 008278) and OraVerse® (NDA 022159) are summarized in Table 2.

Table 2: Clinical pharmacology data of phentolamine

Clinical Pharmacology	**NDA 217064 Ocular (Phentolamine ophthalmic solution 0.75%)**	**NDA 022159 Intraoral submucosal (Listed Drug) Phentolamine mesylate, 0.4 mg/1.7 mL**	**NDA008278 intravenous and intramuscular (Listed Drug) Phentolamine mesylate for injection, 5 mg**
Mechanism of Action	Non-selective alpha-1 and alpha-2 adrenergic antagonist		
PK			
Absorption	Study OPI-NYXRM-302 (MIRA-3) showed the majority of subjects reached the maximum concentrations (Cmax) with a mean value of 0.65 ng/mL at 15 minutes (Tmax) post administration, with levels slowly decreasing over the period of 3 hours with mean concentration of 0.22 ng/mL. The median Cmax was observed at 0.45 ng/mL achieved at 0.25 hour. The mean AUC_{0-3h} was 1.2 ng.h/mL.	Following OraVerse administration, phentolamine is 100% available from the submucosal injection site and peak concentrations are achieved 10-20 minutes after injection. Phentolamine systemic exposure increased linearly after 0.8 mg compared to 0.4 mg OraVerse intraoral submucosal injection. Following submucosal intraoral injection of 0.4 mg phentolamine mesylate, the observed Cmax and AUC_{0-8h} were 1.34 ng/mL and 1.69 ng.h/mL, respectively, when the dose was increased to 0.8 mg, the reported values for Cmax and AUC_{0-8h} were: 2.73 ng/mL and 3.29 ng.h/mL, respectively.	
Elimination	Elimination phase was not fully captured	The terminal elimination half-life was 2-3 hours	Regitine has a half-life in the blood of 19 minutes following intravenous administration. Approximately 13% of a single intravenous dose appears in the urine

			as unchanged drug[1].
Specific population: PK in pediatric subjects	This product is proposed to be used in pediatric subjects of 3-17 years of age. The Applicant has not conducted any dedicated PK studies or an evaluation of phentolamine PK in pediatric or geriatric populations. The Applicant has assessed the safety and efficacy of the proposed regimen in three studies (MIRA-2 and MIRA-3 in adolescent 12-17 years of age, MIRA-4 in subjects of 3-12 years of age). The FDA has previously agreed that pediatric PK studies are not required for the proposed indication as part of the Agreed iPSP.	Following OraVerse administration, the phentolamine Cmax was higher (approximately 3.5-fold) in children who weighed between 15 and 30 kg (33 and 66 lbs) than in children who weighed more than 30 kg. However, phentolamine AUC was similar between the two groups. It is recommended that in children weighing 15-30 kg, the maximum dose of OraVerse should be limited to ½ cartridge (0.2 mg). The PK of OraVerse in adults and in children who weighed more than 30 kg (66 lbs) are similar after intraoral submucosal injection. For further detail, refer to section 4.1.2 in this review)	
Drug Interaction		No known Drug interaction for Phentolamine	

Source: i) NDA217064; CSR of Study No. OPI-NYXRM-302; ii) NDA022159 Clinical Pharmacology Review; Dated 12/17/2007; iii) Regitine Package Insert available at https://www.drugs.com/pro/regitine.html

It is noteworthy that for OraVerse NDA022159 submission, the pertinent Clinical Pharmacology information was derived from Moore et al. 2008 study (NOVA04-PK)[2]. Refer to the clinical pharmacology review for this NDA as well as the published paper[3].

[1] https://www.drugs.com/pro/regitine.html

[2] Moore PA, Hersh EV, Papas AS, Goodson JM, Yagiela JA, Rutherford B, Rogy S, Navalta L. Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. Anesth Prog. 2008 Summer;55(2):40-8. doi: 10.2344/0003-3006(2008)55[40:POLWEF]2.0.CO;2. PMID: 18547152; PMCID: PMC2424015.

[3] *Clinical Pharmacology Review, NDA022159; Dated 12/17/2007*
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022159s000_ClinPharmR.pdf

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

No. Clinical pharmacology information does not provide pivotal or supportive evidence of effectiveness of the proposed Phentolamine ophthalmic solution. The site of drug administration and the site of action is eye, and the systemic exposure to phentolamine is not expected to relate to the efficacy.

Refer to the clinical and statistical reviews for more information on efficacy and safety assessments.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of phentolamine ophthalmic solution (0.75%) was assessed in the three clinical studies (MIRA-2, MIRA-3 and MIRA-4). MIRA-2 and MIRA-3 were double-masked, randomized, placebo-controlled, multi-center trials of Phentolamine ophthalmic solution 0.75% (2 drops) compared with vehicle (placebo) in normal healthy adults and in pediatric subjects 12-17 years of age. The primary clinical outcome of interest was pupil's diameter (PD) measured using a pupillometer (VIP-300) in both MIRA-2 and MIRA-3 studies. The primary efficacy endpoint of the studies was the percentage of subjects' study eyes returning to $\leq$ 0.2 mm from baseline PD at 90 min after study treatment dosing. MIRA-4 was a randomized, parallel-arm, double-masked, placebo-controlled study comparing Phentolamine ophthalmic solution 0.75% (1 drop) and placebo in pediatric subjects 3 to 11 years of age. Refer to clinical/stats review for additional information efficacy/safety information.

The systemic exposure of phentolamine ophthalmic solution (0.75%) was lower in MIRA-3 study than the exposure reported for OraVerse (NDA022159). In MIRA-3 study, Cmax and $AUC_{0\text{-}3h}$ of phentolamine following 1 drop of Phentolamine ophthalmic solution (0.75%) (equivalent to 0.9 mg phentolamine) were 0.65 ng/mL and 1.2 ng.h/mL, respectively. In study NOVA-04-PK, under NDA 022159, following administration of 0.4 mg and 0.8 mg intraoral submucosal injection of phentolamine mesylate, the Cmax and $AUC_{0\text{-}8h}$ of phentolamine were 1.34 ng/mL and 1.69 ng.h/mL; 2.73 ng/mL and 3.29 ng.h/mL, respectively.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, the recommended dosage regimen is different between patients above 12 years of age & adults and pediatric subjects 3-11 years of age. For pediatric patients of 3 to 11 years of age, the proposed dose is 1 drop in each eye. For patients above 12 years of age and adults the proposed regimen is 2 drops in each eye. No systemic exposure in pediatric was assessed for phentolamine ophthalmic solution (0.75%) in the submission. Instead, the efficacy and safety of phentolamine ophthalmic solution (0.75%) was assessed in subjects of 12 -17 years of age in MIRA-2 and MIRA-3 (key efficacy studies). Additionally, MIRA-4 study assessed safety of 1.19 (62.37%) in pediatric subjects of 3-12 years of age. As exploratory objective,

this study also conducted descriptive assessment of efficacy of the product in pediatric subjects by calculating reduction of mean time to return to ≤ 0.2 mm from baseline pupil diameter after pharmacologically induced mydriasis. Among the pediatric subjects treated with POS, 64% had PD returned to ≤ 0.2 mm from baseline PD at 90 min compared to 17% of study eyes treated with placebo. The effect is consistent to those seen in the adult pivotal studies (49% vs 7% in MIRA-2 and 58% vs 6% in MIRA-3). Refer to clinical review and statistical review for additional information.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The drug product is an ophthalmic solution applied locally in the eye; therefore, the issue of a food-drug interaction is not relevant. There is no known drug interaction of phentolamine mesylate.

4 APPENDICES

4.1 Clinical Assessments

4.1.1 Clinical PK assessment in NDA217064

4.1.1.1 Study # OPI-NYXRM-302 (MIRA-3): Clinical PK assessment of Ryzumvi

Systemic exposure of phentolamine following ocular administration of the proposed ophthalmic solution was assessed in this Phase 3 study. 28 healthy, adult subjects (7 males and 21 females) were dosed in the study. The PK position of the MIRA-3 study was conducted at 2 sites in the USA. In this study, 24 subjects received 2 drops (dosed 5 minutes apart) of Phentolamine Ophthalmic Solution in the study eye (OD) (1 hour post mydriatic drug instillation) and 1 drop in the fellow eye (OS). A total administered dose was 0.9 mg. 4 subjects received placebo and were not included in the PK analysis.

4.1.1.1.1 Sample Collection, Bioanalysis, PK Assessments, and Statistical Analysis

In this study, blood samples for PK analysis were collected utilizing following schedule:

- Post dose at 0.25 hours, 1 hour and 3 hours.

The volume of each blood draw volume was 6 mL. A validated bioanalytical method was used for determination of phentolamine in plasma.

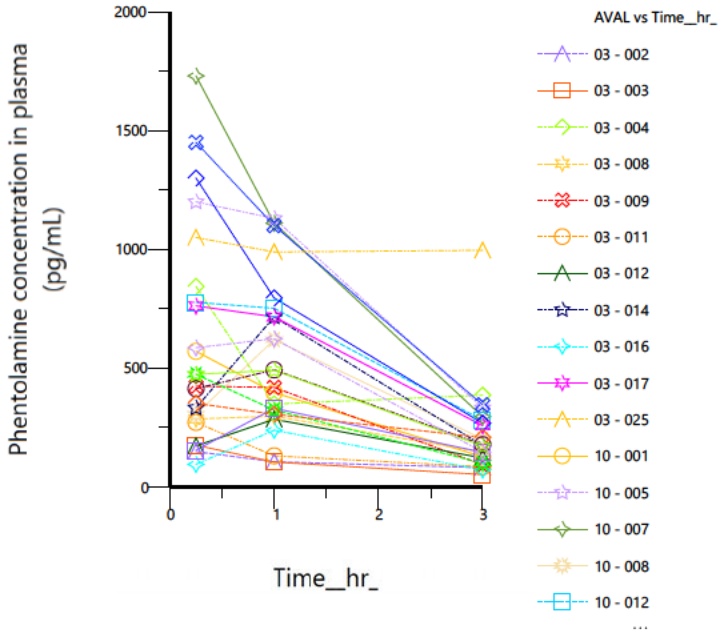
PK/per protocol population (PK/PP) included those subjects who received a dose. Analysis of PK parameters was conducted by (b) (4) using derived dataset as described above in Phoenix WinNonLin ver 8.3 professional PK software (Certara, Princeton, NJ, USA). The PK parameters for phentolamine in plasma were derived using a noncompartmental approach.

There were some limitations to the PK analysis due to sparse PK sampling that included only 3 concentration time points (15 minutes, 1 hour and 3 hours) not fully capturing Tmax and sampling up to 3 hours not providing elimination phase.

4.1.1.1.2 PK data obtained from MIRA-3 Study

For most of the subjects the maximum concentrations with mean value of 0.65 ng/mL were observed at 15 minutes post 3 drops of Phentolamine ophthalmic solution 0.75% administration, and afterwards concentrations slowly decreased over the period of 3 hours with mean concentration of 0.22 ng/mL. The Median Cmax was observed at level of 0.45 ng/mL achieved at 0.25 hours. Mean plasma concentration profile and overall PK parameters are shown in Figure 1 and Table 3. Considering dose linearity obtained from Moore et al study which used OraVerse Injection and showed dose proportional increase in exposure, the Applicant estimated the median exposure following administration of 4 drops of Phentolamine ophthalmic solution (1.2 mg total dose) to be 0.6 ng/mL. Cross study comparison of PK parameters obtained from various studies are shown in Section 4.2.

Figure 1: Mean Plasma Concentration vs Time Profile using Scheduled time of collection - PK Population



Source: Reviewer Analysis from CSR of Study No. opi-nyxrm-302, using ADPC.xpt; \\CDSESUB1\EVSPROD\nda217064\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mydriasis\5351-stud-rep-contr\ocuphire-opi-nyxrm-302\opi-nyxrm-302-16113-pk-report.pdf

Table 3: Phentolamine PK Parameter Values – Study OPI-NYXRM-302 (MIRA-3)

PK parameters	Values reported in Mean (CV%)	Median Values
	Day 1 (n=24)	Day 1 (n=24)

$AUC_{0\text{-}3h}$ (ng.h/mL)	1.19 (62.37%)	1.07
Cmax (ng/mL)	0.65 (65.1%)	0.53
Tmax (h)	0.53 (69.81%)	0.25

Source: Reviewer Analysis from CSR of Study No. Opi-nyxrm-302, using ADPC.xpt; \\CDSESUB1\EVSPROD\nda217064\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mydriasis\5351-stud-rep-contr\ocuphire-opi-nyxrm-302\opi-nyxrm-302-16113-pk-report.pdf

4.1.1.1.3 Summary of Bioanalytical Method Validation and Performance used for MIRA-3 study

The bioanalytical method used for quantification of phentolamine was validated[4] with study protocol no. MC21B-0246. The concentration of phentolamine was determined using High-Performance Liquid Chromatography with Mass Spectrometric Detection (HPLC/MS). The method validation is summarized as below in Table 4.

Table 4: Bioanalytical method assessment

Information Requested	**Data**
Bioanalytical method validation report location	HPLC/MS Method (\\Cdsesub1\evsprod\NDA217064\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\mc21b-0246)
Analyte	Phentolamine
Internal Standard (IS)	Phentolamine D4
Limit of quantitation	LLOQ: 5.00pg/mL, ULOQ : 5000pg/mL
Absolute recovery of analyte (%)	103%
Absolute recovery of IS (%)	96.2 %
Standard curve concentrations (pg/mL)	5.00, 10.0, 20.0, 40.0, 100, 200, 500, 1,000, 2500, 5000 pg/mL
QC Concentrations (pg/mL)	Low QC: 5 pg/mL Med QC: 15 pg/mL Med QC: 1500 pg/mL High QC: 4000 pg/mL
QC Intraday precision range (%)	0.655% to 4.83%

[4] \\Cdsesub1\evsprod\NDA217064\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\mc21b-0246

QC Intraday accuracy range (%)	1.75% to 8.00%	
QC Inter day precision range (%)	1.59% to 2.91%	
QC Inter day accuracy range (%)	2.75% to 6.00%	
Post-Processed stability (h)	Phentolamine in processed extracts stored refrigerated at 10± 5°C for 73 hours	
Post Extraction Bench Top Stability (h)	24 hours at room temperature (in polypropylene vial)	
Freeze-thaw stability (cycles)	4 cycles at -20°C/RT	
Long term storage stability (Days)	176 days at -20°C and -70°C	
Dilution Integrity	10X Single dilution of 10,000 pg/mL: % Accuracy : 3.2% % Precision : 9%	100X Serial dilution of 10000 pg/mL: % Accuracy : 7.63% % Precision : 3%
Selectivity	No significant interference observed in blank human plasma samples	

Source:

i. *Bioanalytical Method Validation Report No. MC21B-0246; \\Cdsesub1\evsprod\NDA217064\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\mc21b-0246*

ii. *Extended stability study report: Evaluation of the Extended Stability of Phentolamine in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection \\CDSESUB1\EVSPROD\nda217064\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\mc21b-0247\mc21b-0247.pdf*

Reviewer's comments:

- *A total of 84 samples were analyzed. The first sample collection date was December 21, 2021 and date of last sample analysis was February 24, 2022 (Duration of maximum storage: 63 days). Thus, all samples were analyzed within established long-term storage duration (176 days).*
- *The Applicant determined that incurred sample re-analysis (ISR) would not be performed due to low sample count. The method was found to produce reproducible results when nineteen (19) samples were reanalyzed and 94.7% confirmed the original value. The method validation report demonstrated reproducibility of the bioanalytical method.*
- *It is reasonable to include PK exposure parameter, Cmax in proposed label from observed PK data in MIRA-3 study. However, we recommend removal of* (b) (4) *As, the Applicant did not experimentally* (b) (4) *of phentolamine following ocular administration.*

4.1.2 Clinical PK assessment in Listed Drug

Single dose PK of OraVerse Injection, NOVA-04-PK and NOVA-05-PEDSPK.

NOVA-04-PK

This was a Phase 1, open-label PK, PD, and safety in healthy adult volunteers. The main study objectives were to determine the PK of phentolamine administered by intraoral submucosal (0.4 and 0.8 mg) and intravenous (IV) injections (0.4 mg) and to determine the effects of NV-101 by intraoral submucosal injection on the PK of lidocaine and epinephrine administered by intraoral submucosal injection (1 or 4 cartridges).

Phentolamine was completely bioavailable after intraoral submucosal injection (104%). The mean phentolamine Cmax and AUC values were dose-proportional. Compared to intravenous injection, OraVerse intraoral submucosal Cmax value was 8 times less. The phentolamine $t_{1/2}$, CL, and V_d values were similar for all treatments. The phentolamine T_{max} was earlier (7 min.) as administered alone compared to that of with a local anesthetic, lidocaine and epinephrine (11 - 15 min).

NOVA-05-PEDSPK

Pediatric PK of intraoral submucosal phentolamine was evaluated in a Phase 1 open label study of OraVerse to evaluate the PK and safety in pediatric dental patients. The objectives of the study were:

1. To evaluate the PK of OraVerse in pediatric dental patients who were undergoing dental procedures under general anesthesia or conscious sedation, to the extent possible with blood sampling limited to the duration of the intravenous (IV) access line after NV-101 administration
2. To evaluate the safety of OraVerse in pediatric dental patients as measured by the incidence and severity of adverse events and concomitant medications.

The mean phentolamine C_{max} plasma concentration in the 0.2-mg dose group (lighter body weight group) was approximately 70% greater the mean in the 0.4-mg group (heavier body-weight group) from 5 to 15 minutes post administration. However, by 30 minutes, the mean plasma concentrations in the two groups were nearly identical and remained similar through the 2-hour sampling point. The mean CL and Vd parameters were noticeably larger in the 0.4-mg group than in the 0.2-mg group.

The following table contains overall PK parameters obtained from the study. It appeared that there is a clear difference in phentolamine Cmax, due to subject body weight. Phentolamine Cmax in subjects who is weighs less than 30 kg (pediatric subjects 3 – 8 years of age) increased approximately 70% compared to > 30 kg body weight.

Table 5: PK parameters reported in OraVerse (NDA022159) obtained from NOVA-04-PK and NOVA-05-PEDSPK

Study	Treatments (Dose, Dosage Form, Route)	Phentolamine PK parameters						
		Cmax (ng/mL)	AUClast (ng.h/mL)	AUCinf (ng.h/mL)	Tmax (h)	t1/2 (h)	Cl (L/h)	Vd (L)
NOVA 04-PK	NV-101, 0.4 mg intraoral submucosal	1.34	1.69	2.88	0.25 ±0.03	3.13 ±0.91	160.93 ± 24.02	470.61 ± 62.72
	NV-101, 0.8 mg intraoral submucosal	2.73	3.29	4.58	0.18 ± 0.016	2.23 ±0.41	203.64 ± 36.21	499.68 ± 60.08
	NV-101, 0.4 mg IV	10.98	1.71	2.76	0.11 ±0.05	2.4 ±0.63	175.49 ± 30.36	441.99 ± 83.68
NOVA 05-PEDS-PK	NV-101, 0.2 mg intraoral submucosal	2.60	1.93	3.62	0.16 ±0.017	2.53 ±0.56	58.79 ± 8.06	190.56 ± 35.69
	NV-101, 0.4 mg intraoral submucosal	1.47	1.81	3.39	0.35 ±0.067	2.98 ±0.93	132.18 ± 17.59	396.50 ± 22.98

Source: Clinical Pharmacology Review, NDA022159; 12/17/2007

4.2 Scientific Bridging Strategy

To establish scientific bridge between listed drug, OraVerse and Ryzumvi ophthalmic solution, the Applicant utilized following strategy relying on the available information in OraVerse publicly available information and published literature study by Moore et al, 2008:

i. The Applicant stated dose-proportionality of phentolamine established by the Applicant of OraVerse during NDA022159 approval. Under NDA022159, study NOVA-04-PK[5] demonstrated that systemic exposure increased linearly after 0.8 mg compared to 0.4 mg OraVerse intraoral submucosal injection. This information is publicly available as published paper by Moore et al 2008 study[6]. In this study, an approximately two-fold increase in exposure was observed for a two-fold increase in dose (Refer to the data in the above Table 2).

ii. In MIRA-3 study, the observed Cmax and AUC0-3h following 3 drops of phentolamine ophthalmic solution (total dose 0.9 mg) were 0.65 ng/mL and 1.2 ng.h/mL, respectively. These values are lower than that of the reported in published literature for OraVerse (Refer to **Table 2**,

[5] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022159s000_ClinPharmR.pdf

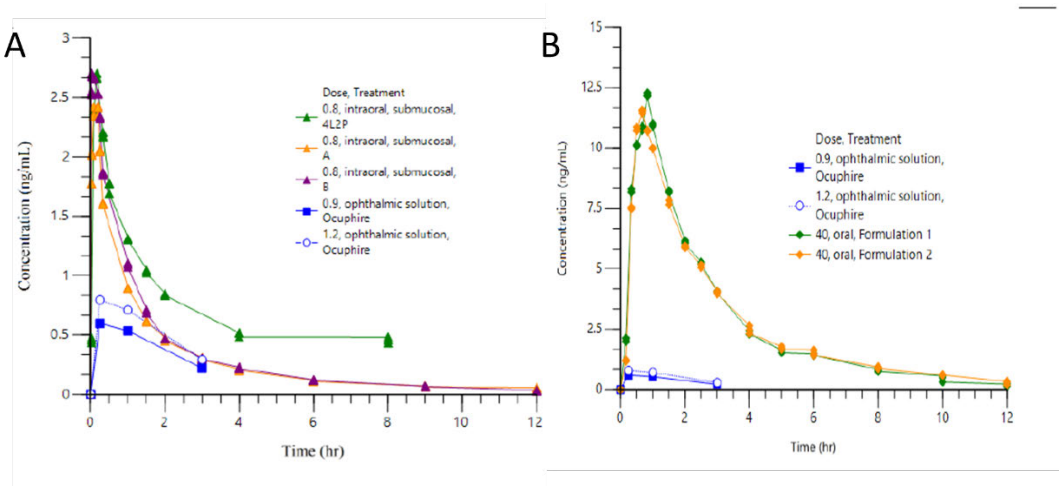
[6] Moore PA, Hersh EV, Papas AS, Goodson JM, Yagiela JA, Rutherford B, Rogy S, Navalta L. Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. Anesth Prog. 2008 Summer;55(2):40-8. doi: 10.2344/0003-3006(2008)55[40:POLWEF]2.0.CO;2. PMID: 18547152; PMCID: PMC2424015.

following submucosal intraoral injection of 0.4 mg phentolamine mesylate, the observed Cmax and $AUC_{0\text{-}8h}$ were 1.34 ng/mL and 1.69 ng.h/mL, respectively, when the dose was increased to 0.8 mg, the reported values for Cmax and $AUC_{0\text{-}8h}$ were: 2.73 ng/mL and 3.29 ng.h/mL, respectively), hence, the scientific bridge was established between the listed drug, OraVerse and proposed phentolamine ophthalmic solution.

4.2.1 Cross study comparison of PK parameters

The PK of phentolamine has been previously characterized following oral, IV and IM dosing (Moore et al. 2008[7]; Silva et al. 2004[8]; Lin et al. 2018[9]; and during OraVerse NDA approval[10]). For completeness of the assessment the Applicant compared the values of PK parameters ($AUC_{0\text{-}3h}$, Cmax, Tmax) from above mentioned studies. The $AUC_{0\text{-}3h}$ was not published for literature data, therefore the applicant determined this based on digitized mean PK concentration plots. Figure 2 provides comparative PK profiles from various studies and Table 6 summarizes the PK parameters from those.

Figure 2: Mean phentolamine PK profiles: a) based on ophthalmic administration in study OPI-NYXRM-302 (MIRA-3) and intraoral submucosal administration in the published literature; b) based on ophthalmic administration in study OPI-NYXRM-302 (MIRA-3) and oral administration in the published literature



Source: NDA217064; Common Technical Document Summary; Section 2.7.2 Summary of Clinical Pharmacology Studies: Figure 2 and Figure 3; \\CDSESUB1\EVSPROD\nda217064\0001\m2\27-clin-sum\272-summary-clin-pharm.pdf

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[9] Lin, Shi-Bei-Lei et al. (2018): Journal of Sichuan University. Medical science edition 49 (6), pp. 929–933.
[10] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022159_oraverse_toc.cfm

Table 6: Mean Phentolamine PK Parameters From OPI-NYXRM-302 (MIRA-3) Clinical Study and Literature Data

Reference study	Route of Administration	Total Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC_{0-3h} (ng.h/mL)	T_{last} (h)
Ocuphire OPI-NYXRM-302 (MIRA-3)	Ocular	0.9 (3 drops)	0.65	0.53	1.2	3
Lin et al. 2018	Intraoral submucosal	0.2	0.71	0.09	0.71	15
		0.4	1.28	0.11	1.37	15
OraVerse (Moore et al. 2008 (NOVA 04-PK))	Intraoral submucosal	0.4	1.39	0.28	2.31	8
	IV	0.4	10.99	0.02	3.01	8
Lin et al. 2018	Intraoral submucosal	0.8	2.55	0.09	2.69	15
OraVerse Moore et al. 2008 (NOVA 04-PK)	Intraoral submucosal	0.8	2.68	0.17	3.59	8
Silva et al. 2004	Oral (Reference formulation 1)	40	12.21	0.83	21.6	12
	Oral (Reference formulation 2)	40	11.52	0.67	20.62	12

Source: NDA217064; Common Technical Document Summary; Section 2.7.2 Summary of Clinical Pharmacology Studies: Table 6; \\CDSESUB1\EVSPROD\nda217064\0001\m2\27-clin-sum\272-summary-clin-pharm.pdf

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