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RESEARCH**

APPLICATION NUMBER:

205388Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	205,388
Submission Date(s)	July 30, 2013
Brand Name	Omidria®
Generic Name	Phenylephrine hydrochloride (PE) and ketorolac tromethamine (KE) injection solution, concentrate intended for admixture with standard irrigation solution
Primary Reviewer	Yoriko Harigaya, Pharm.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Transplant and Ophthalmology Products
Applicant	Omeros corporation
Relevant IND(s)	78,227
Submission Type	Original Submission: Standard Review
Formulation; Strength(s)	Injection solution, concentrate intended for admixture with standard irrigation solution
Proposed Indication	(b) (4) prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain for intraocular lens replacement
Proposed Dosage Regimen	4 mL of phenylephrine hydrochloride 12.37 mg/mL and ketorolac tromethamine 4.24 mg/mL OMS302 must be diluted prior to use; 4.0 mL of OMS302 drug product is diluted in 500 mL of standard irrigation solution (e.g. balanced salt solution), resulting in a solution with PE at a final concentration of approximately 480 µM (0.0098% w/v) and KE at a final concentration of approximately 89 µM (0.0034% w/v)

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1. EXECUTIVE SUMMARY

Omeros corporation submitted the New Drug Application (NDA) for OMS302 (Omidria[®]), which represents a combination of two approved products. OMS302 is a fixed-dose combination drug product containing phenylephrine hydrochloride (PE) 12.37 mg/mL, an α 1-adrenergic receptor agonist, and the non-steroidal anti-inflammatory drug (NSAID) ketorolac tromethamine (KE) 4.24 mg/mL, a nonselective cyclooxygenase (COX) COX-1/COX-2 inhibitor. OMS302 is indicated for (b) (4), prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain for intraocular lens replacement.

PE Ophthalmic Solution 2.5% and 10%, administered one drop at 3 to 5 minute intervals up to a maximum of 3 drops per eye, were approved for 1 year old and older in 1939 by the Agency, which is indicated for dilating the pupil. KE ophthalmic solution 0.5% (Acular[®]), was approved in 1991 by the Agency and is indicated for the treatment of inflammation following cataract surgery and the temporary relief of ocular itching due to seasonal allergic conjunctivitis. The proposed dosage and route of administration for Acular[®] is as follows: one drop should be applied to the affected eye four times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the post-operative period.

In the current NDA, OMS302 (PE 12.37 mg/mL and KE 4.24 mg/mL) is proposed for (b) (4) prevention of intraoperative miosis and reduction of (b) (4) post-operative ocular pain for intraocular lens replacement. The proposed dosage and route of administration for OMS302 for this indication is as follows: 4.0 mL of OMS302, PE 12.37 mg/mL and KE 4.24 mg/mL, is diluted in 500 mL of standard irrigation solution (e.g. balanced salt solution), resulting in a solution with PE at a final concentration of approximately 480 μ M (0.0098% w/v) and KE at a final concentration of approximately 89 μ M (0.0034% w/v). The final irrigation solution is used during the procedure.

The current application presents data from four clinical studies to support the proposed indication of OMS302. These studies include one Phase 1/2 exploratory study designed to evaluate safety and potential efficacy endpoints (Study C07-005), one full-factorial study designed to evaluate the separate contributions of PE and KE to the proposed indication (Study C09-001), and two confirmatory Phase 3 safety and efficacy studies (Studies OMS302-ILR-003 and OMS302-ILR-004). One of the Phase 3 studies (OMS302-ILR-004) includes a pharmacokinetics (PK) substudy.

PE has been also approved for other routes of administration such as oral, intranasal, intravenous, intramuscular, and subcutaneous. KE has been approved for oral, parenteral and nasal administration. Thus, the current NDA (OMS302) also relies on the historical finding safety and efficacy for the currently approved PE and KE products.

1.1 Recommendation

From a Clinical Pharmacology perspective, the NDA submission for OMS302 is acceptable, and the reviewer recommends approval of this product.

1.2 Labeling Recommendations

Please refer to Section 2 for detailed labeling recommendations.

1.3 Phase 4 Requirements

No Phase 4 study recommendation.

1.4 Summary of Important Clinical Pharmacology Findings

OMS302 is a sterile solution concentrate containing 12.37 mg/mL (61 mM) of PE and 4.24 mg/mL (11 mM) of KE in a single-use vial. For administration, OMS302 must be diluted prior to use as follows: 4.0 mL of OMS302 drug product is diluted in 500 mL of standard irrigation solution (e.g. balanced salt solution), resulting in a solution with PE at a final concentration of approximately 480 μ M (0.0098% w/v) and KE at a final concentration of approximately 89 μ M (0.0034% w/v). One clinical PK substudy was conducted to evaluate the systemic exposure to PE and KE following administration of OMS302 during intraocular lens replacement surgery in 26 subjects (14 OMS302 vs. 12 placebo) in Study OMS302-ILR-004. One Phase 1/2 exploratory Study C07-005 was conducted to evaluate safety and potential efficacy endpoints of PE alone vs. OMS302 vs. Vehicle. One Phase 2 Study C09-001 was conducted to evaluate the separate contributions of PE and KE to the proposed indication. Specific clinical pharmacology findings from review of these studies are summarized as follows:

- In Study OMS302-ILR-004, PE plasma concentrations were detectable (range 1.2 to 1.4 ng/mL) in one of 14 subjects [Lower Limit of Quantification (LLOQ) = 1 ng/mL]. The systemic absorption of PE may have been due to application of pre-operative PE ophthalmic solution, since the highest PE concentration observed (i.e., 1.7 ng/mL) was immediately following administration of pre-operative topical drops of PE 2.5% ophthalmic solution (i.e., at approximately 30 minutes, 15 minutes, and 5 minutes before surgery) and before OMS302 was administered.
- In Study OMS302-ILR-004, KE plasma concentrations were detected in 10 of 14 subjects (range 1.0 to 4.2 ng/mL), which were insufficient for PK analysis. The maximum KE concentration (i.e., 15.2 ng/mL) was observed at 24 hours after the initiation of Omidria administration, which may have been due to application of post-operative KE ophthalmic solution.
- [REDACTED] (b) (4) KE did not display any treatment effect in [REDACTED] (u) (4) compared to placebo in Study C09-001 ($p=1.0$), and any additive effect on PE in pupil diameter changes when KE was administered in combination with PE in both Study C07-005 ($p=1.0$) and Study C09-001 ($p=1.0$). [REDACTED] (b) (4)
- In Study C07-005, KE 60 μ M (final concentration) did not provide clinical meaningful effects in the ocular Pain Score. KE at 89 μ M also displayed

contribution to the treatment effect in the ocular Pain Score when KE was administered with PE ($p=0.0093$) in Study C09-001. The justification of the dose selection (i.e., KE 89 μ M) is acceptable.

- PE at 483 μ M displayed slightly higher AUCs of reduced pupil diameter compared to placebo group in Study C07-005 ($p=0.4$) and in Study C09-001 ($p=0.7$). A slight contribution to the treatment effect in the change in pupil diameter was demonstrated when PE was administered in combination with KE in Study C09-001 ($p=0.7$). Although it was not statistically significant, the contribution of PE at 483 μ M to the treatment effect is considered to be acceptable, since the baseline in pupil diameter includes pre-operative mydriatic treatment.
- The administration of topical KE ophthalmic solution before the evaluation of efficacy endpoints at 24-hour time point may change the results of the efficacy analysis in any of the clinical studies.

2. QUESTION BASED REVIEW

Since this submission is a combination of two approved products, only relevant questions from the OCP question-based review (QBR) are addressed below.

General Attributes of the Drug

2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

OMS302 is a sterile, single-use drug formulation intended for admixture with sterile ophthalmic irrigating solutions (e.g. balanced salt solution plus). The finished dosage form contains 61 mM (12.37 mg/mL) PE and 11 mM (4.24 mg/mL) KE, formulated in a ^{(b) (4)} sodium citrate buffer (pH 6.3 ± 0.3). Each vial is filled to allow withdrawal of 4.0 mL of formulation concentrate for admixture with 500 mL of irrigation solution. The sponsor does not intend to provide irrigation solutions with the drug product.

Table 1: Composition of OMS302 Dosage Form and Admixed Solution

Component	Function	Amount per Vial (mg/4.0 mL)	Concentration Solution (mg/mL)	Concentration Admixed Solution (mg/mL)
Phenylephrine HCl, USP	Drug Substance	49.5	12.37	0.0982
Ketorolac Tromethamine, USP	Drug Substance	17.0	4.24	0.0337
Citric Acid monohydrate, USP, Ph. Eur.	(b) (4)	(b) (4)		
Sodium Citrate dihydrate, USP, Ph. Eur.				
Water for Injection, USP, Ph. Eur. ^a				
Sodium Hydroxide, NF, Ph. Eur. ^b				
Hydrochloric Acid, NF, Ph. Eur. ^b				
(b) (4)				

USP: United States Pharmacopia

Ph Eur : European Pharmacopia

NF: National Formulary

2.2 What is the proposed mechanism of drug action and therapeutic indication?

PE is an α 1-adrenergic receptor agonist. The iris dilator muscle expresses α 1-adrenergic receptors that mediate contraction. Thus, PE causes dilation of the pupil and maintains mydriasis.

KE is an NSAID and competitively inhibits both COX-1 and COX-2 by blocking arachidonate binding resulting in analgesic, antipyretic, and anti-inflammatory pharmacologic effects. Thus, KE reduces surgically induced pain and inflammation.

The sponsor states that KE may also inhibit miosis. Prostaglandins are synthesized in the iris and ciliary body, and their release during surgery is triggered by iris trauma or manipulation causing miosis. Blocking prostaglandin synthesis with intraoperatively delivered KE may suppress this miotic response.

General Clinical Pharmacology

2.3 What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

To support the proposed dosing for the (b) (4) prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain, the applicant has conducted one Phase 1/2 Study C07-005 exploratory study to evaluate safety and potential efficacy endpoints of PE vs. OMS302 (PE and KE) vs. Balanced Salt Solution (BSS, vehicle control). In addition, one Phase 2 Study C09-001 evaluating the separate contributions of PE and KE to the proposed indication, and two confirmatory Phase 3 safety and efficacy studies (Studies OMS302-ILR-003 and OMS302-ILR-004) were conducted.

Table 2: List of Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment;	Study Status; Type of Report
Phase 3	OMS302-ILR-004	Efficacy & Safety; PK	Randomized, parallel group, double-masked, placebo-controlled study	OMS302 (483 µM PE and 89 µM KE) or Placebo diluted in balanced salt solution (BSS); Single dose, intraocular irrigation and intracameral perfusion	416 (209 OMS302, 207 Placebo) PK subset: 26 (14 OMS302, 12 Placebo)	Subjects undergoing cataract extraction and lens replacement (CELRL) or refractive lens exchange (RLE)	Single Dose	Complete; Full clinical study report
Phase 3	OMS302-ILR-003	Efficacy & Safety;	Randomized, parallel group, double-masked, placebo-controlled study	OMS302 (483 µM PE and 89 µM KE) or Placebo diluted in BSS; Single dose, intraocular irrigation and intracameral perfusion	405 (203 OMS302, 202 Placebo)	Subjects undergoing CELR or RLE	Single Dose	Complete; Full clinical study report
Phase 2	C09-001	Efficacy & Safety	Randomized, parallel group, double-masked, vehicle-controlled, factorial design study	PE and KE alone and in combination (OMS302), diluted in BSS Four arms: (1) 483 µM PE; (2) 89 µM KE; (3) 483 µM PE and 89 µM KE; or (4) Vehicle control Single dose, intraocular irrigation and intracameral perfusion	223 (56 OMS302, 56 PE, 55 KE, 56 Vehicle)	Subjects undergoing CELR	Single Dose	Complete; Full clinical study report
Phase 1/Phase 2	C07-005	Exploratory Efficacy & Safety	Randomized, controlled, double-masked, vehicle- and phenylephrine HCl-controlled	PE and KE alone and in combination (OMS302), diluted in BSS; Three arms: Initial: (1) 714 µM PE; (2) 714 µM PE; or (3) 90 µM KE; and BSS Vehicle Amended to: (1) 483 µM PE; (2) 483 µM PE and 60 µM KE; or (3) BSS Vehicle Single dose, intraocular irrigation and intracameral perfusion	61	Subjects undergoing CELR	Single Dose	Complete; Full clinical study report

2.5 What are the PK characteristics of the drug?

In the Phase 3 study (OMS302-ILR-004), PK substudy was conducted to evaluate the systemic exposure to PE and KE following administration of OMS302 during intraocular lens replacement surgery was evaluated in 26 subjects (14 OMS302 vs. 12 placebo). The volume of irrigation solution used during surgery ranged between 150 mL to 300 mL (median 212.5 mL). OMS302 administration duration ranged between 3 minutes to 14 minutes (median 5 minutes).

PE plasma concentration was detectable (1.2 to 1.4 ng/mL) in 1 subject out of 14 subjects following administration of OMS302 during the first two hours after the initiation of OMS302 administration. However, the highest concentration (1.7 ng/mL) was observed immediately following administration of pre-operative topical drops of PE 2.5% ophthalmic solution (i.e., one drop at approximately 30 minutes, 15 minutes, and 5 minutes before surgery) and before OMS302 was administered (Figure 1). Therefore, the observed systemic exposure to PE could be due to the pre-operative administration of PE 2.5% ophthalmic solution.

KE plasma concentration was detected in 10 of 14 subjects treated with OMS302 and in 1 of 12 subjects treated with placebo. The plasma KE concentrations observed were between 1.0 and 4.2 ng/mL during the first eight hours after the initiation of OMS302 administration. In 2 subjects in OMS302 arm in Study OMS302-ILR-004 (i.e., ID179011 and ID185005), the significantly higher KE plasma concentrations (i.e., 15.2 and 3.6 ng/mL) were observed at 24 hours after the initiation of OMS302 administration, which is possibly due to the post-operative administration of KE ophthalmic solution which was supposed to be administered after collection of the 24-hour PK blood samples (Figure 1 and Table 3). Administration of topical KE ophthalmic solution before the evaluation of efficacy endpoints at 24-hour time point may change the results of the efficacy analysis in any of the clinical studies. Regarding this issue, the Clinical Pharmacology reviewer defers to the review team's decision.

The concentrations of PE and KE were analyzed by liquid chromatography tandem mass spectrometry (LC/MS/MS) with validated assays that had LLOQs of 1 ng/mL for both PE and KE using 100 mcL of human plasma. Acceptance criteria for accuracy and precision for the bioanalytical method (LC/MS/MS) to determine PE and KE concentrations were met.

Overall, OMS302 administration results in minimal to no systemic absorption of PE and KE that was insufficient for PK analysis.

Figure 1: PE and KE Plasma Concentration Following Topical Ocular Administration of OMS302 in Study OMS302-ILR-004

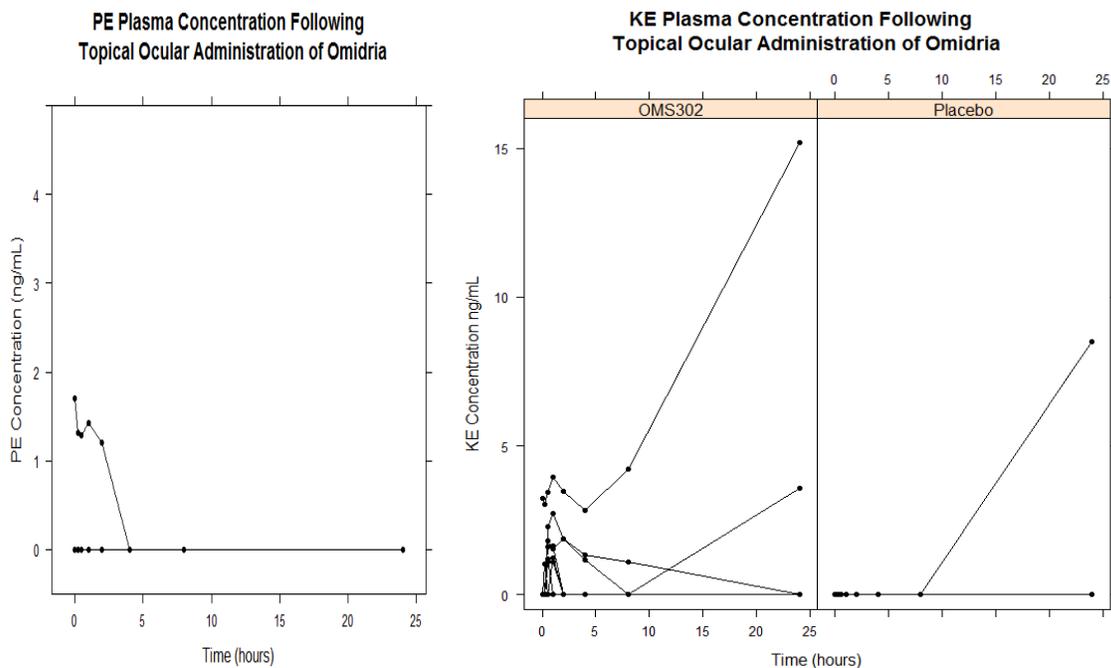


Table 3: KE Plasma Concentration (ng/mL) Following a Topical Ocular Administration of OMS302 in Study OMS302-ILR-004

Time post-dose (subjects)	0 min (n=14)	15 min (n=14)	30 min (n=14)	1 hour (n=14)	2 hour (n=14)	4 hour (n=14)	8 hour (n=14)	24 hour (n=14)	Placebo (n=12)
Minimum	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
Median	<LLOQ	<LLOQ	0.55	0.54	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
Maximum	3.24	3.02	3.45	3.94	3.47	2.81	4.21	15.2	8.51

*LLOQ=1.0 ng/mL

2.6 What are the characteristics of the dose-response relationships for efficacy and safety?

The Phase 1/2 Study C07-005 was a randomized, controlled, double-masked, parallel, three-arm study of PE vs. OMS302 (PE and KE) vs. Balanced Salt Solution (BSS, vehicle control) in subjects undergoing cataract extraction and lens replacement using a coaxial phacoemulsification process with insertion of an acrylic lens (n=60). Subjects were randomized 1:1:1 to OMS302 (the final concentration of PE 714 µM and KE 89 µM), PE alone (714 µM), or vehicle.

Because adequate mydriasis could not be achieved with OMS302 or PE alone in this study, the protocol was amended. In the protocol Amendment 1, all subjects received pre-operative mydriatic treatment (i.e., one drop of PE 2.5% and one drop of tropicamide 1%) at approximately 30 minutes, 15 minutes, and 5 minutes prior to surgery. In addition, the final concentrations of PE and KE were reduced by approximately 33%, resulting in the final concentrations of PE 483 µM and KE 60 µM in the irrigation solution.

The pupil diameter changes are summarized in the following Figures 2 and 3, and Tables 4 and 5. In Study C07-005, as the baseline of pupil diameter in Original Protocol is different from that in Amendment 1 due to administration of pre-operative PE/tropicamide in Amendment 1, it is not possible to conduct PE dose-response analyses in this study. The lower volume of irrigation solution was used in Amendment 1 compared to that in Original Protocol, which may be due to the lack of efficacy in Original Protocol.

A slight PE contribution to the treatment effect in the change in pupil diameter was demonstrated when it was compared to placebo group in the protocol Amendment 1 in Study C07-005 ($p=0.4$). Although it is not statistically significant, it is considered to be acceptable, since the baseline in the change in pupil diameter includes pre-operative mydriatic treatment.

KE did not display any additive effect on PE in pupil diameter changes when KE was administered in combination with PE ($p=1.0$).

Figure 2: Study C07-005 (Original Protocol) AUC of Intraoperative Change in Pupil Diameter (Full Analysis Set Population)

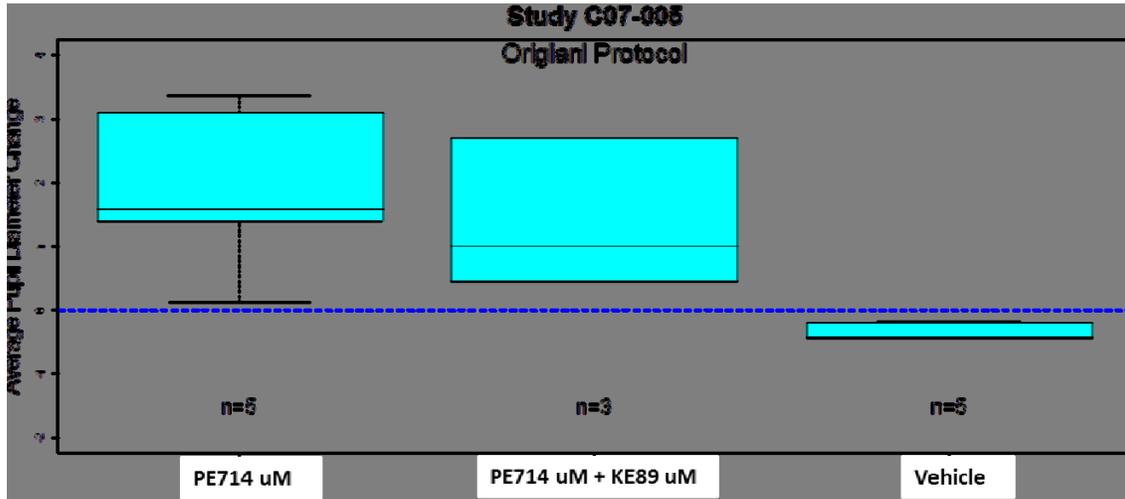


Table 4: Study C07-005 (Original Protocol) AUC of Intraoperative Change in Pupil Diameter and Total Volume of Study Irrigation Used

	714 uM PE N=5 Median (range)	OMS302 714 uM PE 89 uM KE N=3 Median (range)	Vehicle N=5 Median (range)
AUC of Reduced Pupil Diameter	1.57 (0.12 – 3.36)	1.00 (0.45 – 2.69)	-0.43 (-2.63 – -0.17)
Total Volume of Study Irrigation Used	300 mL (205 mL – 450 mL)	400 mL (200 mL – 450 mL)	250 mL (200 mL – 400 mL)

Figure 3: Study C07-005 (Amendment 1) AUC of Intraoperative Change in Pupil Diameter (Full Analysis Set Population)

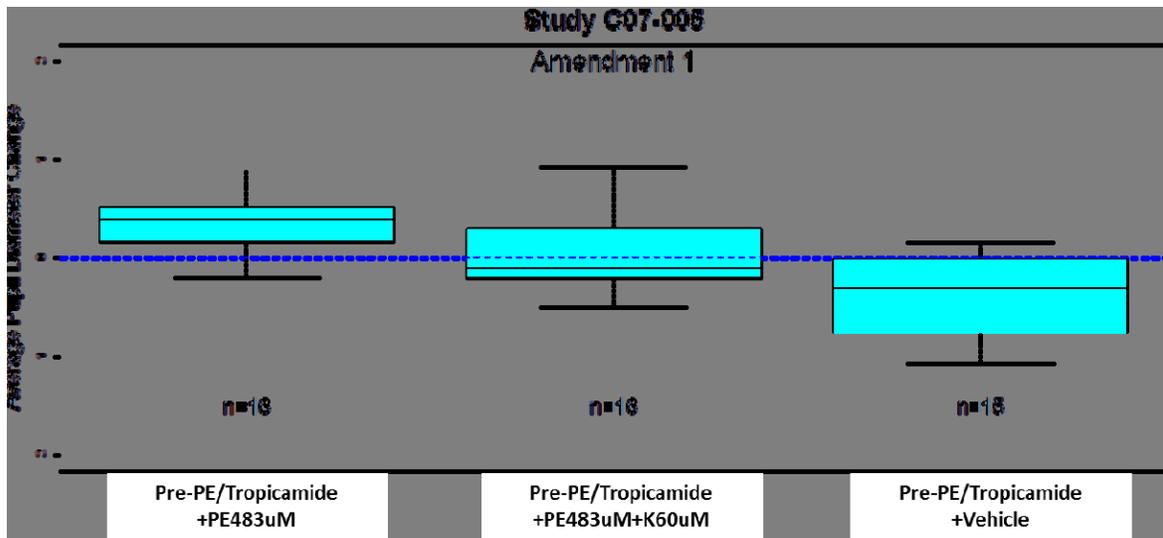


Table 5: Study C07-005 (Amendment 1) AUC of Intraoperative Change in Pupil Diameter and Total Volume of Study Irrigation Used

	Pre-operative PE/tropicamide + 483 uM PE N=16 Median (range)	Pre-operative PE/tropicamide + OMS302 483 uM PE 60 uM KE N=16 Median (range)	Pre-operative PE/tropicamide + Vehicle N=15 Median (range)
AUC of Reduced Pupil Diameter	0.39 (-0.55 – 0.88)	-0.11 (-0.50 – 0.93)	-0.31 (-1.07 – 0.15)
Total Volume of Study Irrigation Used	202 mL (140 mL – 300 mL)	255 mL (151 mL – 420 mL)	270 mL (145 mL – 425 mL)

The Phase 2 Study C09-001 was a randomized, parallel-group, double-masked, vehicle-controlled study of PE, KE, and OMS302 in subjects undergoing cataract extraction and lens replacement using a coaxial phacoemulsification process with insertion of an acrylic lens (n=222). Subjects were randomized to one of the four treatment groups in a 1:1:1:1 fashion.

In Study C09-001, a slight PE contribution to the treatment effect in the change in pupil diameter was demonstrated when PE (final concentration of 483 μ M) was administered in combination with KE in Study C09-001 ($p=0.7$). PE at 483 μ M displayed slightly higher AUCs of intraoperative change in the pupil diameter compared to placebo group in Study C09-001 ($p=0.7$) (Figure 4 and Table 6). Although it is not statistically significant, this is considered to be acceptable, since the baseline in the change in pupil diameter includes pre-operative mydriatic treatment (i.e., PE 2.5% and tropicamide 1%).

The pupil diameter change in PE+KE is comparable to that in PE alone when analyzing the mean AUC of intraoperative change in pupil diameter in Study C09-001 ($p=1.0$). In addition, KE did not display any contribution to the treatment effect in inhibiting miosis compared to placebo arm in Study C09-001 ($p=1.0$). Therefore, KE did not display any contribution to the treatment effect in inhibiting miosis and any additive effect on PE in pupil diameter changes when KE was administered with PE.

Figure 4: Study C09-001: AUC of Intraoperative Change in Pupil Diameter (Mydriasis Analysis Set)

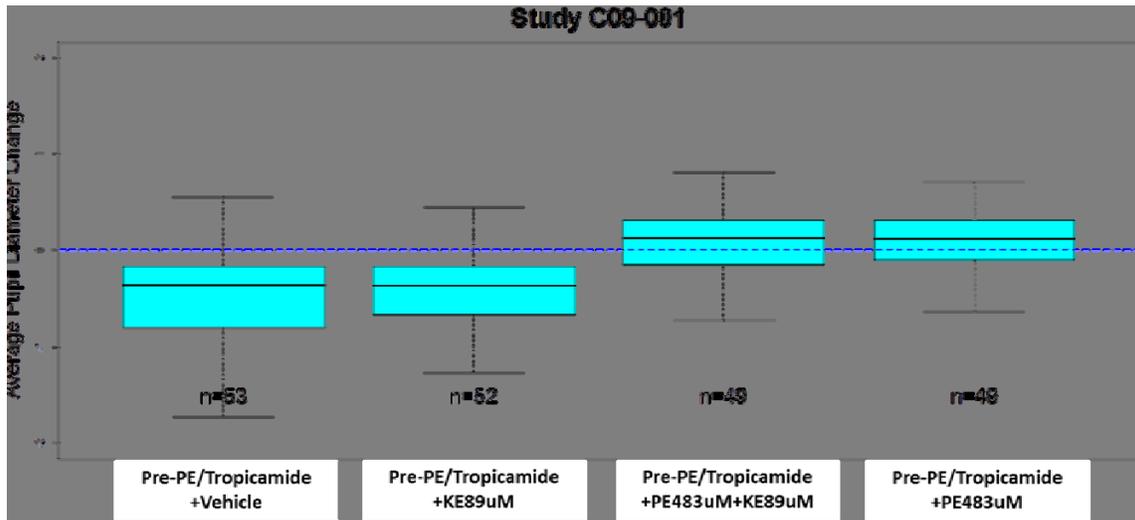


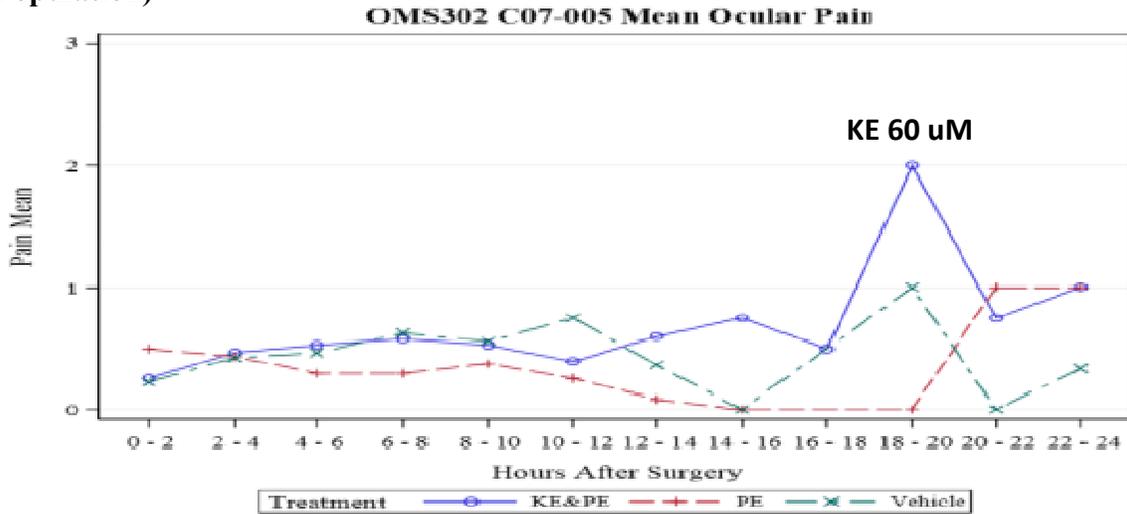
Table 6: Study C07-001 Mean AUC Analysis of Change From Baseline in Pupil Diameter (mm) During CELR Surgery (Mydriasis Analysis Set)

	Vehicle (N=53) n(%)	PE (N=49) n(%)	KE (N=52) n(%)	OMS302 (N=49) n(%)
Mean AUC ^a				
n	53	49	52	49
Mean(SD)	-0.6 (0.7)	0.1 (0.4)	-0.4 (0.5)	0.1 (0.4)
Median	-0.4	0.1	-0.4	0.1
Min. Max	-3.3, 0.6	-1.0, 1.1	-2.1, 0.4	-1.1, 1.4
Difference in Mean AUC ^b				
Least squares mean difference (SE)	0.7 (0.1)		0.6 (0.1)	
95% confidence interval	0.5,0.9		0.4,0.8	
p-value	0.0000		0.0000	

In Study C07-005, the KE final concentration of 89 μM (for the initial 2 subjects) was amended to KE 60 μM . However, the ocular Pain Score during 12 Hours Post-operation did not display clinical meaningful effect of OMS302 at KE 60 μM compared to placebo (Figure 5). Based on the result, the higher concentration of KE (i.e., 89 μM) was selected for Phase 2 and Phase 3 studies.

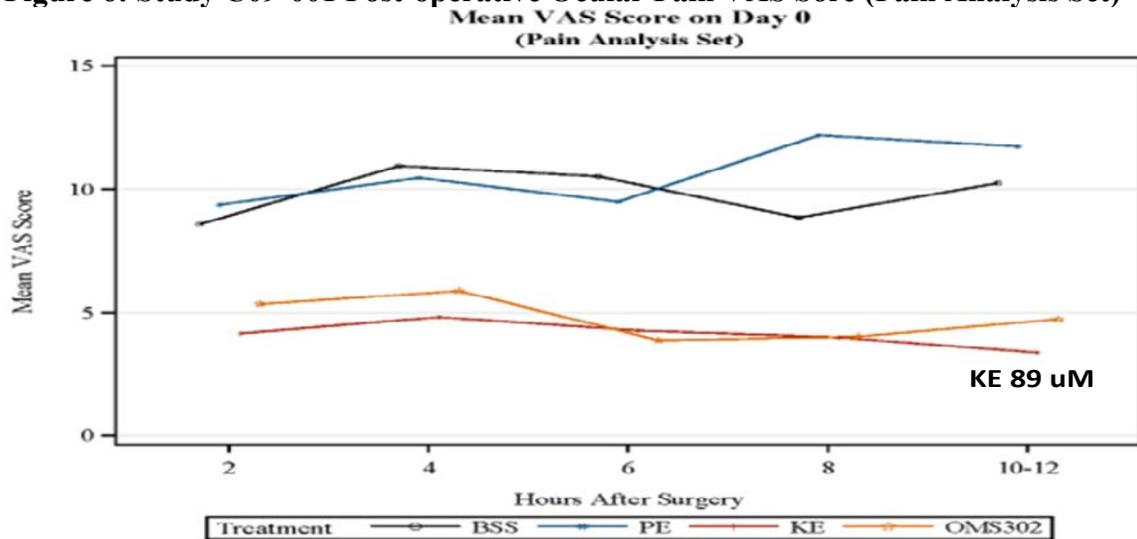
The contribution of KE at 89 μM to the treatment effect in the ocular Pain Score was demonstrated when KE was administered in combination with PE in Study C09-001 ($p=0.0093$) (Figure 6). Thus, the sponsor's proposed dose (i.e., KE89 μM in irrigation solution) is acceptable.

Figure 5: Study C07-005 Post-operative Ocular Pain NRS Grade (Full Analysis Set Population)



0 = None and 3 = Severe

Figure 6: Study C09-001 Post-operative Ocular Pain VAS Score (Pain Analysis Set)



Pain-free (VAS score = 0)

Treatment related systemic and local adverse event rate in OMS302 treatment group was comparable to that in placebo group. In addition, based on the assessment of the PK information in Study OMS302-ILR-004, OMS302 administration results in minimal to no systemic absorption of PE and KE. Thus, there are minimal systemic safety concerns.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3. OCP FILING AND REVIEW FORM

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205,388	Brand Name	Omidria
OCP Division (I, II, III, IV, V)	IV	Generic Name	Phenylephrine hydrochloride (PE) and ketorolac tromethamine (KE) (OMS302) injection solution, concentrate intended for admixture with standard irrigation solution
Medical Division	DTOP	Drug Class	α 1-adrenergic receptor agonist, and nonsteroidal anti-inflammatory drug (NSAID)
OCP Reviewer	Yoriko Harigaya, Pharm.D.	Indication(s)	(b) (4) prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain for intraocular lens replacement
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.	Dosage Form	Injection solution, concentrate intended for admixture with standard irrigation solution
Pharmacometrics Reviewer	N/A	Dosing Regimen	4 mL of phenylephrine hydrochloride 12.37 mg/mL and ketorolac tromethamine 4.24 mg/mL. OMS302 must be diluted prior to use; 4.0 mL of OMS302 drug product is diluted in 500 mL of standard irrigation solution (e.g. balanced salt solution), resulting in a solution with PE at a final concentration of approximately 480 μ M (0.0098% w/v) and KE at a final concentration of approximately 89 μ M (0.0034% w/v)
Date of Submission	July 30, 2013	Route of Administration	Topical administration to the eye
Estimated Due Date of OCP Review	April 25, 2014	Sponsor	Omeros Corporation
Medical Division Due Date	N/A	Priority Classification	Standard
PDUFA Due Date	May 30, 2014		

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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
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:				
multiple dose:				

Patients-				
single dose:	X	1	1	
multiple dose:				
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	2	
Phase 3:	X	(2)	(2)	One Phase 3 study includes PK study above
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
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				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4	4	

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YORIKO HARIGAYA
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