

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205388Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review for NDA 205388

Date	May 27, 2014
From	Wiley A. Chambers, M.D.
NDA #	205388
Applicant	Omeros Corporation 201 Elliott Avenue West Seattle, WA 98119 (206) 676-5000
Date of Submission	7/30/13
Type of Application	505(b)(2)
Name	Omidria (phenylephrine and ketorolac injection), 1%/0.3%
Dosage forms / Strength	Injection (intracameral), 1%/0.3%
Applicant's Proposed Indication(s)	For maintaining pupil size by preventing intraoperative miosis and for reducing postoperative pain
Recommended:	Recommended for Approval

1. Introduction

Omidria, also known as OMS302 is a fixed-dose combination product containing phenylephrine hydrochloride (PE), an α_1 -adrenergic receptor agonist, and ketorolac tromethamine (KE), a non-selective cyclooxygenase inhibitor. Omidria is proposed to be added to an ophthalmic irrigating solution used during cataract surgery. Phenylephrine, has been in wide clinical use in a variety of dosage forms for at least 75 years and KE, an NSAID, was first approved by the United States in 1989 as an injectable drug product for systemic pain relieve and subsequently approved as an ophthalmic topical agent for several ophthalmic indications. OMS302 is the first drug product combining both agents.

Omidria is intended for admixture with sterile ophthalmic irrigating solutions. The finished dosage form will contain 61 mM (12.37 mg/mL) phenylephrine HCl and 11 mM (4.24 mg/mL) ketorolac tromethamine, formulated in a ^{(b)(4)} sodium citrate buffer (pH 6.3 \pm 0.3). Each vial is filled to allow withdrawal of 4 mL of formulation concentrate for admixture with 500 mL of irrigation solution.

During surgical procedures, the admixed irrigation solution is administered either through a phacoemulsification surgical solution tubing set or via plastic syringe and needle. The intracameral space and to a lesser extent the surface of the eye are exposed to the irrigation admixture. This form of administration is expected to limit systemic absorption.

2. Background

Prior Approval/Availability of Proposed Active Ingredients in the United States include, but are not limited to:

- NDA 11663: Cyclomydril (cyclopentolate hydrochloride and phenylephrine hydrochloride)

Ophthalmic Solution (withdrawn FR Effective 04/30/1984).

- ANDA 84300: Cyclopentolate hydrochloride (0.2%) and phenylephrine hydrochloride (1%) ophthalmic solution. Indicated for the production of mydriasis.
- NDA 000607: Isophrin (phenylephrine hydrochloride) Ophthalmic Solution (withdrawn FR effective 03/02/1994).
- ANDA 75222 and multiple others: Ketorolac injection 15 mg/mL and 30 mg/mL indicated for short term (<5 days) management of moderately severe pain.
- NDA 19700: Acular (ketorolac ophthalmic solution), 0.5%, indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of postoperative inflammation in patients who have undergone cataract surgery.
- NDA 203510: Phenylephrine ophthalmic solutions, 2.5% and 10%, indicated to dilate the pupil.

This application (NDA 205388) is submitted as a 505(b)(2) application and relies on the Agency's findings for non-clinical study information, for which the applicant does not have a right to reference, NDA 203510 and NDA 19700. This information is "bridged" by reference to the chemistry/manufacturing information that the same drug substances have been used in higher concentrations. The applicant has conducted their own safety and efficacy clinical studies.

3. CMC

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

		mg/mL
Phenylephrine HCl	Active	12.37
Ketorolac Tromethamine	Active	4.24
Citric acid monohydrate	(b) (4)	(b) (4)
Sodium citrate dihydrate	(b) (4)	(b) (4)
Water for injection	(b) (4)	(b) (4)
Sodium hydroxide	(b) (4)	Adjust to pH 6.3
Hydrochloric acid	(b) (4)	Adjust to pH 6.3
(b) (4)		

The OMS302 drug product is contained in a 5 mL Type 1 (b) (4) clear glass vial. The container closure is an elastomeric stopper with a (b) (4) The container closure is retained by an (u) (4) seal and (u) (4) flip-off cap. The drug product must be protected from ambient light and is therefore packaged for storage in a paper board container system.

Specifications

Test	Method	Acceptance Criteria
Color	Visual	Colorless
Appearance	Visual	Clear solution (b) (4)
Volume	USP <1>	NLT labeled volume of (b) (4)
Subvisible particulates	(b) (4)	(b) (4) *
Spectra	HPLC/UV	Match
Phenylephrine Potency	HPLC/UV	92-108% label claim
Ketorolac Potency	HPLC/UV	92-108% label claim
Degradation Products	HPLC/UV	
(b) (4)	(b) (4)	NMT (b) (4)
Unspecified individual		NMT (b) (4)
Total		NMT (b) (4)
pH	(b) (4)	(b) (4)
Osmolality	(b) (4)	(w) (4) mOsm/kg
Sterility	(b) (4)	Meets
Container Closure Integrity	(b) (4)	NMT (b) (4) cc/s
Endotoxins	(b) (4)	NMT (b) (4) EU/mL

*Specification limit for particles (b) (4) µm applies only if light obscuration method fails and microscopic method is utilized.

The specification limit for particulate matter is not consistent with many other ophthalmic products. The (b) (4) limit should apply to either the light obscuration method or the microscopic method.

The specification limit for unspecified degradation products is not consistent with many other ophthalmic products. Many ophthalmic products include a limit of NMT (b) (4) for unspecified individual impurities.

The product is manufactured at a contract manufacturing facility (b) (4) via a process of (b) (4). The latter two operations have been reviewed by the New Drug Microbiology Staff. Sterility assurance has been evaluated from the Product Quality Microbiology perspective and found adequate. There are no clinical objections to this method.

Phenylephrine HCl is manufactured by (b) (4). The chemistry, manufacturing and controls of the drug substance are documented in Type II DMF (b) (4). This facility was noted to have deficiencies in cGMP last year. The facility addressed those deficiencies and has been re-inspected, but a final assessment of that inspection has not yet been forwarded to the reviewers. Ketorolac tromethamine is manufactured by (b) (4). The chemistry, manufacture and controls of the drug substance are documented in Type II DMF (b) (4).

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review has been completed and recommends approval of the application. Phenylephrine and ketorolac both have a long history of use as topical agents in ophthalmology and there is a significant body of literature on their individual clinical pharmacology. The safety and efficacy data in support of the use of OMS302 for the intended indication relies on historical data as well as nonclinical and clinical studies conducted with OMS302.

A single-dose toxicology study was conducted in African green monkeys exposed during lens replacement surgery to ocular irrigation solutions containing OMS302. No drug related ocular or systemic adverse findings were observed, with combinations of phenylephrine hydrochloride and ketorolac tromethamine in irrigation solution administered at concentrations up to 7200 μM and 900 μM , respectively. These concentrations are over 10-fold higher than the concentrations intended to be administered clinically (480 μM phenylephrine hydrochloride and 89 μM ketorolac tromethamine).

At the NOAEL dose in the ocular toxicology study, the maximal levels of phenylephrine and ketorolac were 7-fold and 4-fold higher in the anterior chamber, and 27-fold and 47-fold higher in the plasma, respectively, than the levels observed after administration of OMS302 in the clinic. The absence of any test article-related findings in assessment of ocular physiology and histopathology and systemic toxicity endpoints supports the safety of the product.

In addition, the existent nonclinical and clinical pharmacokinetic data support that the systemic exposure of phenylephrine and ketorolac at the intended dosing regimen is not expected to be above the range of values already observed after ocular and/or oral administration of FDA approved products.

5. Clinical Pharmacology/Biopharmaceutics

One of the Phase 3 studies (OMS302-ILR-004) includes a pharmacokinetics (PK) substudy; 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 preoperative 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. 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.

6. Sterility Assurance

The drug product is a sterile parenteral solution; therefore, the integrity of the seal generated between the glass vial container and elastomeric closure, as it relates to preventing microbial contamination has been evaluated by performing container closure integrity studies and found to be acceptable.

7. Clinical/Statistical - Efficacy

Study	Phase	Study Design	Test Product	Number of Subjects
OMS302-ILR-004	Phase 3	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	416 total: 209 OMS302 207 Placebo PK subset: 26 total 14 OMS302 12 Placebo
OMS302-ILR-003	Phase 3	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 total: 203 OMS302 202 Placebo
C09-001	Phase 2	Randomized, parallel group, double-masked, vehicle controlled 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 (4) Vehicle control Single dose, intraocular irrigation and intracameral perfusion	223 total: 56 OMS302 56 PE 55 KE 56 Vehicle
C07-005	Phase 1/Phase 2	Randomized, controlled, double-masked, vehicle- and phenylephrine HCl-controlled	PE and KE alone and in combination (OMS302), diluted in BSS; Three arms: (1) 483 µM PE (2) 483 µM PE and 60 µM KE (3) BSS Vehicle Single dose, intraocular irrigation and intracameral perfusion	61

Study OMS302-ILR-003: Pupil Size - Full Analysis Set Population

	Placebo N=201	OMS302 N=201	p-value
Mean AUC			
Number of Patients With Video Data	180	184	
Mean (sd)	-0.5 (.58)	0.1 (.41)	
Min, Max	-2.9, 2.1	-2.7, 1.3	
Difference in Mean AUC			
CMH Weighted Mean Difference (SE)	0.577 (0.052)		<0.0001
95% CI	0.475, 0.678		
Subjects With \geq 6mm At Cortical Clean-up In Subjects With Video Data	139/180 (77.2%)	177/184 (96.2%)	<0.0001
Pupil Diameter (mm) at cortical Clean-up	N=180	N=184	
Mean (sd)	7.1 (2.0)	8.0 (1.8)	<0.0001
Min, Max	3.8, 18.0	2.7, 17.8	
Subjects With Degree of Pupillary Constriction			<0.0001
<0.5mm	9	78	
\geq 0.5 to <1.0mm	24	70	
\geq 1.0 to <1.5mm	41	11	
\geq 1.5 to <2.0mm	36	9	
\geq 2.0 to <2.5mm	20	10	
\geq 2.5mm	50	6	

Study OMS302-ILR-004: Pupil Size - Full Analysis Set Population

	Placebo N=204	OMS302 N=202	p-value
Mean AUC			
Number of Patients With Video Data	200	195	
Mean (sd)	-0.5 (.57)	0.1 (.43)	
Min, Max	-2.3, 1.5	-2.2, 2.3	
Difference in Mean AUC			
CMH Weighted Mean Difference (SE)	0.590 (0.049)		<0.0001
95% CI	0.494, 0.686		
Subjects With \geq 6mm At Cortical Clean-up In Subjects With Video Data	154/200 (77.0%)	187/195 (95.9%)	<0.0001
Pupil Diameter (mm) at cortical Clean-up	N=200	N=195	
Mean (sd)	7.5 (2.5)	8.6 (2.4)	<0.0001
Min, Max	3.3, 18.7	4.8, 19.2	
Subjects With Degree of Pupillary Constriction			<0.0001
<0.5mm	14	92	
\geq 0.5 to <1.0mm	29	58	
\geq 1.0 to <1.5mm	47	26	
\geq 1.5 to <2.0mm	40	13	
\geq 2.0 to <2.5mm	17	4	
\geq 2.5mm	53	2	

Efficacy in maintaining pupil dilation was demonstrated in each study.

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population)

	Placebo N=201	OMS302 N=201	p-value
Mean AUC			
Mean (sd)	9.2 (12.9)	4.1 (8.1)	
Min, Max	0.0, 65.3	0.0, 66.9	
Difference in Mean AUC			
CMH Weighted Mean Difference (SE)	-5.199 (1.076)		<0.0001
95% CI	-7.307, -3.091		
Subjects With Pain Free (VAS=0) At all Timepoints	28	48	0.0108
Subjects with Maximum VAS Score During 12 Hours Post-operatively			0.0002
>=0 to <=5	97	137	
>5 to <=10	23	13	
>10 to <=15	9	14	
>15 to <=20	11	7	
>20	61	30	

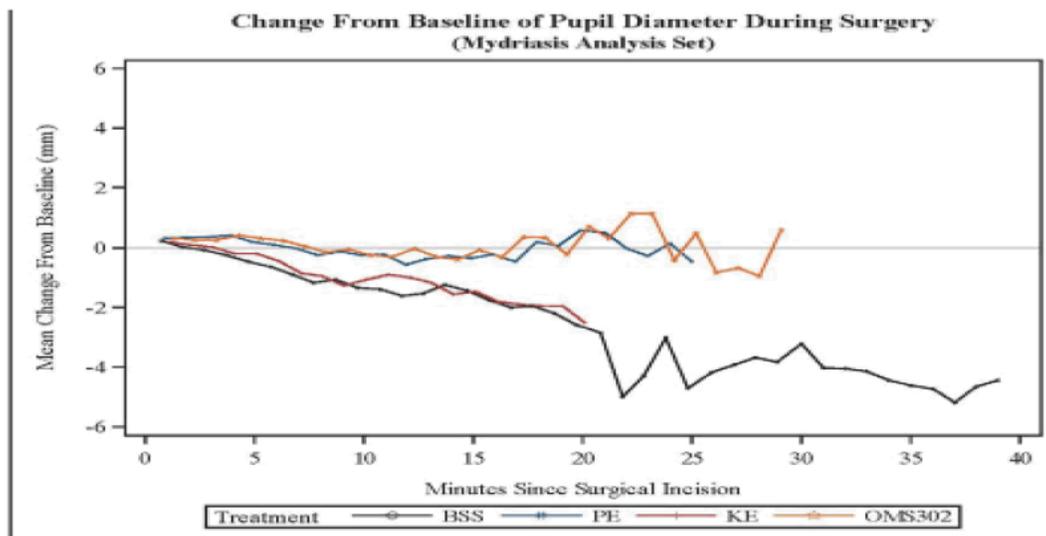
Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population)

	Placebo N=204	OMS302 N=202	p-value
Mean AUC			
Mean (sd)	8.9 (15.2)	4.3 (8.8)	
Min, Max	0.0, 85.8	0.0, 58.4	
Difference in Mean AUC			
CMH Weighted Mean Difference (SE)	-4.580 (1.192)		0.0002
95% CI	-6.917, -2.244		
Subjects With Pain Free (VAS=0) At all Timepoints	41	56	0.0806
Subjects with Maximum VAS Score During 12 Hours Post-operatively			0.0959
>=0 to <=5	101	126	
>5 to <=10	21	20	
>10 to <=15	19	14	
>15 to <=20	10	10	
>20	51	32	

Efficacy for pain relief during the initial 10-12 hours postoperatively was demonstrated in each study.

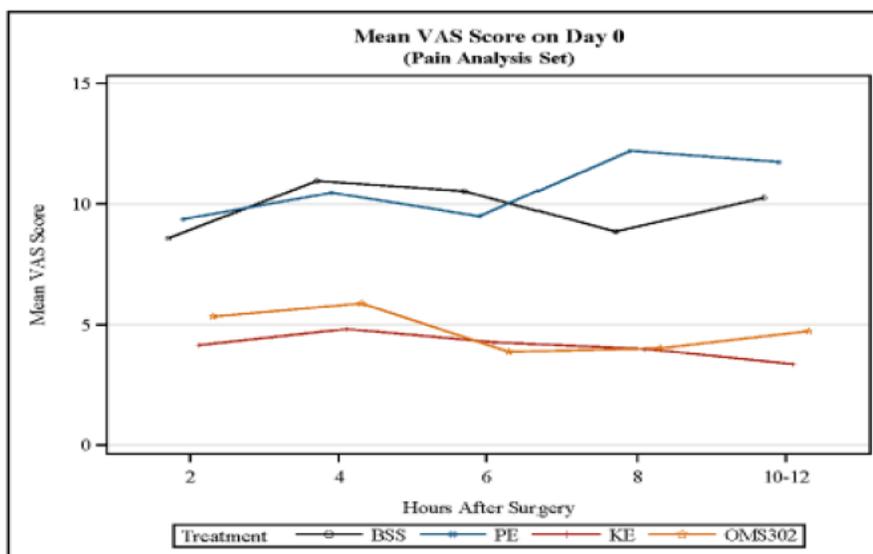
Study C09-001 (full factorial)

Video recordings of each subject's surgical procedure were used to measure the pupil diameter over time. A masked central reader performed the pupil size measurements. Post-operative ocular pain was reported in a subject diary using the VAS at approximately 2 hours, 4 hours, 6 hours, 8 hours, and 10–12 hours post-surgery.



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Pupil diameter decreased throughout the surgical procedure in both the vehicle and KE groups, but mydriasis was consistently maintained in both the PE and OMS302 groups. The superiority of OMS302 over vehicle and KE demonstrates the contribution of PE to maintenance of mydriasis.



Pain score in vehicle and PE groups were consistently higher than in the OMS302 and KE groups. The superiority of OMS302 over PE and vehicle demonstrates the contribution of KE to the reduction of post-operative ocular pain.

Additional Analyses - Analysis of Patients with Distorted Video Images

In the images in which the microscope was not directly above the eye, the ruler is foreshortened compared to the long axis of the iris and the iris diameter is artificially increased due to the angle of the observation. The relative measures of the pupil and iris are not affected when measured during the surgical procedure, but the absolute measures are artificially increased and may result in pupil diameters out of physically plausible range. These images were reviewed and removed from the analyses presented in this review. A full explanation is included in the Medical Officer's Review.

There are no major statistical issues identified for any of three studies.

8. Safety

There were 403 patients in the controlled safety database who received OMS302.

Adverse Events

Study OMS302-ILR-003: Subject Incidence of Treatment-Emergent AEs by System Organ Class

System Organ Class	OMS302		Placebo	
	Study 3, N=201	Study 4, N=202	Study 3, N=201	Study 4, N=204
Any Event	156		154	
Eye disorders	150	22	148	29
Abnormal sensation in eye				1
Anterior chamber fibrin	1			
AC inflammation	19	10	21	8
Conjunctival hemorrhage	1		3	1
Conjunctival hyperemia	1	10		8
Conjunctival edema	1	1	1	
Conjunctivitis	6		4	
Corneal disorder	3		4	1
Corneal edema	7	2	5	3
Corneal pigmentation	1			
CME	1			
Dry eye	1		2	
Eye inflammation	60		58	1
Eye irritation	5	1	2	1
Eye pain	88	6	86	14
Eye pruritus	1			
Eyelid pain		1		
FBS in eyes	1	1		3
Glare		1		
Iridocele				1
Iris disorder				1
Lacrimation increased				1
Miosis				1
Macular degeneration			1	
Macular hole			1	

Mydriasis		1		
Ocular discomfort	2	3	6	5
Photophobia	8	3	7	8
PCO	1		1	
SPK	3		2	
Retinal hemorrhage			1	
Trichiasis	1			
Vision blurred		1	1	1
Visual Acuity reduced	1		1	
Vitreous detachment	1		2	
Vitreous floater	1	1		
GI disorders	2		2	
Abdominal discomfort			1	
Dyspepsia	1			
Nausea	1	1	1	
Infections	2		1	
Bronchitis	1			
Hordeolum	1			
Oral herpes			1	
Injury, Poisoning, and Procedural Complications	1		7	
Corneal abrasion	1		3	
Exoriation			1	
Facial bones fracture			1	
Fall			2	
Foreign body in eye			1	
Laceration			1	
Procedural hypertension			1	
Wrist fracture			1	
Investigations	7		12	
Blood pressure increased			2	
IOP increased	7		10	
Musculoskeletal disorders	6		2	
Arthralgia	2		2	
Back pain	1			
Musculoskeletal pain	1			
Myalgia	1			
Pain in extremity	1			
Nervous system disorders	5		15	
Head discomfort			1	
Headache	5	1	14	2
Psychiatric disorders	0		3	
Anxiety			1	
Insomnia			2	
Respiratory disorders	2		1	

Nasal discomfort	1			
Oropharyngeal pain	1			
Rhinorrhea			1	
Metabolism and nutrition disorders	1		0	
DM	1			
General disorders	1		0	
Electrocution	1			

The most frequently observed AEs overall were eye pain, ocular inflammation, headache, and increased IOP, all anticipated events following cataract or intraocular lens surgery. These events occurred at a similar incidence across the treatment groups.

Deaths

Study OMS302-ILR-003: One subject (Subject 193009) died during the study as a result of electrocution in an industrial accident. This was a 61 year old male who underwent cataract surgery on 12/13/11. He was randomized to the OMS302-treatment group. On (b) (6), the subject was electrocuted and died while working on an (b) (6). The subject was not taking any concomitant medications and had no relevant medical history. Study OMS302-ILR-004: No deaths.

Safety Summary Statement

The safety of Omidria (phenylephrine and ketorolac injection) 1%/0.3% in adults is supported by adequate and well controlled studies. The most frequently observed AEs overall were eye pain, ocular inflammation, headache, and increased IOP, all anticipated events following cataract or intraocular lens replacement (ILR) surgery

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Safety and effectiveness of Omidria in pediatric patients below the age of 18 years have not been established. This application was reviewed by the Pediatric Review Committee (PeRC) and on 10/30/13 and PeRC agreed with the deferral for all pediatric age groups.

While efficacy can be extrapolated from studies in adults and the known pharmacologic action of phenylephrine in pediatric patients. A single pediatric safety study in at least 60 patients (30 per arm) undergoing cataract surgery is planned to be conducted in the U.S. (b) (4)

11. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, CMC, and Biostatistics have recommended approval of this new drug application. A review of the financial disclosure information identified a single investigator with potential financial conflicts. This investigator did not contribute enough patients (total ^(b)₍₄₎ patients) to affect the outcomes of the studies.

OSI

An Office of Scientific Investigations (OSI) audit was requested. The clinical sites of Drs. Dunn, Lim, and Marsico were selected for inspection because they were amongst the highest enrolling for their respective protocols.

Dr. Marsico was issued a Form FDA 483. The final classification of this inspection was Voluntary Action Indicated (VAI). Other than the dispensation of a corticosteroid to all subjects postoperatively after the study data had been collected, there were no deviations noted. The data generated by this clinical site and submitted by the applicant appear adequate in support of the respective indication.

Drs. Dunn and Lim were issued Form FDA 483s. The final classification of these inspections was Voluntary Action Indicated (VAI). The amount of test article withdrawn from the dispensing vials was not documented for C09-001 and/or OMS302-IL-003. This lack of documentation was acknowledged by both Drs. Dunn and Lim. Both investigators implemented corrective actions to capture this data for subsequent study activities. There appears to be sufficient documentation to assure that the drug was available to the site, that the protocol contained specific instructions for preparation of the test article, that study kits were documented as received and used, and that subjects were dispensed the test article. OSI considers the available documentation, in conjunction with the investigators' written responses, to provide reasonable assurance that subjects were treated in compliance with the protocol.

OPDP

A review of the substantially complete labeling was completed by the Office of Prescription Drug Promotion (OPDP).

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) provided a labeling review of the original package insert and original carton and container labeling.

The Cross-Discipline Team Leader Review reconciles differences in opinion between the Clinical, OPDP and DMEPA reviews.

12. Labeling

NDA 205388, Omidria (phenylephrine and ketorolac injection) 1%/0.3% is recommended to be approved for maintenance of pupil size by preventing intraoperative miosis and reduction of postoperative pain with the labeling found at the end of the CDTL review.

13. Recommendations/Risk Benefit Assessment

NDA 205388, Omidria (phenylephrine and ketorolac injection) 1%/0.3% is recommended to be approved for maintenance of pupil size by preventing intraoperative miosis and reduction of postoperative pain pending completion of the facility review for the [REDACTED] (b) (4).

Wiley A. Chambers, MD
Deputy Division Director

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/s/

WILEY A CHAMBERS
05/27/2014

CLINICAL REVIEW

Application Type	NDA
Submission Number	205-388
Submission Code	000
Letter Date	7/30/13
Stamp Date	7/30/13
PDUFA Goal Date	5/30/14
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	3/21/14
Established Name	phenylephrine/ketorolac for injection
(Proposed) Trade Name	Omidria
Therapeutic Class	sympathomimetic/NSAID
Applicant	Omeros
Priority Designation	S
Formulation	solution
Dosing Regimen	ophthalmic irrigation solution
Proposed Indications	For the (b) (4), prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain
Intended Population	Patients undergoing cataract surgery

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 205-388 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Omidria for the (b) (4) prevention of intraoperative miosis) and reduction of (b) (4) post-operative pain.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

OMS302 is a fixed-dose combination product containing phenylephrine hydrochloride (PE), an α_1 -adrenergic receptor agonist, and the NSAID ketorolac tromethamine (KE), a non-selective cyclooxygenase (COX) COX-1/COX-2 inhibitor. OMS302 is added to standard irrigation solution used during cataract surgery.

2.2 Tables of Currently Available Treatments for Proposed Indications

None, for both indications concurrently. There are several NSAIDs approved for topical use, pre-operatively for prevention of miosis and post-operatively for pain.

2.3 Availability of Proposed Active Ingredient in the United States

NDA 11663: Cyclomydril (cyclopentolate hydrochloride and phenylephrine hydrochloride) Ophthalmic Solution (withdrawn FR Effective 04/30/1984).

ANDA 84300: Cyclopentolate hydrochloride and phenylephrine hydrochloride ophthalmic solution. Indicated for the production of mydriasis: Combination of an adrenergic agent (which activates iris dilator muscle) and an anticholinergic agent (which paralyzes the iris sphincter muscle and accommodative muscle of the ciliary body).

NDA 000607: Isophrin (phenylephrine hydrochloride) Ophthalmic Solution (withdrawn FR effective 03/02/1994).

NDA 19700: Acular

ANDA 75222: Ketorolac injection

2.4 Important Safety Issues With Consideration to Related Drugs

The predominant actions of PE are on the cardiovascular system, where it produces significant vasoconstriction, but lacks chronotropic actions on the heart. Systemic side effects have been reported following topical ophthalmic instillation of PE. Uncommon systemic adverse reactions include elevated blood pressure, stroke, rupture of aneurysms, tachycardia, ventricular arrhythmia, myocardial infarction, and subarachnoid hemorrhage. Coronary artery spasm and pulmonary embolism in diabetics and acute pulmonary edema in premature infants have also been reported. The risk of these systemic side effects appears to be related to the PE concentration, ie. 10% PE is associated with a higher risk than 2.5% PE. Patients taking certain systemic medications are more sensitive to the pressor effects of PE; therefore PE should be used with caution in patients on MAO inhibitors.

Ketorolac inhibits COX-1 and COX-2. Systemic adverse reactions are rare following topical ophthalmic instillation of KE. Reports have included exacerbation of asthma due to systemic absorption, gastrointestinal irritation and ulceration, inhibition of platelet function and increased bleeding, and renal disease. Idiosyncratic drug reactions may also occur. The most common adverse reactions are local in nature, such as transient burning, stinging, and conjunctival hyperemia. More serious but less common local reactions include corneal complications such as SPK, epithelial defects, corneal melting, and delayed wound healing and re-epithelialization. Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgical procedures, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, rheumatoid arthritis, or repeat ocular surgical procedures within a short period of time may be at an increased risk for corneal adverse events.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

IND 78227 submitted	1/15/08
EOP2 meeting	7/15/11
Pre-NDA CMC meeting	1/16/12
Pre-NDA Clinical meeting	2/11/13

PSP meeting 5/16/13

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for this study. There were no issues preliminarily identified to indicate a problem with submission integrity or quality.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

See Appendix for Financial Disclosures template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

OMS302 is a preservative-free, bisulfite-free, clear, colorless, sodium citrate-buffered, sterile solution concentrate containing 12.4 mg/mL of phenylephrine hydrochloride and 4.24 mg/mL ketorolac tromethamine in a single-use vial. For administration, OMS302 must be diluted prior to use; 4.0 mL of OMS302 drug product is diluted in 500 mL of standard irrigation solution (ie. 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).

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Pre-clinical Pharmacology/Toxicology

The drug substances in OMS302 have been used individually for many years. Phenylephrine, a α_1 -adrenergic receptor agonist, was initially introduced into clinical use at least 75 years ago and KE (Toradol), an NSAID, was first approved by the United States FDA in 1989. OMS302 is the first drug product containing both agents.

Three non-clinical pharmacology studies and one GLP safety and toxicology study, all involving single administration of PE, KE, or their combination, were conducted in non-human primates. Single-dose nonclinical studies are appropriate because the intended clinical use is a single intraoperative administration. See pharm/tox review for further discussion on these studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Phenylephrine is an α_1 -adrenergic receptor agonist. Ketorolac is a NSAID that inhibits both COX-1 and COX-2.

4.4.2 Pharmacodynamics

See clinical pharmacology review.

4.4.3 Pharmacokinetics

The clinical pharmacokinetics of OMS302 were evaluated in a sub-study of the Phase 3 trial OMS302-ILR-004. The PK sub-study enrolled 26 subjects, with 14 subjects randomized to OMS302 treatment and 12 subjects randomized to placebo treatment (placebo in BSS irrigation solution). Serial plasma samples were collected prior to surgery and OMS302 administration and at several timepoints over the 24 hours after surgery. The concentrations of PE and KE were analyzed by LC/MS/MS with validated assays that had a LLOQ of 1 ng/mL. Plasma concentrations for PE and KE were low or undetectable after OMS302 administration and insufficient for PK analysis.

Only one subject had detectable PE: subject 190063 assigned to OMS302 treatment. The subject's pre-treatment sample (immediately following instillation of topical PE and prior to administration of OMS302) had a phenylephrine concentration of 1.7 ng/mL and the concentration decreased after study drug administration to 1.2 to 1.3 ng/mL during the first two hours and was undetectable at later timepoints. Since the highest PE concentration was observed prior to OMS302 administration, it may have been due to absorption of the preoperative PE 2.5% eye drops. Systemic absorption of preoperative PE instillation appears to be minimal, as 25 of 26 subjects did not have any detectable PE in plasma. Systemic absorption of PE following OMS302 administration is minimal to none, as 13 of 14 subjects did not have any detectable

levels and the low levels detected after dosing in subject 190063 may represent residual PE from the preoperative application. These data show that OMS302 administration results in no detectable systemic exposure to PE.

The KE results showed that 10 of 14 subjects treated with OMS302 and one of 12 subjects treated with placebo had detectable levels in plasma. The placebo-treated subject had a single sample with detectable KE, with a concentration of 8.5 ng/mL, at the 24-hour timepoint. One potential explanation for this result is that the subject may have received the post-operative KE eye drops the day after surgery prior to collection of the 24-hour PK blood sample, contrary to the protocol. The same explanation could also account for 24-hour timepoint results in two OMS302-treated subjects: Subject 18005 who had a concentration of 3.6 ng/mL and no detectable levels at any earlier timepoints, and Subject 179011 who had a concentration of 15.2 ng/mL, which was higher than all earlier timepoints (up to 4.2 ng/mL). Subject 179011 also had a pre-treatment KE concentration of 3.2 ng/mL, which is unexpected and may reflect recent KE use although the subject should not have been exposed to KE prior to surgery. Other than the two values of 8.5 and 15.2 ng/ml discussed earlier that are unlikely to be due to OMS302 administration, the remaining concentrations of ketorolac in subjects with detectable levels were low, in the 1-to-4 ng/mL range, and insufficient for PK analysis.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study	Phase	Study Design	Test Product	Number of Subjects
OMS302-ILR-004	Phase 3	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	416 total: 209 OMS302 207 Placebo PK subset: 26 total 14 OMS302 12 Placebo
OMS302-ILR-003	Phase 3	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 total: 203 OMS302 202 Placebo
C09-001	Phase 2	Randomized, parallel group, double-masked, vehicle controlled study	PE and KE alone and in combination (OMS302), diluted in BSS Four arms: (1) 483 µM PE (2) 89 µM KE	223 total: 56 OMS302 56 PE 55 KE 56 Vehicle

Study	Phase	Study Design	Test Product	Number of Subjects
			(3) 483 µM PE and 89 µM KE (4) Vehicle control Single dose, intraocular irrigation and intracameral perfusion	
C07-005	Phase 1/Phase 2	Randomized, controlled, double-masked, vehicle- and phenylephrine HCl-controlled	PE and KE alone and in combination (OMS302), diluted in BSS; Three arms: (1) 483 µM PE (2) 483 µM PE and 60 µM KE (3) BSS Vehicle Single dose, intraocular irrigation and intracameral perfusion	61

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

Study OMS302-ILR-003

This Phase 3 study was a randomized, parallel-group, double-masked, placebo-controlled study of OMS302 in subjects undergoing ILR (intraocular lens replacement) using a phacoemulsification process with insertion of an acrylic lens. Administration of test irrigation solutions took place in a double-masked fashion. Subjects were randomized 1:1 to OMS302 or placebo. Subjects undergoing CELR or refractive lens exchange (RLE) were eligible. Randomization to treatment group was stratified within site by cataract Lens Opacities Classification System II (LOCS II) Nuclear Color Opalescence with a nuclear grade of N₀ or N₁ classified as low and a nuclear grade of N₂ or N₃ classified as high.

All subjects were to receive standardized preoperative antibiotic treatment (Vigamox qid for three days prior to surgery), mydriatic treatment (one drop of PE 2.5% and one drop of tropicamide 1% at approximately 30 minutes, 15 minutes, and 5 minutes prior to surgery) and anesthesia (topical lidocaine or tetracaine administered according to the manufacturer's instructions). Post-operatively, all subjects continued the Vigamox regimen for seven days. All subjects were discharged with acetaminophen and instructed to contact their physician for pain not controlled by acetaminophen. Maintenance of mydriasis and prevention of miosis was determined by video capture and measurement of pupil diameter by a masked central reader.

Ocular pain and photophobia were assessed by each subject using a VAS and a NRS (numerical rating scale), respectively. Inflammation was assessed using a slit lamp biomicroscope. Safety and tolerability were assessed based on AEs, vital signs, and ocular and systemic measures for 14 days post-operatively. Study procedures were performed at screening, at baseline prior to surgery, intraoperatively, and postoperatively at approximately 2 hours, 4 hours, 6 hours, 8 hours, 10 to 12 hours, 24 hours, 48 hours, 7 days, and 14 days. Daily subject diaries were to be completed once each morning during the first 7 days postoperatively. The length of time for subject participation was approximately 2 to 6 weeks: up to 28 days in the screening process and 14 days in the post-operative period.

The primary objective of this study was to evaluate the effect of OMS302 compared to placebo when administered in irrigation solution during phacoemulsification and ILR surgery on intraoperative pupil diameter.

The primary efficacy endpoint:

- Change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure) determined by video capture during ILR and measured from the video capture by a masked central reader

The secondary efficacy endpoints were:

- Post-operative pain as measured by the VAS at 2, 4, 6, 8, and 10 to 12 hours after ILR surgery
- Post-operative pain as measured by the VAS at 24 hours, 48 hours, and 3 to 7 days, and 14 days after ILR surgery
- Photophobia as measured by the photophobia scale of the NRS at 2, 6, 24, and 48 hours, and at 7 and 14 days after surgery
- BCVA as measured using the ETDRS method at 24 and 48 hours, and at 7 and 14 days after surgery
- Post-operative inflammation as measured using the SOIS at 24 and 48 hours, and at 7 and 14 days after surgery.

The safety endpoints included:

- Adverse events and SAEs
- IOP
- Ophthalmological examinations
- Vital signs

Inclusion Criteria

For inclusion into the trial, subjects were required to fulfill all of the following criteria within 28 days prior to the day of surgery:

- Competent to provide informed consent

- Voluntarily provide informed consent in accordance to governing IRB requirements and providing HIPAA Authorization, prior to any procedures or evaluations performed specifically for the sole purpose of the study
- Indicate they understand and are able, willing, and likely to fully comply with study procedures and restrictions
- Are 18 years of age or older at the time of surgery
- Are to undergo unilateral primary CELR or RLE, under topical anesthesia, with a phacoemulsification device with insertion of an acrylic lens
- Have a BCVA of 20/400 or better in the non-study eye
- Have an IOP between 5-22 mm Hg, inclusive, in the study eye
- For women of childbearing potential, have a negative urine pregnancy test. Women of childbearing potential (ie. not surgically sterilized nor post-menopausal longer than 1 year), must agree to use a medically acceptable form of contraception throughout the study as necessary. Acceptable methods of contraception include a reliable intrauterine device, hormonal contraception or a spermicide in combination with a barrier method

Exclusion Criteria

- Hypersensitivity to phenylephrine, ketoprofen, or other NSAIDs, including aspirin
- Hypersensitivity to Vigamox or any other fluoroquinolone
- Hypersensitivity to tetracaine, lidocaine, Duovisc, or latex
- Women who are nursing a child or plan to nurse a child during the study
- Presence of clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, endocrine, neurological, psychiatric, respiratory, or other medical condition as determined by the Investigator
- Presence of any connective tissue disorder (ie. lupus, rheumatoid arthritis, fibromyalgia)
- Presence of systolic blood pressure of ≥ 160 mmHg or ≤ 90 mmHg, or diastolic blood pressure of ≥ 110 mmHg or ≤ 40 mmHg
- Use of phenylephrine (other than for the screening ophthalmological examination) or NSAIDs, including ketorolac, within seven days prior to the day of surgery
- Use of topical, inhaled, or oral corticosteroids within seven days of surgery, or depot corticosteroids within 30 days of surgery
- Use of MAO inhibitors within 21 days prior to the day of surgery
- Use of ocular mast cell stabilizers within seven days of surgery
- Repeated use of pilocarpine in the study eye within 6 months prior to the day of surgery
- History of use of an α -1- adrenergic antagonist, such as tamsulosin (Flomax), silodosin (Rapaflo), prazosin (Minipress, Hypovase), alfuzosin (Uroxatral), doxazosin (Cardura), or terazosin (Hytrin)
- Presence of narrow-angle glaucoma or unstable glaucoma
- Glaucoma being treated with prostaglandins or prostaglandin analogues such as Xalatan, Lumigan, Travatan, and Rescula, or Alphagan in either eye
- Anticipated to require the use of other topical ocular medications in either eye during the trial except prophylactic antibiotics, topical lid care, allowed glaucoma medications or non-prescription tear replacement solutions

- Presence of pseudo-capsular exfoliation in either eye
- History of iritis, or of any ocular trauma with iris damage in the study eye
- Presence of uncontrolled chronic ocular diseases in either eye
- Presence of active corneal pathology or scarring noted in either eye (except superficial punctate keratopathy in the non-study eye)
- Presence of extraocular/intraocular inflammation in either eye
- Presence of active bacterial and/or viral infection in either eye.
- Participating in any investigational drug or device trial within the 30 days prior to the day of surgery
- History of intraocular non-laser surgery in the study eye within the 3 months prior to the day of surgery, or intraocular laser surgery in the study eye within 30 days prior to the day of surgery
- Requiring or planning other ocular surgery during the study
- Presence of any condition that the Investigator believes would put the subject at risk or confound the interpretation of the study data
- Investigators, employees of the investigative site, and their immediate families. Immediate family is defined as the Investigator's or employees' current spouse, parent, natural or legally adopted child (including a stepchild living in the Investigator's household), grandparent, or grandchild

This study evaluated OMS302 compared to placebo. OMS302 is a combination sterile drug product of PE and KE. A placebo drug product was also provided in a separate sterile vial. The study drugs were added to balanced salt solution (BSS) and were to be used within six hours of preparation for surgery. Placebo drug product was a sterile, clear solution containing 20 mM sodium citrate buffer (pH 6.3 ± 0.5). Commercially-provided BSS was used in the preparation of test irrigation solutions containing OMS302 or placebo. It was provided in a bottle containing 500 mL of BSS with the commercial packaging and labeling intact.

OMS302-ILR-003 Investigator Information

Site Number	Name	Number of Patients Randomized
101	Ronald E.P. Frenkel, MD East Florida Eye Institute 509 SE Riverside Drive, Suite 302 Stuart, FL 34994	12
102	Mark Irvin Rosenblatt, MD, PhD Weill Cornell Eye Associates 1305 York Avenue, 11th Floor New York, NY 10021	2
103	David R. Hardten, MD Minnesota Eye Consultants 9801 DuPont Avenue S., Suite 200	2

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Site Number	Name	Number of Patients Randomized
	Bloomington, MN 55431	
104	Stephen E. Smith M.D. Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	13
105	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. 901 E. Third Street Washington, MO 63090	17
179	Ranjan P. Malhotra, MD Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	19
185	Thomas R. Walters, MD Texan Eye Care 5717 Balcones Drive Austin, TX 78731	18
189	Michael J. Depenbusch, MD Arizona Eye Center 604 West Warner Road, Suite B6 Chandler, AZ 85225	10
190	Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Houston, TX 77024	64
193	Farrell C. Tyson II, MD Cape Coral Eye Center 4120 Del Prado Boulevard Cape Coral, FL 33904	14
195	John M. Lim, MD Houston Eye Associates 915 Gessner, Suite 250 Houston, TX 77024	68
198	Nicholas Marsico, MD East West Eye Institute 420 E. 3rd Street, Suite 603 Los Angeles, CA 90013	39
199	David A. Bernitsky MD 6401 Holly Avenue NE.	14

Site Number	Name	Number of Patients Randomized
	Albuquerque, NM 87113	
200	William J. Flynn, MD R & R Research 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	15
202	James C. Loden, M.D. Loden Vision Center 907 Rivergate Parkway, Suite C2020 Goodlettsville, TN 37072	29
203	Gerald B. Walman, MD Advanced Research Associates 6320A West Union Hills, Suite 110 Glendale, AZ 85308	7
206	William Colby Stewart, M.D Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	62
TOTAL		405

Study Table

Schedule of Events	Day -28 to -1	Day 0				Day 1	Day 2	Day 7 ¹	Day 14 ¹
	Screening	Baseline	Surgery	Post Surgery 2 and 6 hours ¹	Post Surgery 4, 8 and 12 hours ¹	Post Surgery 24 hours ¹	Post Surgery 48 hours ¹		
Informed Consent/HIPAA (Prior to any study-related evaluations)	X								
Inclusion/Exclusion Criteria	X								
Medical History	X	X							
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events		X	X			X	X	X	X
Vital Signs ²	X	X	X						
Urine Pregnancy Test	X								X
Ophthalmological Exam ³	X					X	X	X	X
Pupillary Function ⁴	X	X				X	X	X	X
Examination of Fundus ⁵	X							X	X
Cataract Assessment (LOCS II)	X								
Best-Corrected Visual Acuity ⁶ (BCVA)	X					X	X	X	X
Intraocular Pressure (IOP) ⁷	X					X	X	X	X
Inflammation (SOIS)	X					X	X	X	X
Antibiotic Therapy (Vigamox [®]) ⁸	X	X				X	X	X	X

Continued

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Schedule of Events	Day -28 to -1	Day 0				Day 1	Day 2	Day 7 ¹	Day 14 ¹
	Screening	Baseline	Surgery	Post Surgery 2 and 6 hours ¹	Post Surgery 4, 8 and 12 hours ¹	Post Surgery 24 hours ¹	Post Surgery 48 hours ¹		
Randomization		X							
Preoperative Medications ⁹			X						
Treatment with Study Solution			X						
CELR or RLE Procedure			X						
Video Capture			X						
Ocular Discomfort Assessment (NRS) ¹⁰		X		X		X	X	X	X
Ocular Pain (VAS) ¹¹		X		X	X	X	X	X	X
Review of Subject Diaries						X	X	X	

¹ Visit windows for subject contact are as follows: +/-30 minutes for subject diary entries at 4, 6, and 8 hours, 10 to 12 hours for the postoperative VAS, +/-2 hrs for 24 hr and 48 hr postoperative visits, +/- 1 day for Day 7 postoperative visit and +/-2 days for Day 14 postoperative visits.

¹⁰ Numerical rating system for ocular discomfort.

¹¹ Subjects will complete diaries each day, starting with Day 0, until postoperative Day 7.

² Vital Signs: Screening (blood pressure [BP], heart rate [HR], respiratory rate [RR], temperature [T]), Baseline (BP, HR, RR, T), Intra-operative (BP, HR during surgery just prior to incision, and at 5-min intervals through the end of procedure).

³ (1) Examination of the lid, lashes, and lacrimal apparatus, (2) Pupillary function, (3) Slit lamp examination of lids, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous.

⁴ Performed via swinging-flashlight test. In addition to being performed as a component of each ophthalmologic exam, pupillary function will be assessed at baseline.

⁵ Dilution with phenylephrine is allowed at all study-required timepoints for fundal examination.

⁶ Determined by ETDRS scoring method.

⁷ Measurement by Goldmann Tonometry.

⁸ Place one drop in the surgical eye 4 times a day for 3 days prior to surgery, through the 7 days after surgery.

⁹ During the 60 minutes prior to surgery, the subject will receive topical anesthetics (lidocaine or tetracaine) according to manufacturer's instructions. In addition, at approximately 30 minutes, 15 minutes, and 5 minutes before surgery, the subject will receive, first, one drop of phenylephrine 2.5% (Mydrfin[®] 2.5%) and then one drop of tropicamide 1% (Mydracyl[®] 1%).

¹⁰ Visit windows for subject contact are as follows: +/-30 minutes for subject diary entries at 4, 6, and 8 hours, 10 to 12 hours for the postoperative VAS, +/-2 hrs for 24 hr and 48 hr postoperative visits, +/- 1 day for Day 7 postoperative visit and +/-2 days for Day 14 postoperative visit.

Change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure) was to be summarized using descriptive statistics by treatment group and timepoint (every minute). The primary analysis of the change in pupil diameter was based on the mean area-under-the curve (AUC) pupil diameter change from baseline. First, the AUC of the pupil diameter from surgical baseline to wound closure was to be calculated using the trapezoidal rule. Second, the mean AUC was obtained by dividing the AUC by the total time for surgery. Third, the mean AUC of change from baseline was calculated by subtracting the baseline pupil diameter from the mean AUC. Summary statistics of the mean AUC of change from baseline was to be provided by stratum and treatment arm. The primary analysis of the ocular pain VAS was based on the mean AUC. The AUC of the ocular pain VAS during 12 hours postoperatively was to be calculated by the trapezoidal rule using the actual collection times. The mean AUC was defined as the AUC divided by the number of hours with ocular pain VAS results during the first 12 hours postoperatively.

Study OMS302-ILR-004

This Phase 3 study was a randomized, parallel-group, double-masked, placebo-controlled study of OMS302 in subjects undergoing ILR using a phacoemulsification process with insertion of an acrylic lens. Administration of test irrigation solutions took place in a double-masked fashion. Subjects were randomized 1:1 to OMS302 or placebo. Subjects undergoing CELR or refractive lens exchange (RLE) were eligible. Randomization to treatment group was stratified within site

by cataract Lens Opacities Classification System II (LOCS II) nuclear grade (low defined as No or N₁ and high defined as N₂ or N₃). Approximately 400 subjects were planned to be randomized. All subjects were to receive standardized preoperative antibiotic treatment (Vigamox four times daily for three days prior to surgery), mydriatic treatment (one drop of PE 2.5% and one drop of tropicamide 1% at approximately 30 minutes, 15 minutes, and 5 minutes prior to surgery), and anesthesia (topical lidocaine or tetracaine administered according to the manufacturer's instructions). Post-operatively, all subjects continued the Vigamox regimen for seven days. All subjects were discharged with acetaminophen (paracetamol) and instructed to contact their physician for pain not controlled by acetaminophen (paracetamol).

After Amendment 2.0, all subjects received topical ophthalmic ketorolac on the first postoperative day. The dose was at the investigator's discretion. All subjects were to be treated with topical ketorolac for at least seven days. Topical ophthalmic corticosteroids were not allowed preoperatively or on the day of surgery. An amendment allowed topical ophthalmic corticosteroids on the first postoperative day or later according to the surgeon's standard practice. In the first version of the protocol, the postoperative follow up was 14 days. The protocol was amended following meeting with regulatory authorities who recommended a 90-day follow up. Maintenance of mydriasis and prevention of miosis was determined by video capture and measurement of pupil diameter by a masked central reader. Ocular pain and photophobia were assessed by each subject using a VAS and a NRS, respectively. Inflammation was assessed by the SOIS using a slit lamp biomicroscope. Safety and tolerability were assessed based on AEs, vital signs, and ocular and systemic measures for up to 90 days postoperatively.

Reviewer's Comment:

Since the co-primary endpoint of post-operative pain was at 12 hour timepoint, the amendments noted above would not affect this endpoint. Any analysis of pain after POD#1 could potentially be affected by administration of topical ketorolac and topical steroids.

The co-primary endpoints were:

- Change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure) determined by video capture during ILR
- Post-operative pain as measured by the VAS at 2, 4, 6, 8, and 10 to 12 hours after ILR surgery

The secondary efficacy endpoints were:

- Pupil diameter \geq 6 mm at cortical cleanup
- Pupil diameter $<$ 6 mm at any time during surgery
- Moderate-to-severe ocular pain (VAS \geq 40) at any timepoint during 12 hours post-operatively
- Ocularly pain free (VAS = 0) at all timepoints during 12 hour postoperatively.
- Post-operative pain as measured by the VAS at 24 and 48 hours, at Days 3 to 7, and at
- Day 14 after ILR surgery

- Photophobia as measured by the NRS at 2, 6, 24, and 48 hours, and at 7 and 14 days after surgery
- Post-operative inflammation as measured using the SOIS at 24 and 48 hours, and at 7, 14, and 90 days after surgery
- BCVA as measured using the Early Treatment Diabetic
- Retinopathy Study (ETDRS) method at 24 and 48 hours, and at 7, 14, and 90 days after surgery

Safety endpoints included:

- Adverse events and SAEs
- IOP
- Ophthalmological examinations
- Vital signs

Pharmacokinetic endpoints for PE and KE included:

- Area under the serum concentration-time curve (AUC)

PK Sub-Study

Systemic PK of PE and KE were evaluated in 14 subjects following OMS302 treatment. Plasma samples were drawn from 26 subjects (14 active and 12 placebo) in order to maintain masking. Subjects participating in the PK part of the study were randomized from different blocks than subjects not participating in order to maintain masking. The study protocol specified that PE (other than for the screening ophthalmological examination) and NSAIDs, including KE, were prohibited within seven days prior to surgery. On the day of surgery, all subjects received pre-operative mydriatic treatment as described above. Immediately following instillation of the third set of preoperative eye drops, the pre-treatment PK blood sample was collected. After initiation of surgery and study drug administration, serial PK blood samples were collected at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours. Amendment 2.0 of the protocol specified that postoperative topical ketorolac was to be administered beginning on the day following surgery, after collection of the 24-hour PK blood sample. Plasma was isolated from the PK blood samples, and each sample was analyzed for PE and KE using validated liquid chromatography tandem mass spectrometry methods with a lower level of quantitation (LLOQ) of 1 ng/mL for each assay.

Inclusion Criteria

Identical to Study OMS302-ILR-003.

Exclusion Criteria

Identical to Study OMS302-ILR-003.

OMS302-ILR-004 Investigator Information

Site Number	Name	Number of Patients Randomized
102	Mark Irvin Rosenblatt, MD, PhD Weill Cornell Medical College 525 E 68th St. F-08 New York, NY 10065	1
104	Stephen E. Smith, MD Eye Associates of Fort Myers 4225 Evans Ave. Fort Myers, FL 33901	8
105	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. 901 E. Third St. Washington, MO 63090	17
179	Ranjan P. Malhotra, MD Ophthalmology Associates 12990 Manchester Rd., Suite 200 St. Louis, MO 63131	22
185	Thomas R. Walters, MD Texan Eye Care, PA (Keystone Research) 5717 Balcones Dr. Austin, TX 78731	18
189	Michael Depenbusch, MD Connect Clinical Research Center 335 N. Alma School Road, Suite D Chandler, AZ 85224	8
190	Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	80
195	John M. Lim, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	62
198	Nicholas P. Marsico, M.D. East West Eye Institute 420 E. 3rd Street, Suite 603 Los Angeles, CA 90013	53

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Site Number	Name	Number of Patients Randomized
199	David A. Bernitsky, MD 6401 Holly Ave. NE. Albuquerque, NM 87113	5
200	William J. Flynn, MD R & R Research 5430 Fredericksburg Road, Suite100 San Antonio, TX 78229	26
202	James C. Loden, MD Loden Vision Center 907 Rivergate Parkway, Suite C2020 Goodlettsville, TN 37072	43
206	William Colby Stewart, MD Houston Eye Associates 2855 Gramercy Street Houston, TX 7702	60
207	Khiun F. Tjia, M.D. Isala Klinieken Groot Weezenlanden 20 8011 JW Zwolle, Netherland	12
210	Ula Jurkunas, MD Massachusetts Eye and Ear Infirmary 243 Charles St. Boston, MA 02114	1
TOTAL		416

Reviewer's Comment:

It is noted that 13 of the investigators participated in both studies. This is not the Agency's preference; however there is nothing to suggest that both studies were not performed in compliance with good clinical practices. In addition, Study 003 enrolled patients from 9/22/11-1/31/12 and Study 004 enrolled patients from 4/4/12-1/9/13 therefore investigators could not pick which study to enroll patients in.

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 OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3%

Study Chart

Study OMS302-ILR-004 Schedule of Events	Day -28 to -1	Day 0				Day 1	Day 2	Day 7 ¹	Day 14 ¹	Day 90 ¹ or Early Termination
	Screening	Baseline	Surgery	Post Surgery 2 and 6 hours ¹	Post Surgery 4, 8 and 12 hours ¹	Post Surgery 24 hours ¹	Post Surgery 48 hours ¹			
Informed Consent/HIPAA	X									
Inclusion/Exclusion Criteria	X									
Medical & Surgical History	X	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X			X	X	X	X	X
Vital Signs ²	X	X	X							
Urine Pregnancy Test	X								X	
Ophthalmological Exam ³	X ^B					X	X	X	X ^B	X ^B
Pupillary Function ⁴	X	X				X	X	X	X	X
Examination of Fundus ⁵	X ^B							X	X ^B	X ^B
Cataract Assessment (LOCS II)	X									
Best-Corrected Visual Acuity ⁶ (BCVA)	X ^B					X	X	X	X ^B	X ^B
Intraocular Pressure (IOP) ⁷	X ^B					X	X	X	X ^B	X ^B
Inflammation (SOIS)	X ^B					X	X	X	X ^B	X ^B
Antibiotic Therapy (Vigamox [®]) ⁸	X	X				X	X	X		
Randomization		X								
Preoperative Medications ⁹		X								
Treatment with Study Solution			X							
CELR or RLE Procedure			X							
Video Capture			X							
Pharmacokinetic Blood Sampling		X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰				

Study OMS302-ILR-004 Schedule of Events	Day -28 to -1	Day 0				Day 1	Day 2	Day 7 ¹	Day 14 ¹	Day 90 ¹ or Early Termination
	Screening	Baseline	Surgery	Post Surgery 2 and 6 hours ¹	Post Surgery 4, 8 and 12 hours ¹	Post Surgery 24 hours ¹	Post Surgery 48 hours ¹			
Ocular Discomfort Assessment (NRS) ¹¹		X		X		X	X	X	X	
Ocular Pain (VAS) ¹²		X		X	X	X	X	X	X	
Review of Subject Diaries						X	X	X		

¹ Visit windows for subject contact are as follows: +/-30 minutes for subject diary entries at 2, 4, 6, and 8 hours, 10 to 12 hours for the postoperative VAS, +/-2 hrs for 24 hour and 48 hour postoperative visits, +/- 1 day for Day 7 postoperative visit, +/-2 days for Day 14 postoperative visit and +/- 7 days for the Day 90 postoperative visit.

² Vital Signs: Screening (blood pressure [BP], heart rate [HR], respiratory rate [RR], and temperature [T]), Baseline (BP, HR, RR, T), Intra-operative (BP, HR during surgery just prior to incision, and at 5-minute intervals through the end of procedure).

³ (1) Examination of the lid, lashes and lacrimal apparatus, (2) Pupillary function, (3) Slit lamp examination of lids, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous.

⁴ Performed via swinging-flashlight test. In addition to being performed as a component of each ophthalmologic exam, pupillary function will be assessed at baseline.

⁵ Dilatation with PE is allowed at all study-required timepoints for fundal examination.

⁶ Determined by ETDRS scoring method.

⁷ Measurement by Goldmann Tonometry.

⁸ Place one drop in the surgical eye 4 times per day for 3 days prior to surgery through the 7 days after surgery.

⁹ During the 60 minutes prior to surgery, the subject will receive topical anesthetics (lidocaine or tetracaine) according to manufacturer's instructions. In addition, at approximately 30 minutes, 15 minutes, and 5 minutes before surgery, the subject will receive, first, one drop of PE 2.5% (Mydrin[®] 2.5%) and then one drop of tropicamide 1% (Mydracil[®] 1%).

¹⁰ Subjects participating in the pharmacokinetic part of the study will have blood draws pre-treatment on day of surgery and at approximately 15 and 30 minutes and 1, 2, 4, 8, and 24 hours following the initiation of study drug administration.

¹¹ Numerical rating scale for ocular discomfort.

¹² Subjects will complete diaries each day, starting with Day 0, until postoperative Day 7.

^B Ophthalmic procedures required at Screening, Day 14, and Day 90 should be performed on both eyes. Ophthalmic procedures performed at other visits may be performed on the study eye only.

The co-primary efficacy endpoints of this study were:

- Mydriasis as determined by video capture during ILR using the change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure). Still images obtained from the video recordings of each subject's surgical procedure were used to measure the pupil diameter over time. A trained, masked central reader performed the pupil size measurements.
- Ocular Pain in the early postoperative period was measured by VAS postoperatively. Using subject diaries, pain was measured on a 100-mm scale, where 0 = no pain and 100 = worst pain possible.

Study C09-001

This Phase 2 study was a randomized, parallel-group, double-masked, vehicle-controlled study of PE, KE, and OMS302 in subjects undergoing CELR using a coaxial phacoemulsification process with insertion of an acrylic lens. The study evaluated, using a full-factorial design, the effects of OMS302 on intraoperative pupil diameter and ocular pain in the early postoperative period. The full-factorial design allowed evaluation of the contribution of the two active pharmaceutical ingredients (APIs; PE and KE) alone and in combination to mydriasis and pain. The effects of OMS302, PE, and KE on postoperative inflammation were also assessed.

Subjects were randomized to one of the following four treatment groups in a 1:1:1:1 fashion:

1. Balanced salt solution (BSS) vehicle
2. Single study-drug formulation containing 483 μ M PE
3. Single study-drug formulation containing 89 μ M KE
4. Combination study-drug formulation containing 483 μ M PE/89 μ M KE (OMS302).

Approximately 200 randomized subjects were planned in order to achieve 192 evaluable subjects (48 per treatment group). All subjects were to receive standardized preoperative antibiotic treatment (Vigamox four times daily for three days prior to surgery), mydriatic treatment (one drop of PE 2.5% and one drop of tropicamide 1% at approximately 30 minutes, 15 minutes, and 5 minutes prior to surgery) and anesthesia (topical lidocaine or tetracaine administered according to the manufacturer's instructions). Post-operatively, all subjects continued the Vigamox regimen for seven days. Maintenance of mydriasis was determined by video capture. Ocular pain and ocular discomfort were assessed by each subject using a Visual Analog Scale (VAS) and a Numerical Rating Scale (NRS), respectively. Safety and tolerability were assessed based on AEs, vital signs, and ocular and systemic measures for 30 days post-operatively. Study procedures were performed at screening, at baseline prior to surgery, on the day of surgery intra-operatively, and post-operatively at approximately 2 hours, 4 hours, 6 hours, 8 hours, 10-12 hours, 24 hours, 48 hours, 7 days, 14 days, and 30 days. The length of time for subject participation was approximately 4 to 8 weeks: up to 28 days in the screening process and 30 days in the post-operative period.

Study Schedule

	Day -28 to -1	Day 0				Day1	Day 2	Day 7 ¹	Day 14 ¹	Day 30 ¹
	Screening	Baseline	Surgery	Post Surgery 2 hours ¹	Post Surgery 4, 6, 8, and 12 Hours ¹	Post Surgery 24 hours ¹	Post Surgery 48 hours ¹			
Informed Consent/HIPAA (Prior to any study-related evaluations)	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X	X								
Concomitant Medications	X	X	X	X		X	X	X	X	X
Adverse Events	X	X	X	X		X	X	X	X	X
Vital Signs ²	X	X	X	X		X				X
Urine Pregnancy Test	X									X
Ophthalmological Exam ³	X			X		X	X	X	X	X
Pupillary Function ⁴		X		X		X	X	X	X	X
Examination of Fundus ⁵	X							X	X	X
Cataract Assessment (LOCS II)	X									
Best Corrected Visual Acuity ⁶ (BCVA)	X					X	X	X	X	X
Intraocular Pressure (IOP) ⁷	X					X	X	X	X	X
Inflammation (SOIS)	X			X		X	X	X	X	X
Antibiotic Therapy (Vigamox ⁸) ⁸	X	X				X	X	X		
Randomization		X								
Preoperative Medications ⁹			X							
Treatment with Study Solution			X							
Ocular Discomfort Assessment (NRS) ¹⁰				X		X	X	X	X	X
Ocular Pain (VAS)				X		X	X	X	X	X
Subject Diary ¹¹					X	X	X	X		

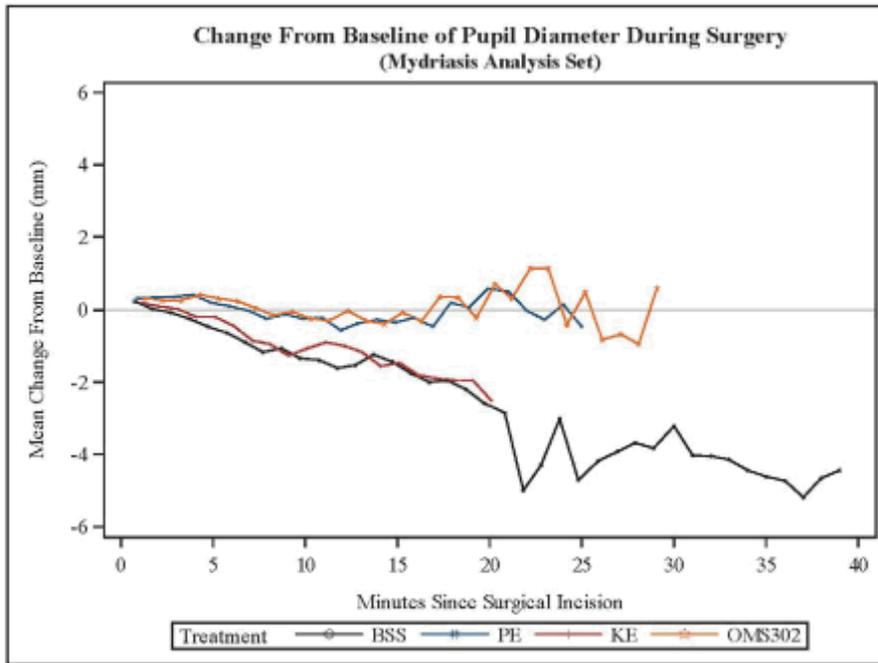
The primary efficacy endpoints of this study were:

- Change in pupil diameter (mydriasis) as determined by video capture during CELR using the change over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure).
- Post-operative ocular pain as measured by the VAS at 2, 4, 6, 8, and 10–12 hours after CELR surgery.

Video recordings of each subject's surgical procedure were used to measure the pupil diameter over time. A masked central reader performed the pupil size measurements. Post-operative ocular pain was reported in a subject diary using the VAS at approximately 2 hours, 4 hours, 6 hours, 8 hours, and 10–12 hours post-surgery.

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Figure 3: Intraoperative Change in Pupil Diameter (Mydriasis Analysis Set)



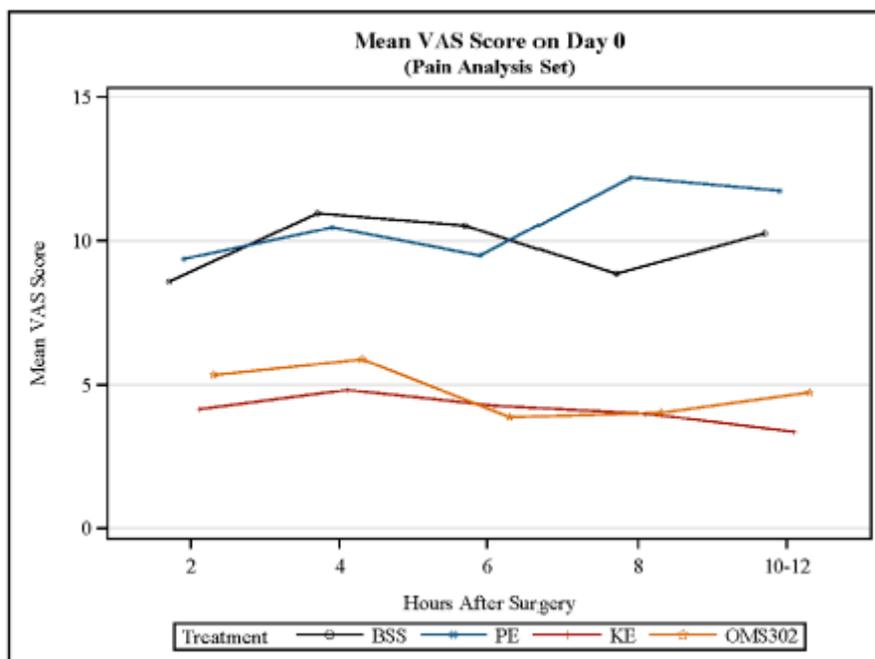
Study C09-001: Repeated Measures Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Mydriasis Analysis Set)

	OMS302-Vehicle	OMS302-KE
Least squares mean difference (SE)	0.9 (0.1)	0.7 (0.1)
95% CI	0.6, 1.1	0.5, 0.9
P-Value	0.0001	0.0001

Reviewer's Comment:

Pupil diameter decreased throughout the surgical procedure in both the vehicle and KE groups, but mydriasis was consistently maintained in both the PE and OMS302 groups. The superiority of OMS302 over vehicle and KE demonstrates the contribution of PE to maintenance of mydriasis.

Figure 4: Postoperative Ocular Pain VAS Score (Pain Analysis Set)



Study C09-001: Repeated Measures Analysis of Ocular Pain VAS Score Within 12 Hours Post-Operatively (Pain Analysis Set)

	OMS302-Vehicle	OMS302-KE
Least squares mean difference (SE)	-4.5 (2.2)	-5.9 (2.2)
95% CI	-8.9, -0.2	-10.3, -1.5
P-Value	0.0001	0.0001

Reviewer’s Comment:

Pain score in vehicle and PE groups were consistently higher than in the OMS302 and KE groups. The superiority of OMS302 over PE and vehicle demonstrates the contribution of KE to the reduction of post-operative ocular pain.

Study C07-005

This Phase 1/2 study was a randomized, controlled, double-masked, parallel, three-arm study of OMS302 (PE and KE) vs. PE vs. Balanced Salt Solution (BSS, vehicle control) in subjects undergoing CELR using a coaxial phacoemulsification process with insertion of an acrylic lens. This exploratory study was used to evaluate the safety and potential clinical benefit of OMS302, as well as to determine clinical endpoints for further assessment in follow-on studies. Sixty subjects undergoing CELR were to participate in this study.

Subjects were randomized to one of the following three treatment groups in a 1:1:1 fashion:

1. BSS vehicle
2. PE 483 μM
3. PE 483 μM and KE 60 μM

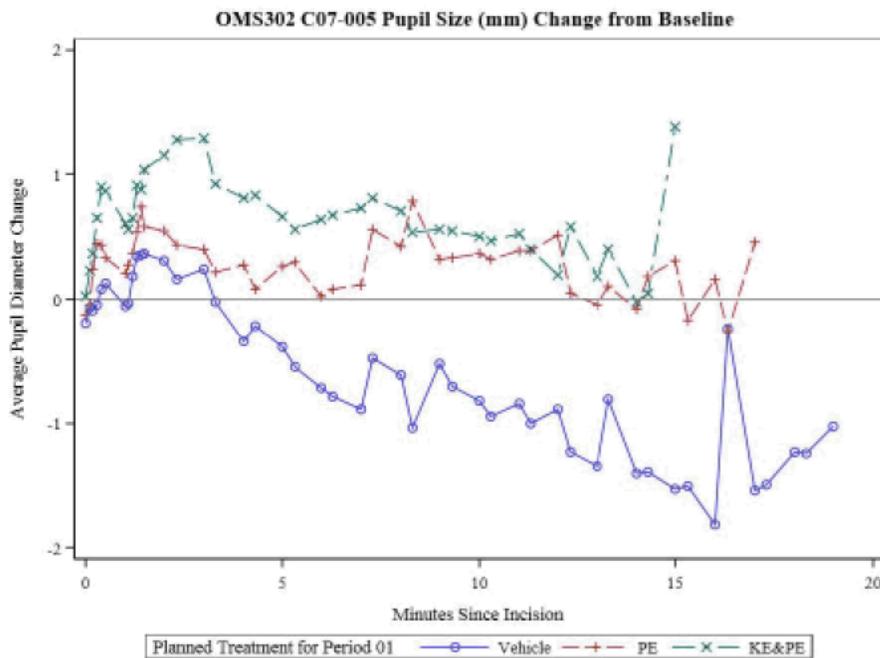
All subjects were to receive standardized preoperative antibiotic treatment (Vigamox four times daily for 3 days prior to surgery) and topical anesthesia (tetracaine). In the original protocol, subjects assigned to the placebo treatment group received mydriatic treatment (1 drop of PE 2.5% and 1 drop of tropicamide 1%) at approximately 30 minutes, 15 minutes, and 5 minutes prior to surgery; and subjects assigned to the PE- or OMS302-treatment groups did not receive preoperative mydriatic treatment. In protocol amendment 1, all subjects received preoperative mydriatic treatment as described above. Other pre-, peri- and postoperative medications were not standardized. Intraoperative mydriasis was measured by video capture. Ocular pain and symptoms of ocular discomfort were assessed using NRS. Safety and tolerability were assessed using AEs, vital signs, and ocular and systemic measures for up to 28 days post-operatively. The number of subjects randomized to each of the study treatment groups was: Vehicle: n = 20; PE: n = 21; and OMS302: n = 20.

Study Schedule

Procedure	Screening	Day 0 ¹ : Pre-operative	Day 0 ¹ : Intra-operative	Day 0 ¹ : Postoperative	Follow-up Day 1 ²	Follow-up Day 3 ²	Follow-up Day 7 ²	Follow-up Day 14 ²	Follow-up Day 28 ²
Sign Informed Consent Form: HIPAA	X								
Ophthalmological, Medical and Surgical History, Inclusion/Exclusion Assessment	X	X							
Prior/Concurrent Use of Medications	X	X		X	X	X	X	X	X
Limited Physical Examination	X			X					X
Vigamox Therapy ⁴	X →	XXXXXXXX		XXXXXXXX	XXXXXXXX	XXXXXXXX	←X		
Cataract Density LOCS III ⁵	X →	←X							
Cells and Flare ⁶	X →	←X			X	X	X	X	
BCVA ⁶	X →	←X			X	X	X	X	X
Flare Meter ^{6,8}	X →	←X			X	X	X	X	X
Ophthalmological Examination ³	X				X	X	X	X	X
IOP ⁷	X →	←X							X
Vital Signs Monitoring ⁷	X	X	X	X					
Urine Pregnancy Test	X								
Subject Randomization		X							
Prepare Test Irrigation Solution		X							
Administer Pre-Operative Drops		X							
Administer Test Irrigation Solution		X	X						
Measure Pupil Size by Video-Photography			X						
Cataract Procedure			X						
Surgeon Postoperative Questionnaire				X					
Recovery Room Entry/Discharge				X					
Iowa Satisfaction with Anesthesia Scale				X					
Subject Diary ⁸		X		X →	XXXXXXXX	XXXXXXXX	XXXXXXXX	←X	
AE & Intercurrent Medical Events				X	X	X	X	X	X

¹ Day of CELR procedure
² The allowed variation in study day is plus or minus 1, 2 or 3 days: Day 1, Day 3 (3 – 4), Day 7 (6 – 8), and Day 14 (12 – 16), and Day 28 (25 – 31)
³ Ophthalmological Examination includes external examination, slit lamp examination, funduscopy and other as detailed in section 8.0
⁴ Vigamox four times a day for three days prior to the operation, the day of the operation and seven days after surgery
⁵ Flare meter at selected sites
⁶ The set of ocular exams, as indented examination at Screen → ← Day 0 can be executed on or between either visit but before the operation.
⁷ Vital signs include heart rate and blood pressure
⁸ Subject diary answered at discharge, every two hours during waking time on day of operation, and then on each day thereafter for the next 14 days

Figure 2: Intraoperative Change in Pupil Diameter (Full Analysis Set Population)



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StudyC07-005: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

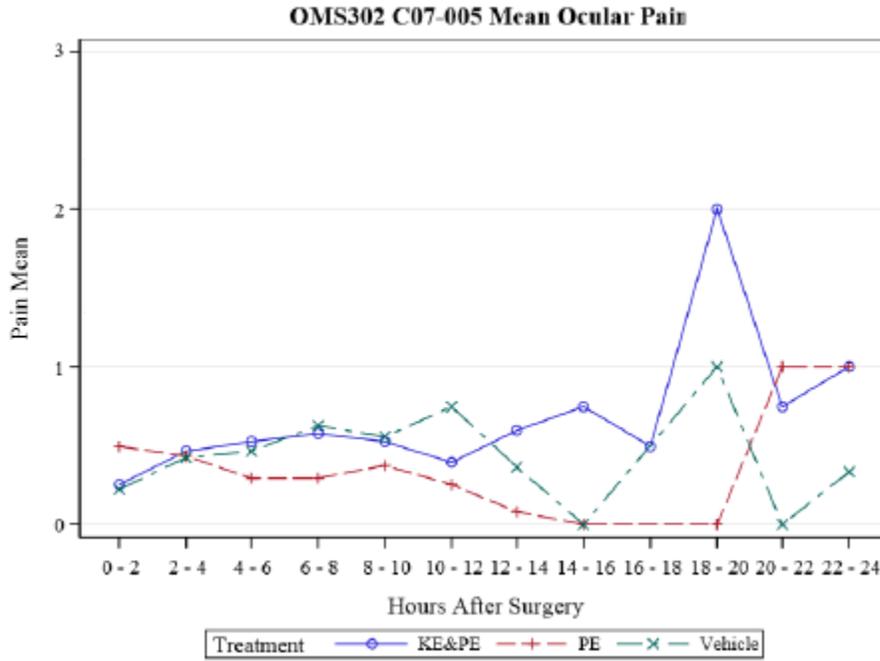
	BSS Vehicle N=20	OMS302 PE 483 µM and KE 60 µM N=19
Mean AUC		
Number of Patients With Video Data	20	18
Mean (sd)	-0.5 (0.6)	0.3 (0.7)
Min, Max	-2.6, 0.2	-0.5, 2.7
Difference in Mean AUC		
Least squares mean difference (SE)	0.7 (0.2)	
95% CI	0.3, 1.2	
P-Value	0.0018	

NRS (Numerical Rating Scale) to Determine Grade of Ocular Symptoms

Grade	Degree of Ocular Discomfort	Definition
0	None	Absent
1	Mild	You experience a symptom, but it does not at all interfere with your completion of daily tasks
2	Moderate	You experience a symptom and it slows you down, but you are able to carry out work of a light or sedentary nature (ie. light house work, office work)
3	Severe	Your experience of a symptom makes you completely unable to carry out any work activities

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Figure 3: Postoperative Ocular Pain NRS Grade (Full Analysis Set Population)



StudyC07-005: Proportion of Subjects With Eye Pain by Days Post-Surgery

Days Post-Surgery	Treatment	1=None	2=Mild	3=Moderate	4=Severe	P-value
Day 1	OMS302	7	9	3	0	0.9538
	PE	8	9	3	1	
	Vehicle	10	8	2	0	
Day 2	OMS302	7	7	5	0	0.4352
	PE	12	6	2	1	
	Vehicle	9	9	2	0	
Day 3	OMS302	11	7	1	0	0.6132
	PE	16	3	2	0	
	Vehicle	13	6	1	0	
Day 4	OMS302	11	8	0	0	0.2247
	PE	16	3	2	0	
	Vehicle	15	4	1	0	
Day 5	OMS302	14	5	0	0	0.8199

	PE	14	4	2	0	
	Vehicle	15	4	1	0	

Reviewer's Comment:

This trial was not powered to demonstrate efficacy. There was no primary efficacy endpoint, only exploratory endpoints. The OMS302 and vehicle treatment groups were compared by mean AUC. OMS302 was superior to vehicle in maintenance of mydriasis. No treatment effect was observed in treatment of post-operative pain in any arm of the trial. Note that the concentration of ketorolac used in C07-005 was 60mM compared to 89mM in the final formulation.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Proposed indication is for (b) (4), the prevention of intraoperative miosis, and the reduction of (b) (4) post-operative pain

6.1.1 Methods

The support for efficacy is from 3 clinical studies (Studies OMS302-ILR-003, OMS302-ILR-004, and C09-001).

6.1.2 Demographics

Study OMS302-ILR-003: Subject Demographics (Full Analysis Population)

Parameter	Placebo N=201	OMS302 N=201
Age		
Mean (sd)	68.5 (9.9)	68.2 (9.6)
Gender		
Male	90	82
Female	111	119
Race		
White	155	165
African-American	26	22
American Indian/Alaskan	1	1
Asian	19	12
Native Hawaiian/Pacific Islander	0	0

Parameter	Placebo N=201	OMS302 N=201
Other	0	1
Ethnicity		
Hispanic/Latino	18	30
Not Hispanic/Latino	183	171

Study OMS302-ILR-004: Subject Demographics (Full Analysis Population)

Parameter	Placebo N=204	OMS302 N=202
Age		
Mean (sd)	67.5 (10.6)	69.2 (9.2)
Gender		
Male	78	85
Female	126	117
Race		
White	158	165
African-American	28	18
American Indian/Alaskan	0	1
Asian	18	16
Native Hawaiian/Pacific Islander	0	1
Other	0	1
Ethnicity		
Hispanic/Latino	21	30
Not Hispanic/Latino	183	172

6.1.3 Patient Disposition

Study OMS302-ILR-003: Patient Disposition (Safety Population)

	Placebo N=201	OMS302 N=201
Number of Subjects Randomized	203	202
Number of Subjects Received Treatment	201	201
Number of Subjects Received CELR Surgery	197	200
Number of Subjects Received RLE Surgery	4	1
Reason for Study Discontinuation		
Completed	201	199
Death	0	1
Withdrawal by Subject	0	1
AE	1	1
Other	1	0

Study OMS302-ILR-004: Patient Disposition (Safety Population)

	Placebo N=204	OMS302 N=202
Number of Subjects Randomized	209	207
Number of Subjects Received Treatment	204	202
Number of Subjects Received CELR Surgery	203	201
Number of Subjects Received RLE Surgery	1	1
Reason for Study Discontinuation		
Completed	201	200
Withdrawal of consent	0	3
Investigator decision	2	0
AE	3	1
Lost to f/u	1	2
Other	2	1

6.1.4 Analysis of Primary Endpoint(s)

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=201	OMS302 N=201
Mean AUC		
Number of Patients With Video Data	180	184
Mean (sd)	-0.5 (.58)	0.1 (.41)
Min, Max	-2.9, 2.1	-2.7, 1.3
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	0.577 (0.052)	
95% CI	0.475, 0.678	
P-Value	<.0001	

Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=204	OMS302 N=202
Mean AUC		
Number of Patients With Video Data	200	195
Mean (sd)	-0.5 (.57)	0.1 (.43)
Min, Max	-2.3, 1.5	-2.2, 2.3
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	0.590 (0.049)	
95% CI	0.494, 0.686	
P-Value	<.0001	

Study OMS302-ILR-003: Supportive Analysis of Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=201	OMS302 N=201
Subjects With ≥ 6 mm At Cortical Clean-up In Subjects With Video Data	139/180 (77.2%)	177/184 (96.2%)
P value		<0.0001
Pupil Diameter (mm) at cortical Clean-up		
N	180	184
Mean (sd)	7.1 (2.0)	8.0 (1.8)
Min, Max	3.8, 18.0	2.7, 17.8
P value		<0.0001
Subjects With Degree of Pupillary Constriction		
<0.5mm	9	78
≥ 0.5 to <1.0mm	24	70
≥ 1.0 to <1.5mm	41	11
≥ 1.5 to <2.0mm	36	9
≥ 2.0 to <2.5mm	20	10
≥ 2.5 mm	50	6
P value		<0.0001

Study OMS302-ILR-004: Supportive Analysis of Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=204	OMS302 N=202
Subjects With ≥ 6 mm At Cortical Clean-up In Subjects With Video Data	154/200 (77.0%)	187/195 (95.9%)
P value		<0.0001
Pupil Diameter (mm) at cortical Clean-up		
N	200	195
Mean (sd)	7.5 (2.5)	8.6 (2.4)
Min, Max	3.3, 18.7	4.8, 19.2
P value		<0.0001
Subjects With Degree of Pupillary Constriction		
<0.5mm	14	92
≥ 0.5 to <1.0mm	29	58
≥ 1.0 to <1.5mm	47	26

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>=1.5 to <2.0mm	40	13
>=2.0 to <2.5mm	17	4
>=2.5mm	53	2
P value		<0.0001

Reviewer's Comment:

Both studies met the primary endpoint of mydriasis with statistical significance.

6.1.5 Analysis of Additional Primary Endpoints(s) and/or Secondary Endpoint(s)

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population)

	Placebo N=201	OMS302 N=201
Mean AUC		
Mean (sd)	9.2 (12.9)	4.1 (8.1)
Min, Max	0.0, 65.3	0.0, 66.9
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	-5.199 (1.076)	
95% CI	-7.307, -3.091	
P-Value	<.0001	

Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population)

	Placebo N=204	OMS302 N=202
Mean AUC		
Mean (sd)	8.9 (15.2)	4.3 (8.8)
Min, Max	0.0, 85.8	0.0, 58.4
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	-4.580 (1.192)	
95% CI	-6.917, -2.244	
P-Value	0.0002	

Study OMS302-ILR-003: Ocular Pain VAS Score During 12 Hours Post-operatively (Full Analysis Set Population)

	Placebo N=201	OMS302 N=201
Subjects With Pain Free (VAS=0) At all Timepoints	28	48
P value		0.0108

Subjects with Maximum VAS Score During 12 Hours Post-operatively		
>=0 to <=5	97	137
>5 to <=10	23	13
>10 to <=15	9	14
>15 to <=20	11	7
>20	61	30
P value		0.0002
Subjects with Moderate to Severe Pain (VAS >=40) At Any Timepoint	30	13
P value		0.0061

Study OMS302-ILR-004: Ocular Pain VAS Score During 12 Hours Post-operatively (Full Analysis Set Population)

	Placebo N=204	OMS302 N=202
Subjects With Pain Free (VAS=0) At all Timepoints	41	56
P value		0.0806
Subjects with Maximum VAS Score During 12 Hours Post-operatively		
>=0 to <=5	101	126
>5 to <=10	21	20
>10 to <=15	19	14
>15 to <=20	10	10
>20	51	32
P value		0.0959
Subjects with Moderate to Severe Pain (VAS >=40) At Any Timepoint	27	16
P value		0.0760

Reviewer’s Comment:

Pain during the initial 10-12 hours postoperatively was significantly less in the Omidria-treated groups than in the placebo-treated groups in both studies.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

In both studies OMS302-ILR-003 and OMS302-ILR-004 subgroup analyses providing descriptive statistics were performed on the mean AUC of change from baseline in intraoperative pupil diameter and the mean AUC of ocular pain VAS score during the first 12 hours postoperatively. Subgroups analyzed were based on LOCS II Grade (high or low), gender, race

(white or non-white), age (< 65 years or ≥ 65 years) and iris color (brown, blue, hazel, green, and gray). In each subgroup having at least one subject in both treatment groups, OMS302 was numerically superior to placebo in both the intraoperative pupil diameter analysis and the ocular pain analysis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen was studied in both Studies OMS302-ILR-003 and OMS302-ILR-004.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated for the clinical studies. The duration of treatment for the subjects in these trials was for one time use during cataract surgery.

6.1.10 Additional Efficacy Issues/Analyses

Analysis Without Dr. Marcisco

Analysis of primary efficacy was also performed removing the data from Dr. Marcisco's investigative site¹. He enrolled 39 patients in Study OMS302-ILR-003.

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full analysis Set Population Without Dr. Marcisco's Patients, Site 198)

	Placebo N=182	OMS302 N=181
Mean AUC		
Number of Patients With Video Data	161	165
Mean (sd)	-0.5 (0.60)	0.1 (0.42)
Min, Max	-2.9, 2.1	-2.7, 1.3
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	0.575 (0.056)	
95% CI	0.466, 0.684	
P-Value	<0.0001	

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population Without Dr. Marcisco's Patients)

	Placebo	OMS302
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¹ A Form FDA 483 was issued at the conclusion of the inspection with a single observation noting that a corticosteroid (mistakenly referred to on the protocol deviation form as Vigamox) was dispensed postoperatively to all subjects without regard to their Summed Ocular Inflammation Score (SOIS), despite the protocol's requirement that the recipients of the corticosteroid exhibit an SOIS inflammatory score of 3 or greater.

	N=182	N=181
Mean AUC		
Mean (sd)	9.3 (12.94)	4.0 (8.17)
Min, Max	0.0, 62.9	0.0, 66.9
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	-5.221 (1.075)	
95% CI	-7.327, -3.115	
P-Value	<.0001	

Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full analysis Set Population Without Dr. Marcisco's Patients, Site 198)

	Placebo N=174	OMS302 N=170
Mean AUC		
Mean (sd)	-0.5 (0.54)	0.1 (0.40)
Min, Max	-2.2, 1.5	-2.2, 2.3
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	0.581 (0.050)	
95% CI	0.483, 0.678	
P-Value	<0.0001	

Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population Without Dr. Marcisco's Patients)

	Placebo N=178	OMS302 N=175
Mean AUC		
Mean (sd)	8.6 (14.59)	4.1 (9.00)
Min, Max	0.0, 85.5	0.0, 58.4
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	-4.347 (1.279)	
95% CI	-6.855, -1.839	
P-Value	0.0009	

Reviewer's Comment:

The results of analysis of both the co-primary endpoints in both Studies OMS302-ILR-003 and OMS302-ILR-004 are almost identical with or without Dr. Marcisco's patients.

Analysis of Patients With Distorted Video Images

In the images in which the microscope is not above the eye, Image J reports the long axis of the iris. If the ruler is parallel to the long axis of the iris, each is measured on the same scale and there is no distortion of the iris measurements. If the ruler is not parallel to the long axis, the ruler is foreshortened compared to the long axis of the iris and the iris diameter is artificially increased due to the angle of the observation. The relative measures of the pupil and iris are not affected when measured during the surgical procedure, but the absolute measures are artificially increased and may result in pupil diameters out of physically plausible range.

A physician reviewed all images of ruler capture and identified 19 subject videos (11 placebo and 8 OMS302) in Study OMS302-ILR-003 and 48 subject videos (23 placebo and 25 OMS302) in Study OMS302-ILR-004 that were recorded at an angle that was not above the study eye and in which the ruler was not measured parallel to the long axis of the iris that were recorded at an angle that was not above the study eye and in which the ruler was not measured parallel to the long axis of the iris.

Study OMS302-ILR-003: Comparison of Results of Pupil Diameter Analyses of the Full Analysis Set (FAS) With and Without Subjects With Distorted Video Images

	All FAS N=184	FAS Without Distorted Images N=176
Mean AUC Change From Baseline		
CMH Weighted Mean Difference	0.577	0.540
P Value	<0.0001	<0.0001
Difference in Incidence of Subjects With Pupil diameter <6mm at Cortical Cleanup	19.0%	19.7%
P-value	<0.0001	<0.0001

Study OMS302-ILR-004: Comparison of Results of Pupil Diameter Analyses of the Full Analysis Set (FAS) With and Without Subjects With Distorted Video Images

	All FAS N=395	FAS Without Distorted Images N=347
Mean AUC Change From Baseline		
CMH Weighted Mean Difference	0.59	0.56
P Value	<0.0001	<0.0001
Difference in Incidence of Subjects With Pupil diameter <6mm at Cortical Cleanup	19.1%	21.3%
P-value	<0.0001	<0.0001

Reviewer's Comment:

Exclusion of subjects due to positional distortion of video images of certain subjects did not alter the treatment effect observed in either study.

A representative number of images in both studies were evaluated as part of this review. The pupil diameter findings were able to be duplicated by this reviewer.

Supportive Analysis Without Dr. Marciso's Patients and Without Distorted Images

Study OMS302-ILR-003: Supportive Analysis of Pupil Diameter (mm) During Surgery (Full Analysis Set Population Without Dr. Marciso's Patients and Distorted Images)

	Placebo N=171	OMS302 N=173
Subjects With >=6mm At Cortical Clean-up In Subjects With Video Data	113/150 (75.3%)	151/157 (96.2%)
P value		<0.0001
Pupil Diameter (mm) at cortical Clean-up		
N	150	157
Mean (sd)	6.7 (1.1)	7.8 (1.0)
Min, Max	3.8, 9.4	4.5, 10.2
P value		<0.0001
Subjects With Degree of Pupillary Constriction		
<0.5mm	8	71
>=0.5 to <1.0mm	21	57
>=1.0 to <1.5mm	38	10
>=1.5 to <2.0mm	32	9
>=2.0 to <2.5mm	14	7
>=2.5mm	37	3
P value		<0.0001

Study OMS302-ILR-004: Supportive Analysis of Pupil Diameter (mm) During Surgery (Full Analysis Set Population Without Dr. Marciso's Patients and Distorted Images)

	Placebo N=169	OMS302 N=162
Subjects With >=6mm At Cortical Clean-up In Subjects With Video Data	123/165 (74.5%)	152/157 (96.8%)
P value		<0.0001
Pupil Diameter (mm) at cortical Clean-up		
N	165	157
Mean (sd)	6.8 (1.1)	7.8 (0.9)

Min, Max	3.3, 9.3	4.8, 10.0
P value		<0.0001
Subjects With Degree of Pupillary Constriction		
<0.5mm	12	80
>=0.5 to <1.0mm	25	50
>=1.0 to <1.5mm	42	16
>=1.5 to <2.0mm	33	7
>=2.0 to <2.5mm	12	2
>=2.5mm	41	2
P value		<0.0001

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Two clinical studies (OMS302-ILR-003 and OMS302-ILR-004) were used to evaluate safety.

7.1.2 Adequacy of Data

Between the 2 studies there were 403 patients in the safety database who received OMS302.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Two studies are used to support the safety of Omidria.

7.2 Adequacy of Safety Assessments

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

Study OMS202-ILR-003: Extent of Exposure

	Placebo N=201	OMS302 N=201
Total Volume of Study Irrigation		

solution (mL)		
Mean (sd)	252.2 (61.7)	248.0 (56.6)
Min, Max	125, 497	150, 470
Study Drug Administration Duration (minutes)		
Mean (sd)	7.7 (4.5)	7.6 (5.0)
Min, Max	1, 35	0, 42

Study OMS202-ILR-004: Extent of Exposure

	Placebo N=204	OMS302 N=202
Total Volume of Study Irrigation solution (mL)		
Mean (sd)	255.8 (70.7)	254.3 (63.4)
Min, Max	125, 500	100, 500
Study Drug Administration Duration (minutes)		
Mean (sd)	7.7 (5.1)	7.3 (4.1)
Min, Max	1, 39	1, 29

7.2.2 Explorations for Dose Response

Only one dosing regimen was studied.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of Omridia given by the intracameral route of administration.

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

See section 2.4.

7.3 Major Safety Results

7.3.1 Deaths

Study OMS302-ILR-003: One subject (Subject 193009) died during the study as a result of electrocution in an industrial accident. This was a 61 year old male who underwent ILR for cataract on 12/13/11. He was randomized to the OMS302-treatment group and received OMS302. On [REDACTED] (b) (6), the subject was electrocuted and died while working on an [REDACTED] (b) (6). The subject was not taking any concomitant medications and had no relevant medical history.

Study OMS302-ILR-004: No deaths.

7.3.2 Nonfatal Serious Adverse Events

See section 7.3.4.

7.3.3 Dropouts and/or Discontinuations

Study OMS202-ILR-003: Reason for Study Discontinuation

	Placebo N=201	OMS302 N=201
Death	0	1
Withdrawal by subject	0	1
Completed	201	199

Study OMS202-ILR-004: Reason for Study Discontinuation

	Placebo N=204	OMS302 N=202
Investigator decision	1	0
Lost to f/u	1	2
Other	1	0
Completed	201	200

7.3.4 Significant Adverse Events

Study OMS202-ILR-003: SAEs

Patient	SAE	Narrative
193009	Electrocution	61-year-old male who underwent ILR for cataract on 12/13/11. He was randomized to the OMS302-treatment group and received OMS302. On [REDACTED] (b) (6), the subject was electrocuted and died while working on an [REDACTED] (b) (6). The subject was

		not taking any concomitant medications and had no relevant medical history.
179010	A fib	79-year-old male who was admitted to the hospital due to atrial fibrillation on (b) (6), the day he reported to the surgery center for cataract extraction. He was randomized to the OMS302-treatment group but, at the time of the event, he had not received investigational product. The subject's relevant medical history included atrial fibrillation, hypertension, and CHF. He reported that, because of the scheduled cataract surgery, he had not taken his blood pressure medications that day, specifically digoxin and Coumadin.
190040	Sepsis	73-year-old female who was admitted to the hospital for sepsis due to bladder and kidney infection on (b) (6). The subject was not randomized and therefore was not administered OMS302.

Study OMS202-ILR-004: SAEs

Patient	SAE	Narrative
105001	Myocardial infraction	67-year old male who underwent ILR and was administered OMS302 on 5/9/12 and experienced unstable angina and a myocardial infarction on (b) (6). The subject had a history of smoking, hypertension, hypercholesterolemia, coronary artery disease (CAD), and prior MI. The subject was reported to be noncompliant with his medications. The subject underwent percutaneous coronary intervention and was discharged on (b) (6). The event was considered resolved.
190060	Pericardial effusion	53-year old female who underwent ILR and received placebo on 8/10/12. On (b) (6), the subject was hospitalized for a pericardial effusion. The subject also reported an event of respiratory arrest with 19 minutes of apnea on (b) (6). No other relevant information is available. The subject was discharged on (b) (6).
195038	Dehydration	68-year old female who underwent ILR and received OMS302 on 6/21/12. On (b) (6), the subject was hospitalized for dehydration that could have been related to a gastrointestinal virus. The subject was hydrated and discharged on (b) (6) with the event resolved.
207008	Malaise	70-year old female who underwent ILR and received placebo on 9/18/12. On (b) (6), the subject was hospitalized for malaise, which was found to be related to lung cancer. The subject was discharged on (b) (6).

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study OMS302-ILR-003: Subject Incidence of Treatment-Emergent AEs by System Organ Class

System Organ Class	Placebo N=201	OMS302 N=201
Any Event	154	156
Eye disorders	148	150
Anterior chamber fibrin	0	1
AC inflammation	21	19
Conjunctival hemorrhage	3	1
Conjunctival hyperemia	0	1
Conjunctival edema	1	1
Conjunctivitis	4	6
Corneal disorder	4	3
Corneal edema	5	7
Corneal pigmentation	0	1
CME	0	1
Dry eye	2	1
Eye inflammation	58	60
Eye irritation	2	5
Eye pain	86	88
Eye pruritus	0	1
FBS in eyes	0	1
Macular degeneration	1	0
Macular hole	1	0
Ocular discomfort	6	2
Photophobia	7	8
PCO	1	1
SPK	2	3
Retinal hemorrhage	1	0
Trichiasis	0	1
Vision blurred	1	0
Visual Acuity reduced	1	1
Vitreous detachment	2	1
Vitreous floater	0	1
GI disorders	2	2
Abdominal discomfort	1	0
Dyspepsia	0	1
Nausea	1	1
Infections	1	2
Bronchitis	0	1
Hordeolum	0	1
Oral herpes	1	0

Injury, Poisoning, and Procedural Complications	7	1
Corneal abrasion	3	1
Exoriation	1	0
Facial bones fracture	1	0
Fall	2	0
Foreign body in eye	1	0
Laceration	1	0
Procedural hypertension	1	0
Wrist fracture	1	0
Investigations	12	7
Blood pressure increased	2	0
IOP increased	10	7
Musculoskeletal disorders	2	6
Arthralgia	2	2
Back pain	0	1
Musculoskeletal pain	0	1
Myalgia	0	1
Pain in extremity	0	1
Nervous system disorders	15	5
Head discomfort	1	0
Headache	14	5
Psychiatric disorders	3	0
Anxiety	1	0
Insomnia	2	0
Respiratory disorders	1	2
Nasal discomfort	0	1
Oropharyngeal pain	0	1
Rhinorrhea	1	0
Metabolism and nutrition disorders	0	1
DM	0	1
General disorders	0	1
Electrocution	0	1

Study OMS302-ILR-004: Subject Incidence of Treatment-Emergent AEs by System Organ Class

System Organ Class	Placebo N=204	OMS302 N=202
Eye disorders	29	22
Abnormal sensation in eye	1	0
AC inflammation	8	10

Conjunctival hemorrhage	1	0
Conjunctival hyperemia	8	10
Conjunctival edema	0	1
Corneal disorder	1	0
Corneal edema	3	2
Eye inflammation	1	0
Eye irritation	1	1
Eye pain	14	6
Eyelid pain	0	1
FBS in eyes	3	1
Glare	0	1
Iridocele	1	0
Iris disorder	1	0
Lacrimation increased	1	0
Miosis	1	0
Mydriasis	0	1
Ocular discomfort	5	3
Photophobia	8	3
Vision blurred	1	1
Vitreous floaters	0	1
GI disorders		
Nausea	0	1
Nervous system disorders		
Headache	2	1

Reviewer’s Comment:

The most frequently observed AEs overall were eye pain, eye inflammation, anterior chamber inflammation, headache, and increased IOP, all anticipated events following ILR surgery. These events occurred at a similar incidence across the treatment groups.

7.4.2 Laboratory Findings

Clinical laboratory assessments were neither planned nor performed during this study. Only baseline pregnancy tests.

7.4.3 Vital Signs

Study OMS302-ILR-003: Mean Systolic BP mmHg (Safety Population)

	Placebo	OMS302
Baseline (sd)	138.8 (20.1) N=201	137.2 (19.0) N=201
5 Minutes From Start of Procedure	137.8 (20.5) N=190	138.0 (19.6) N=191
10 Minutes From Start of Procedure	130.4 (17.6) N=73	133.4 (20.0) N=79
15 Minutes From Start of Procedure	131.2 (14.5) N=35	131.5 (16.9) N=26

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20 Minutes From Start of Procedure	132.9 (14.8) N=11	136.0 (11.6) N=9
25 Minutes From Start of Procedure	143.5 (3.5) N=2	147.3 (13.0) N=4
30 Minutes From Start of Procedure	146.5 (0.7) N=2	144.5 (7.8) N=2
35 Minutes From Start of Procedure	146.0 N=1	143.0 N=1
End of Procedure	138.3 (19.4) N=194	138.2 (19.1) N=197

Study OMS302-ILR-003: Mean Diastolic BP mmHg (Safety Population)

	Placebo	OMS302
Baseline	77.7 (10.0) N=201	76.1 (9.9) N=201
5 Minutes From Start of Procedure	76.6 (10.5) N=190	75.5 (9.9) N=191
10 Minutes From Start of Procedure	73.1 (9.2) N=73	74.2 (9.9) N=79
15 Minutes From Start of Procedure	72.2 (10.7) N=35	72.8 (6.5) N=26
20 Minutes From Start of Procedure	74.1 (12.5) N=11	72.3 (5.1) N=9
25 Minutes From Start of Procedure	82.0 (9.9) N=2	72.0 (3.2) N=4
30 Minutes From Start of Procedure	84.5 (7.8) N=2	71.0 (1.4) N=2
35 Minutes From Start of Procedure	90.0 N=1	65.0 N=1
End of Procedure	76.6 (11.0) N=194	75.9 (9.9) N=197

Study OMS302-ILR-003: Heart Rate (Safety Population)

	Placebo	OMS302
Baseline	68.6 (12.6) N=201	68.3 (12.0) N=201
5 Minutes From Start of Procedure	67.5 (12.0) N=191	67.2 (11.4) N=191
10 Minutes From Start of Procedure	67.4 (12.1) N=74	68.0 (12.0) N=79
15 Minutes From Start of Procedure	67.1 (12.5) N=35	65.4 (11.3) N=26
20 Minutes From Start of Procedure	69.1 (13.9) N=11	64.9 (10.4) N=9
25 Minutes From Start of Procedure	85.0 (9.9) N=2	64.8 (6.3) N=4
30 Minutes From Start of Procedure	86.0 (9.9) N=2	62.5 (0.7) N=2

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35 Minutes From Start of Procedure	92.0 N=1	60.0 N=1
End of Procedure	68.0 (12.1) N=195	67.4 (11.4) N=197

Study OMS302-ILR-004: Mean Systolic BP mmHg (Safety Population)

	Placebo	OMS302
Baseline	132.6 (19.6) N=204	136.5 (18.7) N=202
5 Minutes From Start of Procedure	132.8 (20.5) N=195	135.9 (18.6) N=186
10 Minutes From Start of Procedure	126.8 (21.4) N=71	134.0 (17.4) N=68
15 Minutes From Start of Procedure	129.3 (20.7) N=25	137.4 (16.6) N=22
20 Minutes From Start of Procedure	125.1 (14.6) N=11	140.4 (18.8) N=7
25 Minutes From Start of Procedure	120.5 (5.6) N=4	140.3 (21.6) N=3
30 Minutes From Start of Procedure	126.0 N=1	122.0 N=1
35 Minutes From Start of Procedure	128.0 N=1	
End of Procedure	133.6 (20.1) N=201	136.3 (17.4) N=201

Study OMS302-ILR-004: Mean Diastolic BP mmHg (Safety Population)

	Placebo	OMS302
Baseline	74.1 (11.3) N=204	76.3 (11.0) N=202
5 Minutes From Start of Procedure	74.3 (11.2) N=195	76.3 (9.8) N=186
10 Minutes From Start of Procedure	71.4 (12.0) N=71	74.0 (10.2) N=68
15 Minutes From Start of Procedure	69.8 (9.3) N=25	79.1 (9.6) N=22
20 Minutes From Start of Procedure	70.4 (7.8) N=11	81.4 (7.0) N=7
25 Minutes From Start of Procedure	64.3 (3.9) N=4	83.0 (1.0) N=3
30 Minutes From Start of Procedure	61.0 N=1	84.0 N=1
35 Minutes From Start of Procedure	70.0 N=1	
End of Procedure	74.7 (11.4) N=201	76.2 (10.2) N=201

Study OMS302-ILR-004: Mean Heart Rate (Safety Population)

	Placebo	OMS302
Baseline	67.9 (12.0) N=204	68.4 (12.8) N=202
5 Minutes From Start of Procedure	66.6 (11.8) N=195	67.1 (12.1) N=186
10 Minutes From Start of Procedure	66.8 (11.7) N=71	68.6 (11.1) N=68
15 Minutes From Start of Procedure	65.4 (15.4) N=25	68.4 (9.7) N=22
20 Minutes From Start of Procedure	60.7 (9.1) N=11	71.7 (11.7) N=7
25 Minutes From Start of Procedure	56.5 (9.5) N=4	77.0 (10.1) N=3
30 Minutes From Start of Procedure	67.0 N=1	90.0 N=1
35 Minutes From Start of Procedure	49.0 N=1	
End of Procedure	67.4 (12.0) N=202	67.4 (11.5) N=201

7.4.4 Electrocardiograms (ECGs)

Not performed.

7.4.5 Special Safety Studies

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not performed.

7.5.2 Time Dependency for Adverse Events

Not performed.

7.5.3 Drug-Demographic Interactions

7.5.4 Drug-Disease Interactions

Omidria was evaluated for [REDACTED] (b) (4) the prevention of intraoperative miosis, and the reduction of [REDACTED] (b) (4) post-operative pain with no drug-disease interaction analysis.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between Omidria and any of the concomitant medications allowed in those studies.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of LE in topical preparations, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

Safety and effectiveness of Omidria in pediatric patients below the age of 18 years have not been established. Height and weight data were not collected as part of this protocol.

This application went to PeRC and on 10/30/13 a deferral for all pediatric age groups was granted.

A single pediatric study in at least 60 patients (30 per arm) undergoing cataract surgery is being planned to be conducted in the U.S. [REDACTED] (b) (4)

[REDACTED]

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Omidria is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

On 11/26/13, a 4 month safety update was submitted. The applicant stated no additional safety data had been collected and no new clinical studies with OMS302 had been conducted since the data cut-off date. From January 17, 2013 through the November 15, 2013, there was no new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

8 Post-marketing Experience

None.

9 Appendices

9.1 Literature Review/References

A pub med search did not reveal any new information on Omridia.

9.2 Labeling Recommendations

See Appendix.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

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APPEARS THIS WAY ON
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Appendix 2-Financial Disclosure Template

Clinical Investigator Financial Disclosure Review Template

Application Number: 205-388

Submission Date(s): 7/30/13

Applicant: Omeros

Product: phenylephrine/ketorolac

Reviewer: Sonal D. Wadhwa, MD

Date of Review: 2/19/14

Covered Clinical Study (Name and/or Number): OMS302-ILR-003 and OMS302-ILR-004

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: OMS302-ILR-003: 17 sites and OMS302-ILR-004: 15 sites		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>No.</u></p> <p>Significant payments of other sorts: (b) (6) <i>received payments with a cumulative value of \$30,004.39 for consulting services provided in relation to Omeros' ophthalmic clinical program (Study OMS302-ILR-003 and 004).</i></p> <p>Proprietary interest in the product tested held by investigator: <u>No.</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>No.</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information

minimize potential bias provided:		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

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

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

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

The disclosed financial interests/arrangements do not affect the approvability of the application.

Study OMS302-ILR-003 was a double blind, placebo-controlled, multicenter, randomized trial. (b) (6) was 1 of 18 investigator sites participating in the trial. He was responsible for enrolling only (b) (4) subjects out of a total of 405 subjects in the trial. The two co-primary endpoints in this study were objective measures, neither of which were directly evaluated or assessed by (b) (6) (b) (6) Change in pupil diameter over time from surgical baseline to the end of the surgical procedure which was evaluated by a masked central reader. Early post-operative pain which was obtained from a Visual Analog Scale completed by the subject.

Study OMS302-ILR-004 was a double blind, placebo-controlled, multicenter, randomized trial. (b) (6) was 1 of 16 investigator sites participating in the trial. He was responsible for enrolling only (b) (4) subject out of a total of 416 subjects in the trial. The two co-primary endpoints in this study were objective measures, neither of which were directly evaluated or assessed by (b) (6) (b) (6) Change in pupil diameter over time from surgical baseline to the end of the surgical procedure which was evaluated by a masked central reader. Early post-operative pain which was obtained from a Visual Analog Scale completed by the subject.

² See [web address].

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

/s/

SONAL D WADHWA
05/09/2014

WILLIAM M BOYD
05/09/2014