CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205388
Supplement #:	000
Drug Name:	Omidria™ (Phenylephrine HCL/Ketoroloc Tromethamine)
Indication(s):	(b) (4) prevention of intraoperative miosis, and reduction of postoperative ocular pain
Applicant:	Omeros Corporation
Date(s):	Submitted: 07/30/2013 PDUFA date: 05/30/2014
Review Priority:	Standard
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Keywords: mydriasis, miosis, reduction of postoperative ocular pain

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1 EXECUTIVE SUMMARY

The applicant, Omeros, seeks approval of OMIDRIA (Phenylephrine HCL 1%/Ketoroloc Tromethamine 0.3%, known as OMS302 throughout this review) as an irrigation solution used during intraocular lens replacement (ILR) surgery for (b) (4) the prevention of intraoperative miosis, and the reduction of postoperative pain. OMS302 is a mydriatic/nonsteroidal anti-inflammatory drug (NSAID) combination product. It contains a mydriatic drug phenylephrine HCI (PE), and a nonsteroidal anti-inflammatory drug ketorolac tromethamine (KE). In order to support the approval of OMS302, the applicant submitted three pivotal studies: Study C09-001, Study OMS302-ILR-003, and Study OMS302-ILR-004.

Study C09-001 was a full-factorial design study to evaluate the contribution of each component to the combination product. A total of 222 subjects (56 in vehicle, 53 in PE, 56 in KE, and 56 in OMS302) were enrolled and treated at 23 centers across U.S. The co-primary efficacy endpoints were:

- The change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure). Pupil diameters were captured from snapshots of video at intervals of one minute and were later measured by a masked central reader at each minute throughout the surgery.
- Postoperative pain as measured by the Visual Analog Scale (VAS, 0 – 100) at 2, 4, 6, 8 and 10-12 hours of the end of surgery.

In order to claim success, the study needed to demonstrate superiority of OMS302 versus KE and vehicle in terms of mydriasis and superiority of OMS302 versus PE and vehicle in terms of postoperative ocular pain. Both endpoints were analyzed by repeated measures analyses of variance with treatment (OMS302, KE and vehicle for pupil diameter; OMS302, PE, and vehicle for ocular pain VAS), time point (as a categorical variable), and the stratification factor (cataract Lens Opacities Classification System II: low vs. high) as predictor variables. The model parameters were estimated by a generalized estimating equation (GEE) method with an auto-regressive of order 1 [AR(1)] working correlation structure.

For the change from baseline in pupil diameter over time analysis, 19 (8.5%) subjects were excluded because their video recordings during the cataract extraction with lens replacement (CELR) surgery were not readable (3/56 [5.4%] in vehicle group, 7/56 [12.5%] in PE group, 3/55 [5.5%] in KE group, and 7/55 [12.7%] in OMS302 group). Exclusion of those subjects was due to technical difficulty and not treatment-related; therefore, the statistical reviewer concluded that exclusion of these subjects was unlikely to introduce bias to the study. The least square mean estimators of change from baseline in pupil diameter for OMS302 and KE were -1.2mm and -1.9mm respectively, with treatment difference of 0.7mm (95% confidence interval [CI]: 0.5, 0.9). For the ocular pain VAS during the first 10-12 postoperatively, all subjects were included in the primary analyses; the least square mean estimators for OMS302 and PE were 6.1 and 12.0 respectively, with treatment difference of 5.9 (95% CI: 1.5, 10.3).

Although Study C09-001 was the only study conducted to evaluate the contribution of PE and KE to the proposed indication, the study results were highly significant and consistent; therefore

the statistical reviewer concluded this study was adequate to support the contribution of each component to the combination product.

Both studies OMS302-ILR-003 and OMS302-ILR-004 were similarly designed and compared OMS302 with placebo. The two efficacy endpoints were the same as Study C09-001 except postoperative pain was a co-primary endpoint in Study OMS302-ILR-004; whereas it was the first secondary endpoint in a hierarchical chain in Study OMS302-ILR-003. Both endpoints were analyzed based on mean area-under-curve (AUC) using a generalized Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata. The mean AUC was calculated by dividing the AUC (calculated by the trapezoidal rule over the time period) by the total time.

A total of 402 subjects were randomized and treated at 17 centers across U.S. in Study OMS302-ILR-003, 38 (9.5%) subjects were excluded from the pupil diameter analyses (17/201 [8.5%] subjects in the OMS302 group, 21/201 [10.4%] subjects in the placebo group). In Study OMS302-ILR-004, 406 subjects were randomized and treated at 15 centers across U.S. and less subjects (11 [2.7%]; 7/202 [3.5%] in the OMS302 group and 4/204 [2.0%] subjects in the placebo group) were excluded from the pupil diameter analyses. The subjects excluded from the pupil diameter analyses were excluded because of technical issues related to video recording and not treatment-related; therefore, the statistical reviewer concluded that exclusion of these subjects was unlikely to introduce bias to these studies. For the ocular pain analyses, all but two subjects (0.5%) in study OMS302-ILR-004 (both in placebo group) were included.

In Study OMS302-ILR-003, the mean AUC estimate of change from baseline in pupil diameter was 0.1mm for OMS302 and -0.5mm for placebo; with treatment difference of 0.6mm (95% CI: 0.5, 0.7). The mean AUC estimate of ocular pain VAS score was 4.1 for OMS302 and 9.2 for placebo; the treatment difference was -5.2 (95% CI: -7.3, -3.1). In Study OMS302-ILR-004, the mean AUC estimate of change from baseline in pupil diameter was 0.1mm for OMS302 and -0.5mm for placebo; with treatment difference of 0.6mm (95% CI: 0.5, 0.7). The mean AUC estimate of ocular pain VAS score was 4.3 for OMS302 and 8.9 for placebo; the treatment difference was -4.6 (95% CI: -6.9, -2.2).

The applicant's primary analyses did not present the treatment effects at each time point directly; therefore the statistical reviewer calculated treatment differences and the corresponding 95% CIs in mean change from baseline of pupil diameter between OMS302 and placebo at each time point from the beginning of the surgery till the 20-minute time point for all three studies (Figure 1, Figure 2, Figure 3, and Table 39). The number of subjects at each time point becomes smaller over time because ILR procedures were completed in different amounts of time. Data after the 20-minute time point is not listed since only about 6% or less of subjects in each study were still undergoing surgical procedure after 20 minutes. The statistical reviewer also summarized the proportion of patients with zero VAS score (which means no pain) at each time point within 12 hours post-surgery (Table 1). In these summarized tables and figures, the treatment effects were comparable across all three studies.

In conclusion, OMS302 is effective in maintaining pupil dilution during the intraocular lens replacement surgery compared to KE and placebo and in reducing ocular pain during the first 12 hours postoperatively compared to PE and placebo.

Figure 1: Study C09-001 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline

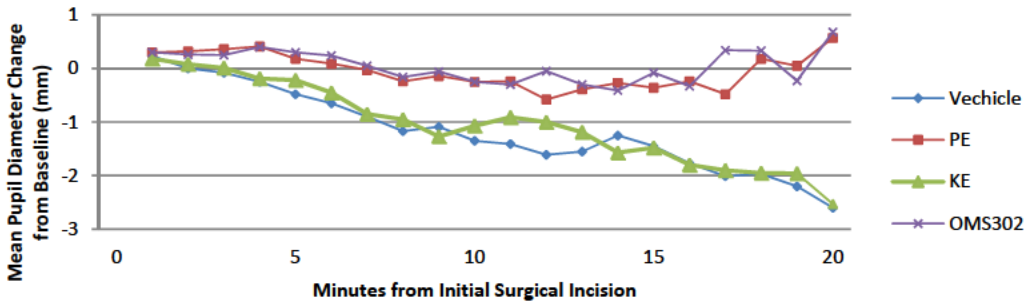


Figure 2: Study OMS302-ILR-003 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline

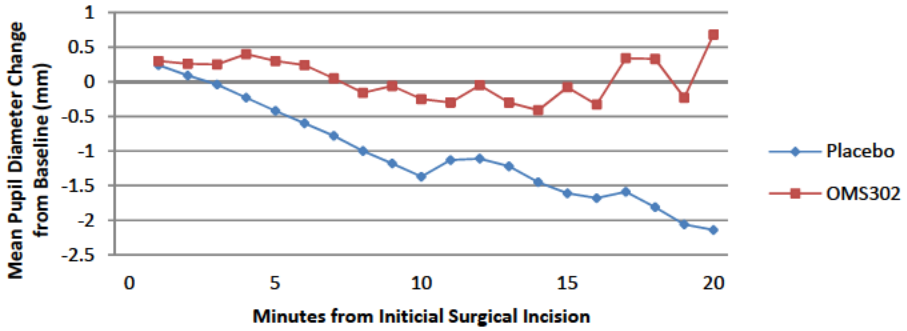
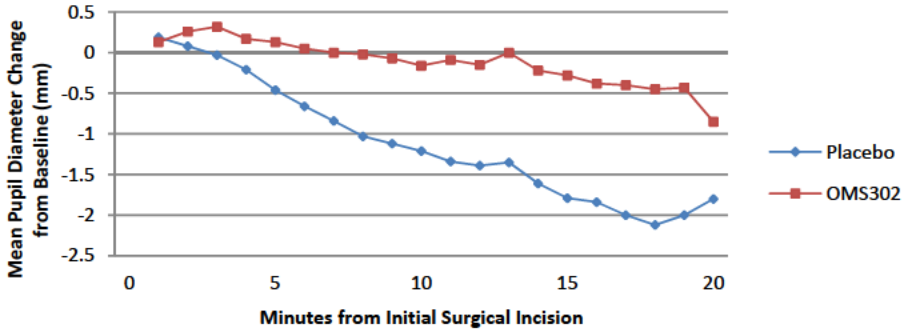


Figure 3: Study OMS302-ILR-004 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline



Source for figures: Table 39.

Table 1: Summary of Proportion of Patients with Zero VAS Scores Post-Surgery at Each Time Point for All Three Studies (All Treated Subjects)

	Study C09-001			Study OMS302-ILR-003			Study OMS302-ILR-004		
	OMS302	PE	Diff (95% CI)	OMS302	Placebo	Diff (95% CI)	OMS302	Placebo	Diff (95% CI)
2 Hours	31/55 (56.4%)	28/56 (50.0%)	6.4% (-12.2%, 24.9%)	81/201 (40.3%)	61/201 (30.4%)	9.9% (0.7%, 19.2%)	101/202 (50.0%)	75/203 (37.0%)	13.1% (3.5%, 22.6%)
4 hours	26/49 (53.1%)	20/52 (38.5%)	14.6% (-4.6%, 33.8%)	94/201 (46.8%)	62/200 (31.0%)	15.8% (6.4%, 25.2%)	111/202 (55.0%)	80/203 (39.4%)	15.5% (5.9%, 25.2%)
6 Hours	29/55 (52.7%)	22/55 (40.0%)	12.7% (-5.8%, 31.2%)	91/201 (45.3%)	59/201 (29.4%)	15.9% (6.6%, 25.3%)	107/202 (53.0%)	80/203 (39.4%)	13.6% (3.9%, 23.2%)
8 Hours	27/51 (52.9%)	18/54 (33.3%)	19.6% (1.0%, 38.2%)	94/201 (46.8%)	58/200 (29.0%)	17.8% (8.4%, 27.1%)	115/202 (56.9%)	84/201 (41.8%)	15.1% (5.5%, 24.8%)
10 to 12 Hours	30/54 (55.6%)	18/55 (32.7%)	22.8% (4.7%, 41.0%)	92/201 (45.8%)	64/199 (32.2%)	13.6% (4.2%, 23.1%)	123/199 (63.3%)	89/202 (44.1%)	19.3% (9.7%, 28.8%)

* 95% CI based on chi-square test
Source: statistical reviewer's analysis.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

OMS302 is a mydriatic/nonsteroidal anti-inflammatory drug (NSAID) combination product. It contains phenylephrine HCI (PE), a mydriatic drug, and ketorolac tromethamine (KE), a nonsteroidal anti-inflammatory drug. The applicant developed OMS302 for adding to irrigation solution during intraocular lens replacement (ILR) surgery to maintain pupil dilation, prevent intraoperative miosis, and reduce early postoperative pain.

The active ingredients in OMS302 Injection, PE and KE, have been individually approved in the US for a number of indications in various commercial products:

- KE for topical ophthalmic use was indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of postoperative inflammation following cataract extraction.
- Phenylephrine hydrochloride alone was approved in March, 2013 by FDA for dilating the pupil. Previously, before the approval, unapproved ophthalmic phenylephrine in varying strengths was used to dilate the pupil before eye examinations, before eye surgery, and to treat certain eye conditions.

2.1.2 History of Drug Development

The applicant had an End-of-Phase 2 meeting with the agency on July 15, 2011. The Agency acknowledged that we had approved combination drugs without replicate factorial studies although we would expect to see replication of the contribution of PE and of KE to the proposed indication. The agency also indicated whether the results of the OMS302 Phase 2 factorial study already conducted by the applicant, together with an analysis of the known pharmacology of the active components in OMS302, supports the proposed indication would be determined during the NDA review.

The agency accepted the applicant's proposed analyses for the primary and secondary efficacy endpoints for both studies OMS302-ILR-003 and OMS302-ILR-004 when their study protocols were submitted for review.

2.1.3 Studies Reviewed

OMS302 clinical development plan included four clinical studies: one Phase 1/2 study (Study C07-005), one full-factorial study (Study C09-001) to evaluate each of the individual components' (PE and KE) contribution to the proposed indication, and two pivotal Phase 3 safety and efficacy studies (Studies OMS302-ILR-003 and OMS302-ILR-004). Study C09-001 was considered as a Phase 2 study by the applicant.

Because Study C07-005 was exploratory in nature and the final OMS302 product was different from what was used in this study, this review does not include Study C07-005. This review focuses on the statistical aspect of the three safety and efficacy studies (studies C09-001, OMS302-ILR-003, and OMS302-ILR-004). Key information of these three studies is presented in the following table.

Table 2: Key Information for Studies C07-005, OMS302-ILR-003, and OMS302-ILR-004

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
C09-001	*Phase 2, randomized, double-masked, vehicle-controlled factorial design*	*Single administration for irrigation during the ILR surgery*	*30 days following surgery*	*OMS302:55 KE: 55 PE: 56 Vehicle: 56*	*Subjects underwent unilateral cataract extraction with lens replacement (CELR)*
OMS302-ILR-003	*Phase 3 randomized, double-masked, placebo-controlled study*	*Single administration for irrigation during the ILR surgery*	*14 days after surgery*	*OMS302: 201 Placebo: 201*	*Subjects underwent ILR with phacoemulsification*
OMS302-ILR-004	*Phase 3 randomized, double-masked, placebo-controlled study*	*Single administration for irrigation during the ILR surgery*	*Up to 90 days after surgery*	*OMS302: 202 Placebo: 204*	*Subjects underwent ILR with phacoemulsification*

Source: Statistical Reviewer's Summary

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies C09-001, OMS302-ILR-003, and OMS302-ILR-004. The study reports are available at: \\Cdsesub1\evsprod\NDA205388\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\intraocular-lens-replacement\5351-stud-rep-contr.

The applicant submitted SAS datasets electronically; the datasets are available at: \\Cdsesub1\evsprod\NDA205388\0000\m5\datasets.

The SAS program codes that were used to generate the results in the study reports are available at: \\Cdsesub1\evsprod\NDA205388\0007\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

During the review process, we had one data related issues identified; and our correspondence with the applicant regarding this issue follows.

In the initial NDA submission, no SAS program codes used to produce the analysis results were submitted. We requested the applicant to submit the SAS program codes to facilitate our review on September 10th, 2013; the applicant responded with completed program codes on November 6th, 2013. The statistical reviewer considered the response acceptable and had no further request regarding SAS program codes.

Overall, the submitted data were in good quality with definition of each variable. Results of the primary and key secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plans (SAPs) for the three studies were submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study C09-001

Study C09-001 was a randomized, multi-center, double-masked, vehicle-controlled study of OMS302, PE, and KE in subjects undergoing cataract extraction with lens replacement (CELR) using a coaxial phacoemulsification process with insertion of an acrylic lens. Phacoemulsification refers to the removal of a cataract by first liquefying the affected lens with ultrasonic vibrations and then extracting it by suction.

The study recruited subjects who underwent unilateral primary CELR. Eligible subjects were randomized in a 1:1:1:1 ratio to one of the following four treatment arms:

- Balanced salt solution (BSS) vehicle
- Single study-drug formulation containing 483 µM PE
- Single study-drug formulation containing 89 µM KE
- Combination study-drug formulation containing OMS (483 µM PE/89 µM KE)

Randomization was stratified by cataract Lens Opacities Classification System II (LOCS II) grade: N_0 and N_I as one stratum (low) versus N_{II} and N_{III} as the other stratum (high). Study treatment was administered as irrigation solution to the anterior chamber of the eye during CELR surgery.

Evaluation of safety and efficacy were performed at screening, at baseline prior to surgery, on the day of surgery intraoperatively, 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. Specifically, during the surgery, eye images were captured by video snapshots at one minute intervals starting from surgical incision to measure the mydriasis effect of each treatment. Ocular pain and ocular discomfort were assessed by each subject using a Visual Analog Scale (VAS) and a Numerical Rating Scale (NRS) at 2, 4, 6, 8, 10-12 hours post-surgery. Inflammation was assessed by the study investigators by the Summed Ocular Inflammation Score (SOIS) using a slit lamp biomicroscope. Subjects were requested to complete daily diaries twice daily during the first 7 days post-surgery. Safety and tolerability were assessed based on adverse events (AEs), vital signs, and ocular and systemic measures for 30 days postoperatively.

The applicant stated that the primary objectives of this study were to:

- Evaluate the safety of OMS302 compared to vehicle when administered during CELR surgery as measured by AEs.
- Evaluate the effect of OMS302 compared to vehicle on intraoperative mydriasis during CELR surgery as measured by intraoperative pupil diameter.
- Evaluate the effect of OMS302 compared to vehicle on ocular pain during the first 12 hours postoperatively.
- Evaluate the effect of OMS302 compared to KE on mydriasis during CELR surgery as measured by pupil diameter.
- Evaluate the effect of OMS302 compared to PE on ocular pain during the first 12 hours postoperatively.

The applicant defined primary endpoints were:

- The change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure). Pupil diameters were captured from snapshots of video at intervals of one minute.
- Postoperative pain as measured by the Visual Analog Scale (VAS) at 2, 4, 6, 8 and 10-12 hours of the end of surgery. The VAS scale was from 0 to 100, where 0 = no pain and 100 = worst pain possible.

For defining the pupil diameter measuring time points, the applicant used the following analytic windows:

Table 3: Applicant-Defined Analytic Window for Pupil Diameter

Analytic Time Point (min)	Actual Time From Surgical Incision (min)
0	0
1	>0 to 1.5
t (for t>1)	>t – 0.5 to t +0.5

Source: Table 2 of Study C09-001 SAP.

The actual date and time of collection for postoperative time points was binned into the analytic windows by the applicant according to **Table 4**.

Table 4: Applicant-Defined Analytic Window for Pain VAS within 12 Hours of End of Surgery

Analytic Time Point	Actual Time From Surgical Incision
2 hours post surgery	> 0 to ≤ 3 hours
4 hours post surgery	> 3 to ≤ 5 hours
6 hours post surgery	> 5 to ≤ 7 hours
8 hours post surgery	> 7 to ≤ 9 hours
10-12 hours post surgery	> 9 to ≤ 18 hours
If there are more than 1 pain VAS scores in the same time-point window, the closest one to the scheduled time point will be used in the analysis. If there are 2 pain VAS scores that are equally spaced from the scheduled time point, the larger score will be used in the analysis. If the collection time is unknown, the pain VAS score will be excluded from the analysis.	

Source: Table 3 of study C09-001 SAP.

3.2.1.2 Studies OMS302-ILR-003 and OMS302-ILR-004

Studies OMS302-ILR-003 and OMS302-ILR-004 were two similar designed phase 3 pivotal studies. Both studies were randomized, multicenter, double-masked, placebo controlled studies in subjects undergoing ILR with phacoemulsification. Both studies were intended to evaluate the effect of OMS302 compared to placebo on intraoperative pupil diameter when administered in irrigation solution during phacoemulsification and intraocular lens replacement, and to evaluate the effect of OMS302 compared to placebo on pain in the early postoperative period. The two studies were similar except:

- In Study OMS302-ILR-004, postoperative pain was a co-primary endpoint; whereas in Study OMS302-ILR-003 it was the key secondary endpoint.
- All subjects received topical ophthalmic ketorolac on postoperative Day 1 after all primary efficacy measures had been obtained in Study OMS302-ILR-004; in Study OMS302-ILR-003, topical ophthalmic non-steroidal anti-inflammatory drugs and corticosteroids were permitted on the first postoperative day or later for subjects who had 3 or higher inflammation on the SOIS scale and for whom the Investigator deemed to be beneficial.
- In Study OMS302-ILR-004, pharmacokinetics was evaluated in a subset of subjects.
- In Study OMS302-ILR-004, subjects had a safety follow-up visit at Day 90; in Study OMS302-ILR-003, subjects' final study visits were on Day 14.

In both studies, eligible subjects who underwent CELR or refractive lens exchange (RLE) were randomized at 1:1 ratio to OMS302 or placebo. Randomization to treatment group was stratified within site by LOCS II (low vs. high). Administration of test irrigation solutions took place in a double-masked fashion during phacoemulsification and intraocular lens replacement. All subjects received standard care for CELR during the study.

Safety and efficacy measurements 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, 14 days, and 90 days (for Study OMS302-ILR-004 only). Daily subject diaries were completed once each morning during the first 7 days postoperatively for both studies. 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 14 days postoperatively.

For Study OMS302-ILR-004, the applicant defined 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
- Postoperative pain as measured by the VAS at 2, 4, 6, 8, and 10 to 12 hours after ILR surgery.

As mentioned previously, for Study OMS302-ILR-003, change in pupil diameter over time was the only primary efficacy endpoint; while postoperative pain as measured by VAS was the first secondary endpoint among a number of secondary endpoints defined by the applicant. The analytic windows for both endpoints were defined the same as the ones in Study C09-001.

For both studies, the sample size estimation of 400 subjects (200 per arm) was based on the following assumptions proposed by the applicant to support the ocular pain endpoint:

- t-test at the 0.05 two-sided level of significance
- difference between the treatment arms of 5.0 mm
- standard deviation of 13.3 mm
- 96% power
- all subjects randomized will be included in the primary analysis population

Two hundred subjects per arm also provided greater than 99% power for the pupil diameter endpoint based on the following assumptions proposed by the applicant:

- t-test at a 0.05 two-sided level of significance
- difference of 0.6 mm
- standard deviation of 0.7 mm
- all subjects randomized will be included in the primary analysis population

According to the applicant, the above mean differences and standard deviation for the estimation of sample size were taken from the completed phase 2 study.

3.2.2 Statistical Methodologies

3.2.2.1 Study C09-001

The study intended to show superiority of OMS302 versus KE and vehicle in terms of mydriasis and superiority of OMS302 versus PE and vehicle in terms of postoperative ocular pain. Therefore the four null hypotheses needed to be tested (summarized by the statistical reviewer) in this study were:

- There was no difference in the change from baseline of post-surgical incision pupil diameter between the OMS302 group and the vehicle group.

- There was no difference in the change from baseline of post-surgical incision pupil diameter between the OMS302 group and the KE group.
- There was no difference in postoperative pain VAS between the OMS302 group and the vehicle group.
- There was no difference in postoperative pain VAS between the OMS302 group and the PE group.

The applicant stated in the SAP that the formal decision rule utilized for this study was based upon all four primary tests being significant at the 5% two-sided level.

For the primary efficacy endpoint of the change in pupil diameter over time, the primary analysis was conducted on the applicant defined Mydriasis Analysis Set (MAS), which included all randomized subjects who received study treatment, had the baseline and at least one post baseline pupil diameters measurement.

For the primary efficacy endpoint of postoperative pain as measured by Visual Analog Scale (VAS) throughout the study, the primary analysis of this endpoint only used the measurements taken on the day of operation at 2, 4, 6, 8, and 10-12 hours postoperatively. The primary analysis was conducted on the applicant defined Pain Analysis Set (PAS), which included all randomized subjects who received study treatment, and had at least one pain VAS score during the first 12 hours post-surgery.

Both endpoints were analyzed by repeated measures analyses of variance with treatment (OMS302, KE and vehicle for pupil diameter; OMS302, PE, and vehicle for VAS), time point (as a categorical variable) and the stratification factor LOCS II grade as predictor variables. The model parameters were estimated by a GEE method with an AR(1) working correlation structure. Based on the analyses SAS codes submitted by the applicant, these analyses assumed constant treatment effect over time. However, the assumption of constant treatment effect over time may not be applicable to the change from baseline of pupil diameter endpoint. Additional sensitivity analyses without such assumption were conducted by the applicant as described in the following paragraphs.

For both primary endpoints, the applicant also conducted additional sensitivity analyses using the applicant defined per protocol (PP) population, which included all subjects in the MAS and PAS populations that complete study with no major protocol violations. In addition, the applicant conducted mean area-under-the-curve (AUC) analysis as part of the sensitivity analyses. In the mean AUC analysis, AUC over the time period of each primary efficacy endpoint was calculated by the trapezoidal rule. The mean AUC was then calculated by dividing the AUC by the duration from the first post-baseline value to the last post-baseline value. Treatment comparison was performed using the analysis of variance (ANOVA) model where the each of the endpoint as the response variable and treatment group and the stratification factor LOCS II grade as covariates. The ANOVA analysis was performed using the MAS and PAS populations respectively.

Post hoc sensitivity analyses for both primary endpoints were conducted based on the Agency's feedback during EOP2 meeting. For the pain endpoint, proportion of subjects who were pain-free

(VAS score = 0) at all time points until 12 hours postoperatively was evaluated using Fisher's exact test to compare between the treatment groups (vehicle vs. OMS302 and PE vs. OMS302). Fisher's exact test was also used to compare intraoperative miosis between the treatment groups (vehicle vs. OMS302 and KE vs. OMS302) by assessing pupil diameter changes from baseline using specific cut-points (≤ −0.5 mm, ≤ −1.00 mm, ≤ −1.5 mm, ≤ −2.00 mm, and ≤ −2.50 mm).

3.2.2.2 Studies OMS302-ILR-003 and OMS302-ILR-004

Both studies OMS302-ILR-003 and 004 intended to evaluate the effect of OMS302 compared to placebo when administered in irrigation solution during phacoemulsification and ILR on intraoperative pupil diameter and pain within 12 hours postoperatively. The difference was that postoperative pain was a co-primary endpoint in Study OMS302-ILR-004 and it was the principal (first) secondary endpoint in Study OMS302-ILR-003. The analysis methods were the same for both endpoints in both studies.

The primary analysis population was the full analysis sent population (FAS), which included all randomized subjects who received any amount of study medication. Subjects who did not start treatment were excluded from the FAS. Subjects in the FAS were analyzed according to their randomized treatment groups.

Both change from baseline in pupil diameter and ocular pain VAS within 12 hours postoperatively were analyzed using a generalized CMH test stratified by the randomization strata based on the mean area-under-curve (AUC). The mean AUC was calculated by dividing the AUC (calculated by the trapezoidal rule over the time period) by the duration from the first post-baseline value to the last post-baseline value.

In addition, according to the applicant, if there were any subjects whose mean AUC of change-from-baseline in pupil diameter or mean AUC of ocular pain VAS during 12 hours postoperatively could not be calculated in the FAS population, these subjects were excluded from the primary analyses and a multiple imputation method utilizing linear regression was used to impute missing mean AUC as a sensitivity analysis. This imputation procedure was outlined by the applicant as:

1) *A linear regression model will be fitted using subjects with non-missing mean AUC. The following variables will be used as the predictors for the linear regression model: age, gender, iris color, randomization strata (the same pooled strata used in the primary analysis if necessary). Based on the fitted regression model, a new regression model is simulated from the posterior predictive distribution of the regression parameters and is used to impute the missing mean AUC. This imputation will be carried out 5 times generating 5 complete datasets. This step will be carried out by the SAS procedure MI.*

2) *For the k_{th} imputed dataset in step 1, the CMH weighted mean difference and its standard error will be calculated:*

$$D_k = \frac{\sum_h w_h d_{hk}}{\sum_h w_h}$$

$$S_k = \frac{(\sum_h w_h^2 \, v_{hok})^{1/2}}{\sum_h w_h}$$

where d_{hk} is the mean difference (OMS302 – placebo) for stratum h, v_{hok} is the variance of d_{hk} under the null hypothesis of no treatment effect. It should be noted that the CMH weight w_h is the same across the imputed datasets (the same weights as the primary analysis).

3) *The combined CMH weighted mean difference, its standard error and the t-test for mean difference will be calculated by the SAS procedure MIANALYZE.*

3.2.2.3 Prevention of Miosis

To evaluate the effect of OMS302 on prevention of miosis, the applicant did additional analyses in each of the three studies (C-09-011, OMS302-ILR-003, and OMS302-ILR-004) based on the proportions of subjects who had < 6 mm pupil diameter at the end of cortical cleanup and at any time during the procedure. According to the applicant, these analyses were recommended by FDA in the End-of-Phase 2 (EOP2) Meeting; therefore, these analyses were prospectively defined in studies OMS302-ILR-003 and OMS302-ILR-004; and were performed retrospectively in the Phase 2 Study C09-001. Furthermore, in Study C09-001, this analysis was only performed using the measured pupil diameter at any time during the procedure because the end of cortical clean-up was not identified by the masked reader when the images were read.

Regarding the endpoint of the proportion of subjects who had < 6 mm pupil diameter, the following is the preliminary response from FDA before the EOP2 meeting and discussion during the EOP2 meeting according to the meeting minutes:

> *"**Question 9: Does the Division agree with the proposed process for measuring pupil size in the proposed Phase 3 studies?***
>
> ***FDA Response**: It is recommended that there be a demonstration of a statistically significant difference between the test treatment group and the vehicle group in the number of patients who have a pupillary diameter of at least 6 millimeters while being stimulated with a pre-specified light syimulus (i.e., specific light level on the operating microscope).*
>
> ***Meeting Discussion**: The Division defines 6 mm as a clinically relevant pupil diameter based on an earlier study conducted in India demonstrating an increase in the number of surgical complications in eyes dilated less than 6 mm. The proposed endpoint needs to be clinically relevant. Consideration should be given to the critical times that the pupil must be well dilated during intraocular lens replacement."*

In addition, regarding the proposed indication of prevention of intraoperative miosis, the following is the FDA's preliminary response for the EOP2 meeting and there was no further discussion during the EOP2 meeting:

"Question 2: Omeros will seek agreement on the proposed indication of prevention of intraoperative miosis and reduction of postoperative pain [redacted]

FDA Response*: Final determination of the labeling requires review of a New Drug application; we will need to review the final protocol and statistical analysis plan. It is recommended that consideration be given to measuring the time to pain relief as opposed to reduction of postoperative pain."*

According to the above record for the EOP2 meeting, the FDA did recommend proportion of subjects who had a pupillary diameter of at least 6 millimeters at critical times that the pupil must be well dilated during intraocular lens replacement as a potential endpoint for measuring efficacy in pupil diameter. However, FDA did not specify that this endpoint as a measure for prevention of miosis. Whether [redacted] prevention of miosis would be considered as [redacted] indications is clinical judgment, this review will focus on the statistical aspects of the proportion of subjects who had a pupillary diameter of at least 6 millimeters.

Except for Study OMS302-ILR-004, the proportions evaluated by the applicant were defined as either supportive or tested post hoc:

- For Study C09-001, the proportion of subjects who had < 6 mm pupil diameter at any time during the procedure was analyzed post hoc.

- For Study OMS302-ILR-003, analysis of the proportion of subjects who had < 6 mm pupil diameter at the end of cortical cleanup was specified as supportive analyses for change in pupil diameter. The SAP did not specify any multiplicity adjustment for controlling type I error rate of testing treatment difference of this proportion. The proportion of subjects who had < 6 mm pupil diameter at any time during the procedure was not specified as an endpoint.

- For Study OMS-302-ILR-004, both proportion of subjects who had ≥ 6 mm pupil diameter at cortical clean-up and proportion of subjects who had < 6 mm pupil diameter anytime during surgery were specified as the first two secondary efficacy endpoints. A step-down approach was specified in the SAP for testing these two secondary endpoints – if both primary efficacy endpoints reach the 0.05 level of significance, the two secondary endpoints would be tested sequentially at the 0.05 level:
    - Pupil diameter ≥ 6mm at cortical clean-up
    - Pupil diameter < 6mm anytime during surgery

In summary, for proportion of subjects who had ≥ 6 mm pupil diameter at cortical clean-up and proportion of subjects who had < 6 mm pupil diameter anytime during surgery, only Study OMS302-ILR-004 pre-specified these two endpoints as formal secondary endpoints and corresponding method for addressing multiplicity related with testing these two endpoints. Study OMS302-ILR-003 specified the proportion of subjects who had < 6 mm pupil diameter at the

end of cortical cleanup as supportive analysis without multiplicity adjustment. The proportion of subjects who had < 6 mm pupil diameter at any time was analyzed retrospectively for both studies C09-001 and OMS302-ILR-003. All these proportions were compared using chi-square test. It is also noted that none of these three studies were powered to test statistical significance on these endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study C09-001

Two hundred and twenty-three subjects were randomized into the study; one of the 223 subjects cancelled the scheduled CELR surgery before receiving any study treatment. All 222 treated subjects were included in the safety population.

For the primary efficacy endpoint of pupil diameter, 203 subjects (among the 222 treated subjects) were included in its primary analysis set – mydriasis analysis set (MAS); 19 (8.5%) subjects were excluded from the MAS because their video recordings during the CELR were not readable (3/56 [5.4%] in vehicle group, 7/56 [12.5%] in PE group, 3/52 [5.5%] in KE group, and 6/55 [10.9%] in OMS302 group). The applicant-reported reasons that subjects did not have interpretable videos included: ruler not captured so pupil diameter could not be measured, pupil was mechanically opened, the image was too dark or blurry to be read, DVD recording began after surgery start or finished prior to the end of surgery, the surgery was not recorded, and the DVD was corrupted and could not be read postoperatively. It appears that exclusion of these subjects is not treatment-related and hence unlikely to introduce any bias to the study. Unlike studies OMS302-ILR-003 and OMS302-ILR-004, the applicant did not perform sensitivity analysis using multiple imputation method to impute missing data from these excluded subjects. The statistical reviewer conducted additional sensitivity analysis for mean AUC of change-from-baseline in pupil diameter using the applicant-proposed multiple imputation method as detailed in Section 3.2.2.2.

For the primary efficacy endpoint of ocular pain VAS, all 222 treated subjects were included in its primary analysis set – pain analysis set (PAS). For both MAS and PAS, subjects were analyzed according to the treatment they were randomized to.

Table 5: Study C09-001 Analysis Population

	Vehicle (N=56) n (%)	**PE (N=56) n (%)**	**KE (N=55) n (%)**	**OMS302 (N=55 [a]) n (%)**	**Total (N=222 [a]) n (%)**
Safety Population	56 (100.0%)	56 (100.0%)	55 (100.0%)	55 (100.0%)	222 (100.0%)
MAS	53 (94.6%)	49 (87.5%)	52 (94.5%)	49 (89.1%)	203 (91.4%)
Reason for exclusion from MAS population					
No pupil diameter data at baseline or post-baseline	3 (5.4%)	7 (12.5%)	3 (5.5%)	6 (10.9%)	19 (8.6%)
PAS	56 (100.0%)	56 (100.0%)	55 (100.0%)	55 (100.0%) [a]	222 (100.0%)

[a] One subject cancelled the scheduled CELR surgery before receiving any study treatment.
Source: Table 23 of Study C09-001 report.

As presented in the following table, there were no noted imbalances among the treatment groups in demographics or baseline characteristics listed.

Table 6: Study C09-001 Demographic and Baseline Characteristics by Treatment Groups

Characteristics	Vehicle (N=57)	PE (N=54)	KE (N=55)	OMS302 (N=56)	Total (N=222)
	n (%)	n (%)	n (%)	n (%)	n (%)
Gender					
Male	24 (42.1%)	20 (37.0%)	22 (40.0%)	19 (33.9%)	85 (38.3%)
Female	33 (57.9%)	34 (63.0%)	33 (60.0%)	37 (66.1%)	137 (61.7%)
Age					
Mean (Std)	68.5 (9.6)	67.6 (10.6)	66.8 (8.6)	66.4 (11.2)	67.3 (10.0)
Median	69	68	67	68	68
Min, Max	44, 89	43, 92	51, 86	23, 86	23, 92
Race					
White/Caucasian	46 (80.7%)	42 (77.8%)	46 (83.6%)	45 (80.4%)	179 (80.6%)
Black/African American	4 (7.0%)	6 (11.1%)	1 (1.8%)	6 (10.7%)	17 (7.7%)
American Indian/Alaska Native	0	1 (1.9%)	0	0	0
Asian	6 (10.5%)	5 (9.3%)	7 (12.7%)	5 (8.9%)	23 (10.4%)
Native Hawaiian/Other Pacific Island	1 (1.8%)	0	0	0	1 (0.5%)
Other	0	0	1 (1.8%)	0	1 (0.5%)
Hispanic Origin					
Yes	6 (10.5%)	4 (7.4%)	3 (5.5%)	3 (5.4%)	16 (7.2%)
No	51 (89.5%)	50 (92.6%)	52 (94.5%)	53 (94.6%)	206 (92.8%)
Color/Opalescence					
N0	1 (1.8%)	1 (1.9%)	0	1 (1.8%)	3 (1.4%)
Ni	14 (24.6%)	12 (22.2%)	13 (23.6%)	12 (21.4%)	51 (23.0%)
Nii	22 (38.6%)	26 (48.1%)	29 (52.7%)	24 (42.9%)	101 (45.5%)
Niii	20 (35.1%)	15 (27.8%)	13 (23.6%)	19 (33.9%)	67 (30.2%)
LOCS II Stratification					
Group 1	15 (26.3%)	13 (24.1%)	13 (23.6%)	13 (23.2%)	54 (24.3%)
Group 2	42 (73.7%)	41 (75.9%)	42 (76.4%)	43 (76.8%)	168 (75.7%)
Cortical					
Ci	12 (21.1%)	13 (24.1%)	14 (25.5%)	10 (17.9%)	49 (22.1%)
Cii	8 (14.0%)	17 (31.5%)	17 (30.9%)	17 (30.4%)	59 (26.6%)
Ciii	5 (8.8%)	3 (5.6%)	4 (7.3%)	5 (8.9%)	17 (7.7%)
Civ	2 (3.5%)	2 (3.7%)	3 (5.5%)	2 (3.6%)	9 (4.1%)
Ctr	30 (52.6%)	18 (33.3%)	17 (30.9%)	21 (37.5%)	86 (38.7%)
Unknown	0	1 (1.9%)	0	1 (1.8%)	2 (0.9%)
Posterior subcapsular					
P0	31 (54.4%)	31 (57.4%)	32 (58.2%)	32 (57.1%)	126 (56.8%)
Pi	9 (15.8%)	10 (18.5%)	9 (16.4%)	9 (16.1%)	37 (16.7%)
Pii	6 (10.5%)	6 (11.1%)	10 (18.2%)	7 (12.5%)	29 (13.1%)
Piii	11 (19.3%)	7 (13.0%)	4 (7.3%)	8 (14.3%)	30 (13.5%)

Characteristics	Vehicle (N=57)	PE (N=54)	KE (N=55)	OMS302 (N=56)	Total (N=222)
	n (%)	n (%)	n (%)	n (%)	n (%)

Source: Table 5 of Study C09-001 report.

3.2.3.2 Study OMS302-ILR-003

Four hundred and five subjects were randomized at 17 study sites for the study; three of the 405 subjects did not undergo the scheduled surgery and therefore did not receive any study treatment. Among the 402 subject who received study treatments, one subjects discontinued from the study before receiving any follow-up assessments; and two subjects in the OMS302 treatment group discontinued from the study before completing all the follow-up assessments – one subject withdrew consent on Study Day 3 and another subject died due to a workplace accident on Study Day 13. The following table summarizes subjects' disposition for all randomized subjects.

Table 7: Study OMS302-ILR-003 Subjects' Disposition

	Placebo (N=203) n (%)	OMS302 (N=202) n (%)	Total (N=405) n (%)
Number of Subjects Randomized	203 (100.0%)	202 (100.0%)	405 (100.0%)
Number of Subjects Receiving Study Treatment	201 (99.0%)	201 (99.5%)	402 (99.3%)
Number of Subjects Receiving CELR Surgery	197 (97.0%)	200 (99.0%)	397 (98.0%)
Number of Subjects Receiving RLE Surgery	4 (2.0%)	1 (0.5%)	5 (1.2%)
Number of Subjects Completed Study	201 (99.0%)	199 (98.5%)	400 (98.8%)
Reason for Study Discontinuation			
Death	0	1 (0.5%)	1 (0.2%)
Withdrawal by Subject	0	1 (0.5%)	1 (0.2%)

Source: Tables 15 and 16 of Study OMS302-ILR-003 report.

Among the 405 randomized subjects, all 402 treated subjects were included in the safety population. Three-hundred and sixty-four subjects (among the 402 treated subjects) were included in the pupil diameter (the primary efficacy endpoint) analyses; 38 (9.5%) subjects were excluded because their video recordings during the CELR were not readable because according to the applicant:

- Surgical videos not interpretable (e.g., no ruler images, corrupted video files, or recording only captured a portion of the procedure): 17 subjects in the OMS302 treatment group and 21 subjects in the placebo treatment group.

The following table lists the details of the reason for excluding these 38 subjects from the pupil diameter analyses due to un-interpretable video. It appears that exclusion of these subjects from the pupil diameter (the primary efficacy endpoint) analyses is not treatment-related and hence unlikely to introduce any bias to the study.

Table 8: Listing of Subjects Who Were Excluded from the Pupil Diameter Analyses (Study OMS302-ILR-003)

Site	Subject	Arm	Description	Details
101	005	OMS302	Video recording incomplete. Video unrecoverable.	
	009	OMS302	Video recording incomplete. Video unrecoverable.	
	010	PLACEBO	Video recording incomplete	Video shows only partial of the eye during surgery. Unable to clearly obtain.
	011	PLACEBO	Video recording does not capture ruler	
179	005	OMS302	Video recording does not capture ruler	Video recording does not capture ruler placement
	008	OMS302	Video recording incomplete. Video unrecoverable.	
185	008	PLACEBO	Video recording incomplete or missing	Video Recording incomplete-DVD begins after procedure begins. The PI to ensure that all study procedures are done according to the protocol.
190	004	PLACEBO	Video does not capture rulers, neither horizontal or vertical.	
	020	OMS302	Video does not capture ruler. Unable to obtain capturable image of Vertical ruler.	
	058	OMS302	Video not available	
193	004	PLACEBO	Video recording incomplete or missing	Surgery not recorded or DVD recording begins after surgery begins or ends prior to end of procedure. DVD is blank. Site reminded of DVD collection requirements.
	012	PLACEBO	Video recording not appropriately labeled	The video contains three sets of subject identification: Subject number 193010 (at 00:04), 193011 (00:28), and 193012 (00:36)
	014	PLACEBO	Video recording not appropriately labeled	The video contains three sets of subject identification: Subject number 193010 (at 00:04), 193011 (00:28), and 193014 (00:37)
	015	OMS302	Video recording not appropriately labeled	The video contains three sets of subject identification: Subject number 193010 (at 00:04), 193011 (00:28), and 193015 (00:35)
195	001	PLACEBO	Video recording incomplete	Unable to open/read DVD
	002	OMS302	Video recording incomplete	Unable to open/read DVD
	003	OMS302	Video recording incomplete	Unable to open/read DVD
	005	OMS302	Video recording incomplete	Unable to open/read DVD
	013	PLACEBO	Video recording incomplete	Video stops after ruler placement
	014	PLACEBO	Video recording incomplete	Unable to open/read DVD
	015	PLACEBO	Video recording incomplete	Unable to open/read DVD
	026	PLACEBO	Video recording incomplete	Video unrecoverable
	039	PLACEBO	Video recording incomplete	Video unrecoverable
	049	PLACEBO	Video recording incomplete	Video unrecoverable
	053	PLACEBO	Video recording incomplete	Video Freezes during surgery
	058	OMS302	Video recording incomplete	Surgery not recorded on DVD
198	007	OMS302	Video recording incomplete	Video recording does not capture either Vertical or Horizontal ruler. Video can not be used.
202	001	OMS302	Video recording missing	Subject 202001 had an error with the recording of the DVD; it was ejected from their machine and a recording was not made of the surgery. Site will use their own DVDs since the ones provided by the sponsor were incompatible with the site recorder
206	002	OMS302	Video recording incomplete	Unable to open/read DVD
	003	OMS302	Video recording incomplete	Unable to open/read DVD
	004	PLACEBO	Video recording incomplete	Unable to open/read DVD

	005	OMS302	Video recording incomplete	Unable to open/read DVD
	006	OMS302	Video recording incomplete	Unable to open/read DVD
	008	PLACEBO	Video recording incomplete	Unable to open/read DVD
	009	OMS302	Video recording incomplete	Unable to open/read DVD
	010	PLACEBO	Video recording incomplete	The recording stops prior to incision and then start recording after incision. Time of incision is not recorded on video.
	042	PLACEBO	Video not available	
	049	PLACEBO	Video not available	

Source: Applicant's protocol deviation listing for Study OMS302-ILR-003

For the secondary efficacy endpoint of ocular pain VAS, all 402 treated subjects were included in its primary analysis set. For both endpoints, subjects were analyzed according to the treatment they were randomized to.

Table 9: Study OMS302-ILR-003 Analysis Population

	Placebo (N=201) n (%)	**OMS302 (N=201) n (%)**	**Total (N=402) n (%)**
Safety Population	201 (100.0%)	201 (100.0%)	402 (99.3%)
Subjects included in the pupil diameter analyses	180 (88.7%)	184 (91.5%)	364 (90.5%)
Reason for exclusion from pupil diameter analyses			
No pupil diameter data at baseline or post-baseline	21 (10.3%)	17 (8.5%)	38 (9.5%)
Subjects included in the ocular pain VAS analyses	201 (100.0%)	201 (100.0%)	402 (100.0%)

Source: Statistical reviewer's summary.

As presented in the following table, there were no noted differences in demographics or baseline characteristics between the treatment groups.

Table 10: Study OMS302-ILR-003 Demographic and Baseline Characteristics

Characteristics	**Placebo (N=201)**	**OMS302 (N=201)**	**Total (N=402)**
	n (%)	**n (%)**	**n (%)**
Gender			
Male	90 (44.8%)	82 (40.8%)	172 (42.8%)
Female	111 (55.2%)	119 (59.2%)	230 (57.2%)
Age			
Mean (Std)	68.5 (9.9)	68.2 (9.6)	68.4 (9.7)
Median	69	69	69
Min, Max	39, 89	31, 88	31, 89
Race			
White/Caucasian	155 (77.1%)	165 (82.1%)	320 (79.6%)
Black/African American	26 (12.9%)	22 (10.9%)	48 (11.9%)
American Indian/Alaska Native	1 (0.5%)	1 (0.5%)	2 (0.5%)
Asian	19 (9.5%)	12 (6.0%)	31 (7.7%)
Other	0	1 (0.5%)	1 (0.2%)
Hispanic Origin			
Yes	18 (9.0%)	30 (14.9%)	48 (11.9%)
No	183 (91.0%)	171 (85.1%)	354 (88.1%)

Characteristics	Placebo (N=201)	OMS302 (N=201)	Total (N=402)
	n (%)	n (%)	n (%)
Color/Opalescence			
N0	7 (3.5%)	8 (4.0%)	15 (3.7%)
Ni	34 (16.9%)	38 (18.9%)	72 (17.9%)
Nii	98 (48.8%)	100 (49.8%)	198 (49.3%)
Niii	62 (30.8%)	55 (27.4%)	117 (29.1%)
LOCS II Stratification			
Group 1	41 (20.4%)	46 (2.9%)	87 (21.6%)
Group 2	160 (79.6%)	155 (77.1%)	315 (78.4%)
Cortical			
Ci	41 (20.4%)	40 (19.9%)	81 (20.1%)
Cii	61 (30.3%)	67 (33.3%)	128 (31.8%)
Ciii	15 (7.5%)	13 (6.5%)	28 (7.0%)
Civ	4 (2.0%)	1 (0.5%)	5 (1.2%)
Ctr	80 (39.8%)	80 (39.8%)	160 (39.8%)
Posterior subcapsular			
P0	131 (65.2%)	124 (61.7%)	255 (63.4%)
Pi	29 (14.4%)	32 (15.9%)	61 (15.2%)
Pii	27 (13.4%)	35 (17.4%)	62 (15.4%)
Piii	13 (6.5%)	10 (5.0%)	23 (5.7%)
Unknown	1 (0.5%)	0	1 (0.2%)

Source: Table 4 of Study OMS302-ILR-003 report.

3.2.3.3 Study OMS302-ILR-004

Four hundred and sixteen subjects were randomized at 15 study sites for the study; ten of the 416 subjects did not receive any study treatment. Among the 406 subject who received study treatments, one subjects discontinued from the study before receiving any follow-up assessments; and five subjects discontinued from the study before completing all the follow-up assessments. The following table summarizes subjects' disposition for all randomized subjects.

Table 11: Study OMS302-ILR-004 Subjects' Disposition

	Placebo (N=209) n (%)	OMS302 (N=207) n (%)	Total (N=416) n (%)
Number of Subjects Randomized	209 (100.0%)	207 (100.0%)	416 (100.0%)
Number of Subjects Receiving Study Treatment	204 (97.6%)	202 (97.6%)	406 (97.6%)
Number of Subjects Receiving CELR Surgery	203 (97.1%)	201 (97.1%)	404 (97.1%)
Number of Subjects Receiving RLE Surgery	1 (0.5%)	1 (0.5%)	2 (0.5%)
Number of Subjects Completed Study	201 (96.2%)	200 (96.6%)	401 (96.4%)
Reason for Study Discontinuation			

Investigator Decision	1 (0.5%)	0	1 (0.2%)
Lost to Follow-Up	1 (0.5%)	2 (1.0%)	3 (0.7%)
Other	1 (0.5%)	0	1 (0.2%)

Source: Tables 15 and 16 of Study OMS302-ILR-004 report.

Among the 416 randomized subjects, all 406 treated subjects were included in the safety population. Three-hundred and ninety-five subjects (among the 406 treated subjects) were included in the pupil diameter analyses; 11 (2.6%) subjects were excluded because according to the applicant:

- Video recordings that were incomplete, missing, or did not capture the ruler for 10 subjects (six in the OMS302 treatment group and four in the placebo treatment group). One additional subject (Subject 195060) was not included in the analysis of intraoperative pupil diameter. The video of this subject was read three times according to the procedure outlined in the central reading charter and the readings could not be reproduced within allowable limits due to glare from the cornea during the procedure. Therefore, this subject was excluded from the pupil diameter analyses only.

The following table lists the details of the reason for excluding those 10 subjects from the pupil diameter analyses. It appears that exclusion of these subjects from the pupil diameter (the primary efficacy endpoint) analyses is not treatment-related and hence unlikely to introduce any bias to the study.

Table 12: Listing of Subjects Who Were Excluded from the Pupil Diameter Analyses (Study OMS302-ILR-004)

Site	Subject	Arm	Description	Details
185	018	PLACEBO	Video recording does not capture ruler	DVD image or ruler not correctly capture on video
190	057	OMS302	Video recording incomplete or missing	Video recording missing. Surgery not recorded, DVD recording begins after surgery begins or ends prior to end of procedure, or DVD not readable
	081	OMS302	Video recording does not capture ruler	Video recording does not capture ruler or initial incision.
198	017	OMS302	Video recording incomplete or missing	Video recording incomplete. Unable to open DVD.
	038	OMS302	Video recording incomplete or missing	Video recording incomplete. Unable to open DVD.
200	001	OMS302	Video recording does not capture ruler	Video recording does not capture rulers.
	017	PLACEBO	Video recording does not correctly capture ruler per protocol	Video recording does not capture vertical or horizontal rulers.
	022	OMS302	Video recording does not correctly capture ruler per protocol	Video recording does not capture vertical or horizontal rulers.
	026	PLACEBO	Video recording does not capture ruler	Video recording does not capture initial incision.
	028	PLACEBO	Video recording does not correctly capture ruler	DVD image or ruler not correctly capture on video

Source: applicant's protocol deviation listing for Study OMS302-ILR-004

For the ocular pain VAS analyses, 404 subjects were included in its primary analysis set; two subjects (both in the placebo group) were excluded because they did not provide any VAS data on the day of surgery. For both endpoints, subjects were analyzed according to the treatment they were randomized to.

Table 13: Study OMS302-ILR-004 Analysis Population

	Placebo (N=204) n (%)	OMS302 (N=202) n (%)	Total (N=406) n (%)
Safety Population	204 (100.0%)	202 (100.0%)	406 (100.0%)
Subjects included in the pupil diameter analyses	200 (98.1%)	195 (96.6%)	395 (97.4%)
Reason for exclusion from pupil diameter analyses			
No pupil diameter data at baseline or post-baseline	4 (1.9%)	7 (3.4%)	11 (2.6%)
Subjects included in the ocular pain VAS analyses	202 (99.1%)	202 (100.0%)	404 (99.5%)
Reason for exclusion from pain VAS analyses			
No pupil diameter data at baseline or post-baseline	2 (0.9%)	0	2 (0.5%)

Source: Statistical reviewer's summary.

As presented in the following table, there were no noted differences in demographics or baseline characteristics among the treatment groups.

Table 14: Study OMS302-ILR-004 Demographic and Baseline Characteristics

Characteristics	Placebo (N=204)	OMS302 (N=202)	Total (N=406)
	n (%)	n (%)	n (%)
Gender			
Male	78 (38.2%)	85 (42.1%)	163 (40.1%)
Female	126 (61.8%)	117 (57.9%)	243 (59.9%)
Age			
Mean (Std)	67.5 (10.6)	69.2 (9.2)	68.3 (10.0)
Median	69.0	70.0	69.0
Min, Max	26, 90	39, 87	26, 90
Race			
White/Caucasian	158 (77.5%)	165 (81.7%)	323 (79.6%)
Black/African American	28 (13.7%)	18 (8.9%)	46 (11.3%)
American Indian/Alaska Native	0	1 (0.5%)	1 (0.2%)
Asian	18 (8.8%)	16 (7.9%)	34 (8.4%)
American Indian/Alaska Native	0	1 (0.5%)	1 (0.2%)
Other	0	1 (0.5%)	1 (0.2%)
Hispanic Origin			
Yes	21 (10.3%)	30 (14.9%)	51 (12.6%)
No	183 (89.7%)	172 (85.1%)	355 (87.4%)
Color/Opalescence			
N0	10 (4.9%)	7 (3.5%)	17 (4.2%)
Ni	23 (11.3%)	26 (12.9%)	49 (12.1%)
Nii	93 (45.6%)	104 (51.5%)	197 (48.5%)
Niii	78 (38.2%)	65 (32.2%)	143 (35.2%)
LOCS II Stratification			
Group 1	33 (16.2%)	33 (16.3%)	66 (16.3%)

Characteristics	Placebo (N=204)	OMS302 (N=202)	Total (N=406)
	n (%)	n (%)	n (%)
Group 2	171 (83.8%)	169 (83.7%)	340 (83.7%)
Cortical			
Ci	36 (17.6%)	40 (19.8%)	76 (18.7%)
Cii	40 (19.6%)	50 (24.8%)	90 (22.2%)
Ciii	21 (10.3%)	13 (6.4%)	34 (8.4%)
Civ	6 (2.9%)	3 (1.5%)	9 (2.2%)
Ctr	101 (49.5%)	96 (47.5%)	197 (48.5%)
Posterior subcapsular			
P0	137 (67.2%)	127 (62.9%)	264 (65.0%)
Pi	26 (12.7%)	32 (15.8%)	58 (14.3%)
Pii	20 (9.8%)	25 (12.4%)	45 (11.1%)
Piii	21 (10.3%)	17 (8.4%)	38 (9.4%)
Unknown	0	1 (0.5%)	1 (0.2%)

Source: Table 5 of Study OMS302-ILR-004 report.

3.2.4 Results and Conclusions

3.2.4.1 Pupil Diameter

3.2.4.1.1 Study C09-001

During the CELR surgery, the surgical procedure was video recorded. Pupil diameter captured based on the video recording of the surgery was measured by a masked central reader at each minute throughout the surgery. Among the 222 subjects who received any study treatment, 19 (8.5%) subjects were excluded from the pupil diameter analyses because their video recordings during the CELR were not readable due to technical issues (3/56 [5.4%] in vehicle group, 7/56 [12.5%] in PE group, 3/52 [5.5%] in KE group, and 6/56 [10.9%] in OMS302 group).

Most subjects had completed the surgical procedure by fifteen minutes; at the 20-minute time point, only 2 placebo-treated subjects, 2 KE-treated subjects, 2 PE-treated subjects, and 3 OMS302-treated subjects were still undergoing surgery.

The applicant listed mean change from baseline of pupil diameter at each time point for each treatment but not the treatment difference at each time point. Therefore, the statistical reviewer calculated treatment differences and the corresponding 95% CIs in mean change from baseline of pupil diameter between OMS302 and placebo at each time point from the beginning of the surgery till the 20-minute time point for this study.

For the mean change from baseline of pupil diameter, treatment difference between OMS302 and vehicle increased over time during the surgery from 0.08 mm at 1 minute to 1.37 at 15 minutes; the lower bound of the 95% CI for this difference was above zero at majority of the time points except at 1, 14, 16, 19 and 20 minutes. The treatment difference between OMS302 and KE also increased over time during the surgery from 0.13 mm at 1 minute to 1.39 at 15 minutes; the

lower bound of the 95% CI for this difference was above zero at majority of the time points except at 1, 2, 3, 16, and 19 minutes. The treatment difference between OMS302 and PE was similar throughout the surgery ranging from -0.14 mm to 0.82 mm.

Table 15: Study C09-001 Summary for Mean Change from Baseline of Pupil Diameter (mm) at Each Time Point during CELR Surgery (Subjects with Readable Video Recording)

Time	Vehicle		PE		KE		OMS302		OMS302 vs. Vehicle	OMS302 vs. PE	OMS302 vs. KE
	n	Mean	n	Mean	n	Mean	n	Mean	Difference (95% CI)*	Difference (95% CI)*	Difference (95% CI)*
1 minute	53	0.23	48	0.30	52	0.18	48	0.30	0.08 (-0.13, 0.29)	0.00 (-0.22, 0.24)	0.13 (-0.09, 0.34)
2 minute	53	0.00	49	0.32	52	0.08	49	0.26	0.26 (0.05, 0.47)	-0.06 (-0.31, 0.18)	0.18 (-0.04, 0.40)
3 minute	53	-0.08	49	0.36	52	0.01	49	0.25	0.33 (0.09, 0.57)	-0.12 (-0.40, 0.16)	0.24 (-0.03, 0.51)
4 minute	52	-0.25	49	0.41	52	-0.19	49	0.40	0.65 (0.35, 0.94)	-0.01 (-0.32, 0.31)	0.60 (0.32, 0.88)
5 minute	52	-0.48	49	0.18	51	-0.22	48	0.30	0.78 (0.50, 1.06)	0.12 (-0.13, 0.36)	0.52 (0.24, 0.79)
6 minute	51	-0.65	45	0.09	50	-0.45	48	0.24	0.90 (0.54, 1.25)	0.16 (-0.13, 0.44)	0.69 (0.37 1.01)
7 minute	45	-0.90	37	-0.03	44	-0.85	43	0.05	0.95 (0.56, 1.34)	0.08 (-0.22, 0.37)	0.90 (0.51, 1.29)
8 minute	34	-1.17	28	-0.24	40	-0.95	36	-0.16	1.02 (0.52, 1.50)	0.09 (-0.29, 0.46)	0.79 (0.39 1.20)
9 minute	27	-1.09	25	-0.14	32	-1.27	32	-0.06	1.02 (0.47, 1.58)	0.08 (-0.26, 0.41)	1.21 (0.66, 1.76)
10 minute	26	-1.35	19	-0.25	25	-1.07	28	-0.25	1.10 (0.58, 1.62)	0.00 (-0.39, 0.40)	0.82 (0.27, 1.38)
11 minute	24	-1.41	18	-0.24	22	-0.91	27	-0.30	1.11 (0.64, 1.58)	-0.06 (-0.43, 0.31)	0.61 (0.11, 1.11)
12 minute	22	-1.61	17	-0.58	20	-1.00	23	-0.05	1.56 (0.91, 2.22)	0.53 (0.00, 1.05)	0.96 (0.45, 1.47)
13 minute	14	-1.55	13	-0.39	16	-1.19	17	-0.30	1.25 (0.44, 2.06)	0.09 (-0.53, 0.71)	0.89 (0.40, 1.38)
14 minute	10	-1.25	8	-0.27	13	-1.57	10	-0.41	0.84 (-0.30, 1.97)	-0.14 (-1.25, 0.98)	1.16 (0.27, 2.06)
15 minute	8	-1.45	7	-0.36	8	-1.48	9	-0.08	1.37 (0.33, 2.41)	0.27 (-0.42, 0.96)	1.39 (0.68, 2.10)
16 minute	7	-1.77	6	-0.24	7	-1.80	6	-0.33	1.44 (-0.37, 3.24)	-0.10 (-1.73, 1.54)	1.47 (-0.03, 2.98)
17 minute	7	-2.01	5	-0.48	6	-1.90	5	0.34	2.35 (1.08, 3.63)	0.82 (-0.33, 1.98)	2.25 (1.49, 3.00)
18 minute	6	-1.97	3	0.18	5	-1.95	5	0.33	2.30 (0.87, 3.72)	0.15 (-0.86, 1.17)	2.29 (1.13, 3.45)
19 minute	3	-2.20	3	0.05	4	-1.96	5	-0.23	1.98 (-0.88, 4.84)	-0.28 (-2.54, 1.99)	1.73 (-0.58, 4.04)
20 minute	2	-2.60	2	0.57	2	-2.53	3	0.68	3.28 (-1.32, 7.88)	0.12 (-2.16, 2.39)	3.21 (0.24, 6.18)

* 95% CI based on two-sample t-test
Source: Statistical reviewer's analysis.

In the applicant-proposed primary analysis method – repeated measures ANOVA to test for differences in change from baseline in pupil diameter, OMS302 demonstrated superiority to both vehicle and KE with a p-value < 0.0001 (Table 16).

Table 16: Study C09-001 Repeated Measures Analysis of Change from Baseline in Pupil Diameter (mm) during CELR Surgery (Subjects with Readable Video Recording)

	Vehicle	KE	OMS302
Least Square Mean (SE)	-2.03 (0.28)	-1.9 (0.25)	-1.2 (0.26)
Least Square Mean Difference (SE) (OMS302 – Vehicle or KE)	0.9 (0.1)	0.7 (0.1)	
95% Confidence Interval	0.6, 1.1	0.5, 0.9	
p-value	<0.0001	<0.0001	

Repeated measures model includes treatment (OMS302, KE, and vehicle), time-point, and LOCS II grades as covariates.
Source: Table 6 of Study C09-001 Report.

In addition, mean area-under-the-curve (AUC) analysis (as part of sensitivity analyses) also confirmed the primary efficacy analyses findings of OMS302 comparing to both vehicle and KE.

Table 17: Study C09-001 Mean AUC Analysis of Change from Baseline in Pupil Diameter during CELR Surgery (Subjects with Readable Video Recording)

	Vehicle (N=53)	KE (N=52)	OMS302 (N=49)
Mean AUC (SD)	-0.6 (0.7)	-0.4 (0.5)	0.1 (0.4)
Difference in Mean AUC (OMS302 – Vehicle or KE)			
Least square mean difference (SE)	0.7 (0.1)	0.6 (0.1)	
95% confidence interval	0.5, 0.9	0.4, 0.8	
p-value	<0.0001	<0.0001	

Treatment differences (OMS302 - vehicle) and (OMS302 - KE) are based on ANOVA model with covariates treatment (OMS302, KE and vehicle) and stratification factor LOCS II grade.
Source: Table 40 of Study C09-001 Report.

Sensitivity analysis using multiple imputation to impute mean AUC values for those excluded subjects due to video recording error was conducted by the statistical reviewer; the analysis support the results of the applicant's mean AUC analysis and is consistent with the primary analysis results.

3.2.4.1.2 Studies OMS302-ILR-003 and OMS302-ILR-004

A total of 402 subjects were randomized and treated in Study OMS302-ILR-003, 38 (9.5%) subjects were excluded from the pupil diameter analyses (17/201 [8.5%] subjects in the OMS302 group and 21/201 [10.4%] subjects in the placebo group). In Study OMS302-ILR-004, much less subjects (11 [2.7%]; 7/202 [3.5%] in the OMS302 group and 4/204 [2.0%] subjects in the placebo group) were excluded from the pupil diameter analyses. All subjects in both studies were excluded because of technical issues related with video recording and not treatment-related.

Most subjects had completed the surgical procedure by fifteen minutes. For Study OMS302-ILR-003, at the 22-minute time point only six (3.3%) placebo-treated subjects and six (3.2%) OMS302-treated subjects were still undergoing surgery. And for Study 004, at the 22-minute time point, only eight (4.0%) placebo-treated subjects and five (2.6%) OMS302-treated subjects were still undergoing surgery.

The applicant listed mean change from baseline of pupil diameter at each time point for each treatment but not the treatment difference at each time point. Therefore, the statistical reviewer calculated treatment differences and the corresponding 95% CIs in mean change from baseline of pupil diameter between OMS302 and placebo at each time point from the beginning of the surgery till the 20-minute time point for both studies.

As presented in Table 18, treatment difference between OMS302 and placebo increased over time during the surgery; the lower bound of the 95% CI for this difference was above zero at majority of the time points except at 1 minute in Study 003 and at 1, and 20 minutes in Study 004.

Table 18: Studies OMS302-ILR-003 and OMS302-ILR-004 Treatment Difference in Change from Baseline of Mean Pupil Diameter (mm) at Each Time Point during CELR Surgery (Subjects with Readable Video Recordings)

	Study 003					Study 004				
	Placebo		OMS302		OMS302 vs. Placebo	Placebo		OMS302		OMS302 vs. Placebo
Time	n	Mean	n	Mean	Difference (95% CI)*	n	Mean	n	Mean	Difference (95% CI)*
1 minute	180	0.24	183	0.17	-0.07 (-0.17, 0.04)	200	0.19	194	0.13	-0.06 (-0.17, 0.05)
2 minute	179	0.09	184	0.25	0.16 (0.03, 0.28)	200	0.08	195	0.26	0.18 (0.06, 0.30)
3 minute	180	-0.04	184	0.26	0.30 (0.16, 0.44)	200	-0.03	195	0.32	0.35 (0.22, 0.48)
4 minute	180	-0.23	183	0.16	0.40 (0.25, 0.55)	200	-0.21	195	0.17	0.39 (0.26, 0.52)
5 minute	178	-0.42	184	0.10	0.52 (0.36, 0.68)	199	-0.46	190	0.13	0.59 (0.46, 0.73)
6 minute	169	-0.60	159	0.09	0.69 (0.52, 0.86)	182	-0.66	170	0.05	0.72 (0.56, 0.88)
7 minute	149	-0.78	130	0.06	0.84 (0.62, 1.06)	161	-0.84	140	0.00	0.84 (0.64, 1.05)
8 minute	123	-1.00	111	-0.15	0.85 (0.61, 1.08)	136	-1.03	114	-0.02	1.01 (0.80, 1.23)
9 minute	104	-1.18	94	-0.11	1.06 (0.75, 1.37)	101	-1.12	90	-0.07	1.05 (0.78, 1.33)
10 minute	87	-1.37	81	-0.10	1.27 (0.91, 1.62)	85	-1.21	75	-0.16	1.05 (0.73, 1.37)
11 minute	67	-1.13	66	-0.17	0.96 (0.59, 1.34)	67	-1.34	62	-0.09	1.24 (0.92, 1.57)
12 minute	55	-1.11	57	-0.17	0.94 (0.59, 1.28)	53	-1.39	53	-0.15	1.24 (0.82, 1.65)
13 minute	53	-1.22	50	-0.21	1.01 (0.63, 1.38)	47	-1.35	42	0.00	1.35 (0.90, 1.81)
14 minute	47	-1.45	43	-0.28	1.16 (0.74, 1.58)	39	-1.61	35	-0.22	1.39 (0.87, 1.92)
15 minute	36	-1.61	37	-0.21	1.40 (0.91, 1.89)	31	-1.79	27	-0.28	1.50 (0.88, 2.13)
16 minute	28	-1.68	27	-0.36	1.33 (0.68, 1.98)	23	-1.84	23	-0.38	1.46 (0.68, 2.24)
17 minute	23	-1.59	17	0.08	1.67 (1.03, 2.32)	19	-2.00	16	-0.40	1.59 (0.68, 2.51)
18 minute	21	-1.81	12	0.25	2.06 (1.27, 2.84)	15	-2.12	12	-0.45	1.67 (0.57, 2.76)
19 minute	16	-2.06	9	0.21	2.28 (1.39, 3.16)	12	-2.00	9	-0.43	1.58 (0.19, 2.97)
20 minute	15	-2.14	7	0.29	2.43 (1.42, 3.44)	9	-1.80	6	-0.85	0.96 (-0.98, 2.89)

* 95% CI based on two-sample t-test
Source: statistical reviewer's analysis.

The applicant-defined primary efficacy analysis was change in pupil diameter based on the mean AUC pupil diameter change from baseline using generalized CMH test stratified by the randomization strata (LOCSII low vs. high). For both Studies 003 and 004, OMS302 was superior to placebo ($p < 0.0001$) based on the applicant proposed primary analysis.

Table 19: Mean AUC Analysis of Change from Baseline in Pupil Diameter (mm) during Surgery for Studies OMS302-ILR-003 and 004 (Subjects with Readable Video Recordings)

	OMS302-ILR-003		OMS302-ILR-004	
	Placebo (N=180)	OMS302 (N=184)	Placebo (N=200)	OMS302 (N=195)
Mean AUC (SD)	-0.5 (0.58)	0.1 (0.41)	-0.5 (0.57)	0.1 (0.43)
Difference in Mean AUC (OMS302 – Placebo)				
CMH weighted mean difference (SE)	0.577 (0.052)		0.590 (0.049)	
95% confidence interval	0.5, 0.9		0.5, 0.7	
p-value	<0.0001		<0.0001	

Source: Table 5 of Study OMS302-ILR-003 Report and Table 6 of Study OMS302-ILR-004 Report.

In addition, repeated measures ANOVA for testing differences in change in pupil diameter between OMS302 and placebo (as part of pre-specified sensitivity analyses) also confirmed the primary efficacy analyses findings of OMS302 comparing to vehicle in both studies.

Table 20: Repeated Measures Analysis of Change from Baseline in Pupil Diameter (mm) during CELR Surgery for Study 003 and 004 (Subjects with Readable Video Recordings)

	OMS302-ILR-003		OMS302-ILR-004	
	Placebo (N=180)	OMS302 (N=184)	Placebo (N=200)	OMS302 (N=195)
Least Square Mean (SE)	-1.34 (0.13)	-0.68 (0.12)	-1.41 (0.16)	-0.78 (0.15)
Least Square Mean Difference (SE)	0.66 (0.059)		0.63 (0.060)	
95% confidence interval	0.54, 0.77		0.51, 0.75	
p-value	<0.0001		<0.0001	

Repeated measures model includes treatment (OMS302, KE, and vehicle), time-point, and LOCS II grades as covariates.
Source: Table 25 of Study OMS302-ILR-003 Report and Table 26 of Study OMS302-ILR-004 Report.

Sensitivity analyses including multiple imputation, and per-protocol analyses were performed by the applicant in both studies. These analyses support the results of the primary analyses.

3.2.4.1.3 Prevention of Miosis

To evaluate the effect of OMS302 on prevention of miosis, the applicant performed additional analyses in each of the three studies based on the proportions of subjects who had < 6 mm pupil diameter at the end of cortical cleanup (studies OMS302-ILR-003 and OMS302-ILR-004) and at any time during the procedure (studies C09-001, OMS302-ILR-003, and OMS302-ILR-004). The statistical reviewer analyzed the data with subjects who had unreadable video recordings being included as treatment failures or as treatment successes; both had similar results as the applicant's analyses results listed in Table 21.

As noted in 3.2.2.3, only Study OMS302-ILR-004 pre-specified these two proportions as formal secondary endpoints and corresponding multiplicity adjustment. For studies C09-11 and OMS302-ILR-003, the proportions were either analyzed post hoc or as supportive analyses without pre-specified multiplicity adjustment. However, based on the highly significant results supporting the treatment effects in all three studies ($p < 0.0001$), this statistical reviewer

concludes that OMS302 is superior to placebo in maintaining pupil diameter above 6 mm during ILR procedure [redacted] (b) (4)

Table 21: Analyses of Proportions of Subjects Who Had < 6 mm Pupil Diameter at the End of Cortical Cleanup and at Any Time during the Surgery (Subjects with Readable Video Recordings)

	C09-001		OMS302-ILR-003		OMS302-ILR-004	
	KE	OMS302	Placebo	OMS302	Placebo	OMS302
Subjects with < 6 mm at cortical cleanup	Data not collected		41/180 (22.8%)	7/184 (3.8%)	46/200 (23.0%)	8/195 (4.1%)
p-value[a]			<0.0001		<0.0001	
Difference (95% CI)			19.0% (12.3%, 25.7%)		18.9% (12.4%, 25.4%)	
Subjects with < 6 mm at any time during surgery	18/52 (34.6%)	3/49 (6.1%)	85/180 (47.2%)	19/184 (10.3%)	76/200 (38.0%)	18/195 (9.2%)
p-value[a]		0.0004		<0.0001		<0.0001
Difference (95% CI)	28.5 (13.9%, 43.1%)		36.9% (28.4%, 45.4%)		28.8% (20.9%, 36.6%)	

[a] p-value based on Chi-Square test
Source: Table 23 of applicant's summary of clinical efficacy and statistical reviewer's analysis.

3.2.4.1.4 Summary of the Three Studies

For all the three studies (C09-001, OMS-ILR-003, and OMS-ILR-004), in terms of change from baseline of pupil diameter, observed treatment difference between OMS302 and placebo increased over time during the surgery. Based on the primary and supportive efficacy results, OMS302 demonstrated superiority to placebo/vehicle in maintaining pupil diluted for all three studies; and in Study C09-11, OMS302 demonstrated superiority to KE, which showed the contribution of PE as the mydriatic component to this combination product.

3.2.4.2 Ocular Pain VAS

3.2.4.2.1 Study C09-001

After the surgery, postoperative ocular pain was measured by VAS (based on 0 to 100 score) at 2, 4, 6, 8, and 10-12 hours. All 222 randomized and treated subjects were included in the pain analysis set (PAS). Ocular pain VAS scores were lower in both OMS302 and the KE groups comparing with vehicle and PE groups.

Table 22: Study C09-001 Ocular Pain VAS Score within 12 hours Postoperatively (All Treated Subjects)

Time	Vehicle (N=56)	PE (N=56)	KE (N=55)	OMS302 (N=54)
2 hours				
n	56	55	55	54
Mean (STD)	8.6 (14.7)	9.4 (16.8)	4.1 (12.7)	5.3 (11.8)
4 hours				

n	53	52	49	49
Mean (STD)	10.9 (19.3)	10.5 (16.9)	4.8 (12.3)	5.9 (12.4)
6 hours				
n	54	54	47	53
Mean (STD)	10.5 (17.2)	9.5 (14.9)	4.3 (10.9)	3.9 (8.6)
8 hours				
n	53	54	47	50
Mean (STD)	8.9 (14.7)	12.2 (16.9)	4.0 (11.0)	4.0 (10.5)
10 to 12 hours				
n	54	52	52	52
Mean (STD)	10.3 (18.3)	11.8 (17.1)	3.4 (9.2)	4.7 (13.4)

Source: Table 26 of Study C09-001 Report.

The applicant proposed repeated measures ANOVA to compare ocular pain score based on VAS, OMS302 was statistically superior to vehicle and PE (**Table 23**).

Table 23: Study C09-001 Repeated Measures Analysis of Ocular Pain VAS Score within 12 Hours Postoperatively (All Treated Subjects)

	Vehicle	PE	OMS302
Least Square Mean (SE)	10.6 (1.8)	12.0 (2.2)	6.1 (1.8)
Least Square Mean Difference (SE) (OMS302 – Vehicle or PE)	4.6 (2.2)	5.9 (2.2)	
95% Confidence Interval	0.2, 8.9	1.5, 10.3	
p-value	0.0421	0.0093	

Repeated measures model includes treatment (OMS302, KE, and vehicle), time-point, and LOCS II grades as covariates.
Source: Table 7 of Study C09-001 Report.

In addition, the statistical reviewer summarized the proportion of patients with zero VAS score (which means no pain) at each time point within 12 hours post-surgery. Although, the treatment differences of the proportion of patients who were pain free favored OMS302 over either vehicle or PE at all time points, the lower bounds of the 95% CI were below zero at majority of the time points (4 out of 5 for OMS302 vs. Vehicle; 3 out of 5 for OMS vs. PE). It should be noted that with relatively small sample size this study was underpowered to detect such differences.

Table 24: Study C09-001 Proportion of Patients with Zero VAS Scores Post-Surgery over Time (All Treated Subjects)

	OMS302	Vehicle	PE	OMS302 vs. Vehicle Difference (95% CI)*	OMS302 vs. PE Difference (95% CI)*
2 Hours	31/55 (56.4%)	27/56 (48.2%)	28/56 (50.0%)	8.2% (-10.4%, 26.7%)	6.4% (-12.2%, 24.9%)
4 Hours	26/49 (53.1%)	21/53 (39.6%)	20/52 (38.5%)	13.4% (-5.8%, 32.6%)	14.6% (-4.6%, 33.8%)
6 Hours	29/55 (52.7%)	21/55 (38.3%)	22/55 (40.0%)	14.6% (-3.9%, 33.0%)	12.7% (-5.8%, 31.2%)
8 Hours	27/51 (52.9%)	19/53 (35.9%)	18/54 (33.3%)	17.1% (-1.7%, 35.9%)	19.6% (1.0%, 38.2%)
10 to 12 Hours	30/54 (55.6%)	17/54 (31.5%)	18/55 (32.7%)	24.3% (6.0%, 42.6%)	22.8% (4.7%, 41.0%)

* 95% CI calculated using chi-square test
Source: Statistical reviewer's analysis.

3.2.4.2.2 Studies OMS302-ILR-003 and OMS302-ILR-004

For Study OMS302-ILR-003, all 402 randomized and treated subjects were included in the ocular pain analyses. For Study OMS302-ILR-004, 404 subjects were included in ocular pain analyses; two subjects (both in the placebo group) were excluded because they did not provide any VAS data on the day of surgery. Ocular pain VAS scores were lower in OMS302 group comparing with the placebo group.

Table 25: Studies OMS302-ILR-003 and 004 Ocular Pain VAS Score within 12 hours Postoperatively (All Treated Subjects)

Time	OMS302-ILR-003		OMS302-ILR-004	
	Placebo (N=201)	OMS302 (N=201)	Placebo (N=204)	OMS302 (N=202)
2 hours				
n	200	198	198	197
Mean	9.9	5.8	10.4	6.4
4 hours				
n	194	195	200	198
Mean	9.7	3.2	9.3	3.8
6 hours				
n	196	198	197	199
Mean	9.1	3.5	8.3	4.0
8 hours				
n	196	198	201	200
Mean	8.8	4.4	8.3	3.8
10 to 12 hours				
n	197	196	197	198
Mean	8.2	3.9	6.9	4.2

Source: Table 20 of Study OMS302-ILR-003 Report and Table 21 of Study OMS302-ILR-004 Report.

For both studies, the efficacy analysis used mean AUC of the ocular pain VAS during 12 hours postoperatively. Based on the applicant defined generalized CMH test stratified by the randomization strata, OMS302 was superior to placebo in both studies.

Table 26: Mean AUC Analysis of Ocular Pain VAS Score within 12 Hours Postoperatively for Studies OMS302-ILR-003 and 004 (All Treated Subjects)

	OMS302-ILR-003		OMS302-ILR-004	
	Placebo (N=201)	OMS302 (N=201)	Placebo (N=202)	OMS302 (N=202)
Mean AUC (SD)	9.2 (12.9)	4.1 (8.07)	8.9 (15.19)	4.3 (8.75)
Difference in Mean AUC				
CMH weighted mean difference (SE)	-5.199 (1.076)		-4.580 (1.192)	
95% confidence interval	-7.307, -3.091		-6.917, -2.244	
p-value	<0.0001		0.0002	

Source: Table 6 of Study OMS302-ILR-003 Report and Table 7 of Study OMS302-ILR-004 Report.

In addition, the statistical reviewer summarized the proportion of patients with zero VAS score (which means no pain) at each time point within 12 hours post-surgery as shown in the following table. For both studies 003 and 004, the treatment difference in terms of the proportion of patients who were pain free favored OMS302 as versus placebo; and all the lower bounds of the 95% CI for the post-baseline treatment difference were above zero. Moreover, the treatment differences within 12 hours post-surgery were consistent across both Studies 003 and 004; and these differences were also similar with what were observed in Study C09-001.

Table 27: Proportion of Patients with Zero VAS Scores Post-Surgery over Time for Studies OMS302-ILR-003 and OMS302-ILR-004 (All Treated Subjects)

	Study OMS302-ILR-003			Study OMS302-ILR-004		
	OMS302	**Placebo**	**Difference (95% CI)***	**OMS302**	**Placebo**	**Difference (95% CI)***
2 Hours	81/201 (40.3%)	61/201 (30.4%)	9.95% (0.7%, 19.2%)	101/202 (50.0%)	75/203 (37.0%)	13.1% (3.5%, 22.6%)
4 hours	94/201 (46.8%)	62/200 (31.0%)	15.8% (6.4%, 25.2%)	111/202 (55.0%)	80/203 (39.4%)	15.5% (5.9%, 25.2%)
6 Hours	91/201 (45.3%)	59/201 (29.4%)	15.9% (6.6%, 25.3%)	107/202 (53.0%)	80/203 (39.4%)	13.6% (3.9%, 23.2%)
8 Hours	94/201 (46.8%)	58/200 (29.0%)	17.8% (8.4%, 27.1%)	115/202 (56.9%)	84/201 (41.8%)	15.1% (5.5%, 24.8%)
10 to 12 Hours	92/201 (45.8%)	64/199 (32.2%)	13.6% (4.2%, 23.1%)	123/199 (63.3%)	89/202 (44.1%)	19.3% (9.7%, 28.8%)

* 95% CI calculated using chi-square test
Source: Statistical reviewer's analysis.

3.2.4.2.3 Summary of the Three Studies

For all the three studies (C09-001, OMS302-ILR-003, and OMS302-ILR-004), based on the applicant proposed primary analyses and the statistical reviewer's analyses, OMS302 demonstrated superiority to placebo/vehicle in reducing ocular pain during the first 10-12 hours postoperatively; and in Study C09-11, OMS302 demonstrated superiority to PE, which showed the contribution of KE as the anti-inflammatory component to this combination product.

3.3 Evaluation of Safety

3.3.1 Treatment Exposure

Study treatment was administered as one-time irrigation solution to the anterior chamber of the eye during surgery. The following tables present the summary of study drug administration for studies C09-001, OMS302-ILR-003, and OMS302-ILR-004. For all these three studies, treatment exposures were similar between treatments in terms of both irrigation volume and irrigation duration. Moreover, treatment exposures were also consistent across all three studies.

Table 28: Study Drug Administration (All Treated Subjects)

Study C09-001				
	Vehicle (N=57) n (%)	**PE (N=54) n (%)**	**KE (N=55) n (%)**	**OMS302 (N=56) n (%)**
Total volume of study irrigation solution (ml)				
Mean (STD)	266 (65.7)	258 (67.8)	267 (78.8)	259 (72.2)
Median	270	250	250	250
Min, Max	104, 450	150, 405	150, 425	104, 475
Study drug administration duration (minutes)				
Mean (STD)	7 (4.7)	6 (3.7)	8 (4.4)	8 (4.1)
Median	7.0	5.5	8.0	8.0
Min, Max	1, 32	1, 21	1, 26	1, 22
Study OMS302-ILR-003				
	Placebo (N=201)		OMS302 (N=201)	
Total volume of study irrigation solution (ml)				
Mean (STD)	252.2 (61.7)		248.9 (56.6)	
Median	245		250	
Min, Max	125, 497		150, 497	
Study drug administration duration (minutes)				
Mean (STD)	7.7 (4.5)		7.6 (5.0)	
Median	7		7	
Min, Max	1, 35		0, 42	
Study OMS302-ILR-004				
	Placebo (N=201)		OMS302 (N=201)	
Total volume of study irrigation solution (ml)				
Mean (STD)	255.8 (70.7)		254.3 (63.4)	
Median	250		250	
Min, Max	125, 500		100, 500	
Study drug administration duration (minutes)				
Mean (STD)	7.7 (5.1)		7.3 (4.1)	
Median	7		7	
Min, Max	1, 39		1, 29	

Source: Table 15 of Study C09-001 report, Table 10 of Study OMS302-ILR-003 report, and Table 11 of Study OMS302-ILR-004 report.

3.3.2 Adverse Events

The following tables present the common treatment-emergent adverse events with subject incidence of ≥ 2% in any OMS302 arm and the treatment-related adverse events with subject incidence of ≥ 1% in any OMS302 arm with corresponding incidence rate in vehicle/placebo arm for all three reviewed studies (C09-001, OMS302-ILR-003, and OMS302-ILR-004). Overall, OMS302 had similar adverse events rates as placebo/vehicle-treated groups. Please see the review of the medical reviewer for details of the safety evaluation.

Table 29: Common Treatment-Emergent Adverse Events with Subject Incidence of ≥ 2% in any OMS302 arm

	C09-001		OMS302-ILR-003		OMS302-ILR-004	
	Vehicle	**OMS302**	**Placebo**	**OMS302**	**Placebo**	**OMS302**
	(N=57)	**(N=56)**	**(N=201)**	**(N=201)**	**(N=204)**	**(N=202)**
Any Event	**45 (78.9%)**	**47 (83.9%)**	**150 (74.6%)**	**152 (75.6%)**	**128 (62.7%)**	**102 (50.5%)**
Eye Pain	16 (28.1%)	17 (30.4%)	86 (42.8%)	88 (43.8%)	76 (37.3%)	34 (16.8%)
Eye Inflammation	5 (8.8%)	11 (19.6%)	58 (28.9%)	60 (29.9%)	4 (2.0%)	3 (1.5%)
Headache	5 (8.8%)	4 (7.1%)	14 (7.0%)	5 (2.5%)	24 (11.8%)	21 (10.4%)
Anterior Chamber Inflammation	1 (1.8%)	1 (1.8%)	21 (10.4%)	19 (9.5%)	13 (6.4%)	17 (8.4%)
Ocular Discomfort	5 (8.8%)	1 (1.8%)	6 (3.0%)	2 (1.0%)	15 (7.4%)	10 (5.0%)
Photophobia	1 (1.8%)	4 (7.1%)	7 (3.5%)	8 (4.0%)	13 (6.4%)	4 (2.0%)
Intraocular Pressure Increased	1 (1.8%)	1 (1.8%)	10 (5.0%)	7 (3.5%)	4 (2.0%)	12 (5.9%)
Posterior Capsule Opacification	1 (1.8%)	0	1 (0.5%)	1 (0.5%)	14 (6.9%)	17 (8.4%)
Corneal Oedema	1 (1.8%)	0	5 (2.5%)	7 (3.5%)	7 (3.4%)	4 (2.0%)
Foreign Boday Sensation in Eyes	1 (1.8%)	0	0	1 (0.5%)	10 (4.9%)	7 (3.5%)
Vision Blurred	0	0	1 (0.5%)	0	16 (7.8%)	5 (2.5%)
Conjunctival Hyperaemia	3 (5.3%)	0	0	1 (0.5%)	10 (4.9%)	10 (5.0%)
Inflammation	13 (22.8%)	11 (19.6%)	0	0	0	0
Pain	11 (19.3%)	9 (16.1%)	0	0	3 (1.5%)	1 (0.5%)
Iritis	0	3 (5.4%)	0	0	3 (1.5%)	2 (1.0%)
Eye Irritation	0	0	2 (1.0%)	5 (2.5%)	4 (2.0%)	4 (2.0%)
Conjunctivitis	0	0	4 (2.0%)	6 (3.0%)	0	2 (1.0%)
Back Pain	0	1 (1.8%)	0	1 (0.5%)	3 (1.5%)	4 (2.0%)
Corneal Disorder	0	0	4 (2.0%)	3 (1.5%)	2 (1.0%)	0
Dry Eye	2 (3.5%)	1 (1.8%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	0
Nausea	0	2 (3.6%)	1 (0.5%)	1 (0.5%)	0	5 (2.5%)
Cystoid Macular Oedema	0	2 (3.6%)	0	1 (0.5%)	0	1 (0.5%)
Anterior Chamber Cell	3 (5.3%)	1 (1.8%)	0	0	0	0
Arthritis	1 (1.8%)	2 (3.6%)	0	0	0	0

Source: Table 12 of the applicant's Integrated Summary of Safety (ISS).

Table 30: Any Treatment-Related Adverse Events with Subject Incidence of ≥ 1% in any OMS302 arm

	C09-001		OMS302-ILR-003		OMS302-ILR-004	
	Vehicle	**OMS302**	**Placebo**	**OMS302**	**Placebo**	**OMS302**
	(N=57)	**(N=56)**	**(N=201)**	**(N=201)**	**(N=204)**	**(N=202)**
Eye Disorders						
Anterior Chamber Inflammation	0	0	13 (6.5%)	8 (4.0%)	8 (3.9%)	10 (5.0%)
Conjunctival Hyperaemia	0	0	0	0	8 (3.9%)	10 (5.0%)
Corneal Oedema	0	0	1 (0.5%)	4 (2.0%)	3 (1.5%)	2 (1.0%)
Eye Inflammation	0	0	4 (2.0%)	2 (1.0%)	1 (0.5%)	0
Eye Pain	2 (3.5%)	5 (8.9%)	16 (8.0%)	11 (5.5%)	14 (6.9%)	6 (3.0%)
Foreign Body Sensation in Eyes	0	0	0	0	3 (1.5%)	1 (0.5%)
Ocular Discomfort	0	0	2 (1.0%)	1 (0.5%)	5 (2.5%)	3 (1.5%)
Photophobia	1 (1.8%)	1 (1.8%)	6 (3.0%)	4 (2.0%)	8 (3.9%)	3 (1.5%)
General Disorders and Administration Site Conditions						
Inflammation	3 (5.3%)	6 (10.7%)	0	0	0	0
Pain	1 (1.8%)	1 (1.8%)	0	0	0	0
Nervous System Disorders						
Headache	0	0	2 (1.0%)	0	2 (1.0%)	1 (0.5%)

Source: Table 6 of the applicant's ISS.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Iris Color, and LOCSII Grade

Subgroup analyses based on gender, race, and age were performed. Treatment effects might be different for subjects with different iris color or LOCSII grade (two baseline characteristics); therefore subgroup analyses based on these two parameters were also conducted for studies OMS302-ILR-003 and OMS302-ILR-004. Subgroup analyses for iris color was not performed for Study C09-001 since the iris color information was not collected. All three studies were conducted in the United States; hence subgroup analyses based on region were not presented in this review.

4.1.1 Study C09-001

The following table presents the mean AUC of change from baseline in intraoperative pupil diameter based on gender, race (white or non-white), age (<65 years or > 65 years), and LOCSII grade. Efficacy was observed regardless of age, gender, race, ethnicity, or cataract grade. In general, there were no marked differences in the efficacy results among the various subpopulations.

Table 31: Mean AUC of Change from Baseline in Pupil Diameter Based on Gender, Age, Race, and LOCSII Grade

	Vehicle		KE		OMS302		OMS302 vs. Vehicle	OMS302 vs. KE
	n	Mean	n	Mean	n	Mean	Difference (95% CI)	Difference (95% CI)
Male	24	-0.46	21	-0.52	17	0.06	0.52 (0.14, 0.89)	0.55 (0.33, 0.78)
Female	29	-0.67	31	-0.40	32	0.15	0.82 (0.54, 1.11)	0.58 (0.25, 0.90)
Age < 65 years	15	-0.64	18	-0.56	15	0.03	0.67 (0.16, 1.18)	0.60 (0.25, 0.95)
Age ≥ 65 years	38	-0.55	34	-0.39	34	0.15	0.71 (0.47, 0.94)	0.54 (0.34, 0.74)
White	43	-0.63	44	-0.46	39	0.13	0.76 (0.51, 1.01)	0.59 (0.39, 0.79)
Non-White	10	-0.32	8	-0.38	10	0.09	0.42 (-0.03, 0.86)	0.47 (0.12, 0.82)
LOCS II Grade (Low)	13	-0.62	12	-0.50	12	0.07	0.69 (0.19, 1.20)	0.57 (0.16, 0.99)
LOCS II Grade (High)	40	-0.56	40	-0.43	37	0.13	0.69 (0.45, 0.94)	0.57 (0.37, 0.77)

Source: statistical reviewer's analysis.

The following table presents the mean AUC of ocular pain VAS score during the first 12 hours postoperatively based on gender, race (white or non-white), age (<65 years or > 65 years), and LOCSII grade. In general, there were no marked differences in the efficacy results among the various subpopulations.

Table 32: Mean AUC of Ocular Pain VAS Based on Gender, Age, Race, and LOCSII Grade

	Vehicle		PE		OMS302		OMS302 vs. Vehicle	OMS302 vs. PE
	n	Mean	n	Mean	n	Mean	Difference (95% CI)	Difference (95% CI)
Male	24	11.66	20	10.41	19	3.59	-8.07 (-15.17, 0.97)	-6.82 (-14.46, 0.82)
Female	32	8.03	36	10.97	36	4.89	-3.14 (-8.73, 2.46)	-6.08 (-11.83, 0.33)

Age < 65 years	16	7.47	20	18.23	16	6.91	-0.57 (-12.28, -1.71)	-11.32 (-21.96, -0.68)
Age ≥ 65 years	40	10.43	36	6.63	39	3.43	-7.00 (-12.28, -1.71)	-3.20 (-7.21, 0.82)
White	45	10.90	44	11.40	44	5.11	-5.88 (-11.18, -0.40)	-6.29 (-11.67, -0.91)
Non-White	11	4.20	12	8.46	11	1.76	-2.44 (-7.28, 2.40)	-6.70 (-14.60, 1.20)
LOCS II Grade (Low)	14	7.32	14	19.70	13	7.99	0.67 (-9.64, 10.98)	-11.71 (-25.92, 2.49)
LOCS II Grade (High)	42	10.34	42	7.79	42	3.34	-6.99 (-11.97, 2.02)	-4.45 (-8.07, -0.83)

Source: statistical reviewer's analysis.

4.1.2 Study OMS302-ILR-003 and Study OMS302-ILR-004

The following table presents the mean AUC of change from baseline in intraoperative pupil diameter based on gender, race (white or non-white), age (<65 years or > 65 years), iris color, and LOCSII grade. Efficacy was observed regardless of age, gender, race, ethnicity, cataract grade, or iris color for both studies. In general, there were no marked differences in the efficacy results among the various subpopulations.

Table 33: Mean AUC of Change from Baseline in Pupil Diameter Based on Gender, Age, Race, Iris Color, and LOCSII Grade (Studies OMS302-ILR-003 and OMS302-ILR-004)

	Study 003			Study 004		
Study Drug	**n**	**Mean**	**Difference (95% CI)**	**n**	**Mean**	**Difference (95% CI)**
Male						
Placebo	99	-0.52	0.63	77	-0.38	0.53
OMS302	109	0.11	(0.47, 0.79)	81	0.15	(0.37, 0.70)
Female						
Placebo	81	-0.50	0.54	123	-0.56	0.62
OMS302	75	0.04	(0.40, 0.68)	114	0.05	(0.50, 0.74)
Age < 65 years						
Placebo	57	-0.61	0.74	53	-0.39	0.54
OMS302	54	0.13	(0.57, 0.90)	52	0.15	(0.31, 0.76)
Age ≥ 65 years						
Placebo	123	-0.46	0.50	147	-0.53	0.61
OMS302	130	0.04	(0.37, 0.63)	143	0.07	(0.50, 0.72)
White						
Placebo	139	-0.51	0.60	155	-0.49	0.57
OMS302	151	0.10	(0.49, 0.71)	161	0.08	(0.46, 0.68)
Non-White						
Placebo	41	-0.51	0.46	45	-0.51	0.67
OMS302	33	-0.05	(0.19, 0.73)	34	0.16	(0.43, 0.92)
Brown Iris						
Placebo	96	-0.51	0.64	107	-0.49	0.55
OMS302	100	0.04	(0.45, 0.83)	101	0.06	(0.41, 0.69)
Blue Iris						
Placebo	43	-0.51	0.64	55	-0.46	0.65
OMS302	52	0.13	(0.45, 0.83)	61	0.20	(0.47, 0.84)
Hazel Iris						
Placebo	24	-0.52	0.56	21	-0.47	0.46
OMS302	19	0.04	(0.30, 0.82)	18	-0.02	(0.18, 0.73)
Green Iris						

Study Drug	Study 003			Study 004		
	n	Mean	Difference (95% CI)	n	Mean	Difference (95% CI)
Placebo	15	-0.54	0.61	12	-0.67	0.78
OMS302	12	0.07	(0.28, 0.94)	13	0.11	(0.44, 1.12)
Grey Iris						
Placebo	2	-0.28	n/a	3	-0.58	0.20
OMS302	1	0.19		2	-0.38	(-1.05, 1.45)
LOCS II Grade (Low)						
Placebo	35	-0.5	0.65	33	-0.53	0.38
OMS302	41	0.12	(0.41, 0.90)	33	0.10	(0.13, 0.63)
LOCS II Grade (High)						
Placebo	145	-0.5	0.55	167	-0.33	0.63
OMS302	143	0.55	(0.44, 0.67)	162	0.05	(0.52, 0.74)

Source: statistical reviewer's analysis.

The following table presents the mean AUC of ocular pain VAS score during the first 12 hours postoperatively based on gender, race (white or non-white), age (<65 years or > 65 years), and LOCSII grade. In general, there were no marked differences in the efficacy results among the various subpopulations.

Table 34: Mean AUC of Ocular Pain VAS Based on Gender, Age, Race, Iris Color, and LOCSII Grade (Studies OMS302-ILR-003 and OMS302-ILR-004)

Study Drug	Study 003			Study 004		
	n	Mean	Difference (95% CI)	n	Mean	Difference (95% CI)
Male						
Placebo	90	7.92	-4.12	77	6.36	-2.30
OMS302	82	3.80	(-6.77, -1.46)	85	4.06	(-5.39, 0.77)
Female						
Placebo	111	10.27	-6.02	125	10.49	-6.10
OMS302	119	4.25	(-9.15, -2.88)	117	4.39	(-5.37, 0.77)
Age < 65 years						
Placebo	62	8.46	-2.85	53	11.14	-7.06
OMS302	58	5.60	(-6.55, 0.85)	53	4.08	(-12.07, -2.05)
Age ≥ 65 years						
Placebo	139	9.55	-6.11	149	8.12	-7.06
OMS302	143	3.44	(-8.68, -3.54)	149	4.31	(-12.07, -2.05)
White						
Placebo	155	9.22	-5.58	156	8.62	-4.55
OMS302	165	3.64	(-7.87, -3.30)	165	4.07	(-7.26, -1.84)
Non-White						
Placebo	46	9.19	-3.16	46	9.90	-4.85
OMS302	36	6.03	(-8.66, 2.33)	37	5.04	(-10.26, 0.55)
Brown Iris						
Placebo	105	9.01	-4.90	105	8.90	-4.75
OMS302	108	4.11	(-7.74, -2.06)	106	4.15	(-7.91, -1.59)
Blue Iris						
Placebo	50	11.29	-7.85	57	8.77	-4.86
OMS302	59	3.44	(-11.80, -3.91)	63	3.91	(-9.56, -0.16)
Hazel Iris						
Placebo	24	9.25	-1.86	21	8.93	-4.05

Study Drug	Study 003			Study 004		
	n	Mean	Difference (95% CI)	n	Mean	Difference (95% CI)
OMS302	20	7.40	(-10.86, 7.14)	18	4.88	(-12.39, 4.30)
Green Iris						
Placebo	20	4.39	-2.65	12	8.73	-2.44
OMS302	13	1.73	(-5.96, -0.65)	13	6.29	(-12.43, 7.55)
Grey Iris						
Placebo	2	15.87	n/a	4	3.63	-2.19
OMS302	1	0.00		2	1.44	(-6.28, 1.90)
LOCS II Grade (Low)						
Placebo	41	8.51	-3.27	33	10.08	-5.81
OMS302	46	5.23	(-7.84, 1.29)	33	4.26	(-11.43, -0.20)
LOCS II Grade (High)						
Placebo	160	9.41	-5.69	169	8.69	-4.44
OMS302	155	3.72	(-8.05, -3.32)	169	4.25	(-7.11, -1.76)

Source: statistical reviewer's analysis.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for all three studies.

Although only one study (C09-001) was conducted to evaluate the contribution of PE and of KE to the proposed indication, because of this study's results were highly significant and consistent, the statistical reviewer concludes one study is adequate to support the contribution of each component to the combination product.

In Study C09-001, 19 (8.5%) subjects were excluded from the pupil diameter analyses because their video recordings during the CELR were not readable (3/56 [5.4%] in vehicle group, 7/56 [12.5%] in PE group, 3/52 [5.5%] in KE group, and 6/56 [10.7%] in OMS302 group). In Study OMS302-ILR-003, 38 (9.5%) subjects were excluded from the pupil diameter analyses (17/201 [8.5%] subjects in the OMS302 group and 21/201 [10.4%] subjects in the placebo group). In Study OMS302-ILR-004, much less subjects (11 [2.7%]; 7/202 [3.5%] in the OMS302 group and 4/204 [2.0%] subjects in the placebo group) were excluded from the pupil diameter analyses. All subjects were excluded because of technical issues related with video recording and not treatment-related. In addition, sensitivity analyses using multiple imputation to impute mean AUC values for those excluded subjects due to video recording error were conducted by the applicant for studies OMS302-ILR-003 and 004 and by the statistical reviewer for Study C09-001, the analyses results were consistent with the primary analyses results. Therefore, the statistical reviewer concluded that excluding these subjects was unlikely to introduce any bias to these studies.

5.2 Collective Evidence

In Study C09-001, OMS302 demonstrated statistical superiority to KE in terms of change from baseline of pupil diameter during the surgical procedure based on repeated measure ANOVA, which showed the contribution of PE as the mydriatic component to this combination product (Table 35). OMS302 also demonstrated statistical superiority to PE in terms of ocular pain Visual Analog Scale (VAS) score during the initial 10-12 hours postoperatively based on repeated measure ANOVA, which showed the contribution of KE as the anti-inflammatory component to this combination product (Table 36).

The applicant's primary analyses did not present the treatment effects at each time point directly; therefore the statistical reviewer calculated treatment differences and the corresponding 95% CIs in mean change from baseline of pupil diameter between OMS302 and placebo at each time point from the beginning of the surgery till the 20-minute time point for all three studies (Table 39). The number of subjects at each time point becomes smaller over time because ILR procedures were completed in different amounts of time. Data after the 20-minute time point is not listed since only about 6% or less of subjects in each study were still undergoing surgical procedure after 20 minutes. Treatment effects observed for intraoperative pupil diameter during the surgical procedure at each time point were comparable across all three studies.

For both studies OMS302-ILR-003 and OMS-ILR-004, based on mean AUC using a generalized Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata analyses, OMS302 demonstrated statistical superiority over placebo in both change from baseline of pupil diameter during the surgical procedure and ocular pain VAS score during the initial 10-12 hours postoperatively (Table 37 and Table 38).

In addition, the statistical reviewer also summarized the proportion of patients with zero VAS score (which means no pain) at each time point within 12 hours post-surgery (Table 1). Treatment effects observed for postoperative pain during the initial 10-12 hours postoperatively were also comparable across all three studies.

Table 35: Study C09-001 Repeated Measures Analysis of Change from Baseline in Pupil Diameter (mm) during CELR Surgery (Patients who had readable video recording)

	Vehicle	KE	OMS302
Least Square Mean (SE)	-2.03 (0.28)	-1.9 (0.25)	-1.2 (0.26)
Least Square Mean Difference (SE)	0.9 (0.1)	0.7 (0.1)	
95% Confidence Interval	0.6, 1.1	0.5, 0.9	
p-value	<0.0001	<0.0001	

Repeated measures model includes treatment (OMS302, KE, and vehicle), time-point, and LOCS II grades as covariates.
Source: Table 6 of Study C09-001 Report.

Table 36: Study C09-001 Repeated Measures Analysis of Ocular Pain VAS Score within 12 Hours Postoperatively (All Treated Subjects)

	Vehicle	PE	OMS302
Least Square Mean (SE)	10.6 (1.8)	12.0 (2.2)	6.1 (1.8)
Least Square Mean Difference (SE)	4.6 (2.2)	5.9 (2.2)	

95% Confidence Interval	0.2, 8.9	1.5, 10.3
p-value	0.0421	0.0093

Repeated measures model includes treatment (OMS302, KE, and vehicle), time-point, and LOCS II grades as covariates.
Source: Table 7 of Study C09-001 Report.

Table 37: Studies OMS302-ILR-003 and OMS302-ILR-004 Mean Area-Under-the-Curve Analysis of Change-from-Baseline in Pupil Diameter (mm) during Surgery (Patients who had readable video recording of the surgery)

	OMS302-ILR-003		OMS302-ILR-004	
	Placebo	**OMS302**	**Placebo**	**OMS302**
Mean AUC				
n	180	184	200	195
Mean (STD)	-0.51 (0.58)	0.07 (0.41)	-0.49 (0.57)	0.09 (0.43)
Difference (OMS302 – Placebo or KE)				
CMH weighted mean difference (SE)	0.58 (0.05)		0.59 (0.05)	
95% Confidence Interval (CI)	0.47, 0.68		0.49, 0.69	
p-value	<0.001		<0.001	

Source: Table 5 of Study OMS302-ILR-003 report, and Table 6 of Study OMS302-ILR-004 report.

Table 38: Studies OMS302-ILR-003 and OMS302-ILR-004 Mean Area-Under-the-Curve Analysis of Ocular Pain VAS Score 10-12 Hours Postoperatively (Full Analysis Set)

	OMS302-ILR-003		OMS302-ILR-004	
	Placebo	**OMS302**	**Placebo**	**OMS302**
Mean AUC				
n	201	201	202	202
Mean (STD)	9.22 (12.93)	4.07 (8.07)	8.91 (15.19)	4.25 (8.75)
Difference (OMS302 – Placebo or PE)				
CMH weighted mean difference (SE)	-5.20 (1.08)		-4.58 (1.19)	
95% Confidence Interval (CI)	-7.31, -3.09		-6.92, -2.24	
p-value	<0.001		<0.001	

Source: Table 6 of Study OMS302-ILR-003 report, and Table 7 of Study OMS302-ILR-004 report.

Table 39: Summary of Change from Baseline of Mean Pupil Diameter (mm) at Each Time Point during CELR Surgery for All Three Studies (Subjects with Readable Video Recordings)

	C09-001					OMS302-ILR-003					OMS302-ILR-004				
	KE		OMS302			Placebo		OMS302			Placebo		OMS302		
MIN	**n**	**Mean**	**n**	**Mean**	**Diff (95% CI)**	**n**	**Mean**	**n**	**Mean**	**Diff (95% CI)**	**n**	**Mean**	**n**	**Mean**	**Diff (95% CI)**
1	52	0.18	48	0.30	0.13 (-0.09 0.34)	180	0.24	183	0.17	-0.07 (-0.17 0.04)	200	0.19	194	0.13	-0.06 (-0.17 0.05)
2	52	0.08	49	0.26	0.18 (-0.04 0.40)	179	0.09	184	0.25	0.16 (0.03 0.28)	200	0.08	195	0.26	0.18 (0.06 0.30)
3	52	0.01	49	0.25	0.24 (-0.03 0.51)	180	-0.04	184	0.26	0.30 (0.16 0.44)	200	-0.03	195	0.32	0.35 (0.22 0.48)
4	52	-0.19	49	0.40	0.60 (0.32 0.88)	180	-0.23	183	0.16	0.40 (0.25 0.55)	200	-0.21	195	0.17	0.39 (0.26 0.52)
5	51	-0.22	48	0.30	0.52 (0.24 0.79)	178	-0.42	184	0.10	0.52 (0.36 0.68)	199	-0.46	190	0.13	0.59 (0.46 0.73)
6	50	-0.45	48	0.24	0.69 (0.37 1.01)	169	-0.60	159	0.09	0.69 (0.52 0.86)	182	-0.66	170	0.05	0.72 (0.56 0.88)
7	44	-0.85	43	0.05	0.90 (0.51 1.29)	149	-0.78	130	0.06	0.84 (0.62 1.06)	161	-0.84	140	0.00	0.84 (0.64 1.05)
8	40	-0.95	36	-0.16	0.79 (0.39 1.20)	123	-1.00	111	-0.15	0.85 (0.61 1.08)	136	-1.03	114	-0.02	1.01 (0.80 1.23)
9	32	-1.27	32	-0.06	1.21 (0.66 1.76)	104	-1.18	94	-0.11	1.06 (0.75 1.37)	101	-1.12	90	-0.07	1.05 (0.78 1.33)
10	25	-1.07	28	-0.25	0.82 (0.27 1.38)	87	-1.37	81	-0.10	1.27 (0.91 1.62)	85	-1.21	75	-0.16	1.05 (0.73 1.37)
11	22	-0.91	27	-0.30	0.61 (0.11 1.11)	67	-1.13	66	-0.17	0.96 (0.59 1.34)	67	-1.34	62	-0.09	1.24 (0.92 1.57)

12	20	-1.00	23	-0.05	0.96 (0.45 1.47)	55	-1.11	57	-0.17	0.94 (0.59 1.28)	53	-1.39	53	-0.15	1.24 (0.82 1.65)
13	16	-1.19	17	-0.30	0.89 (0.40 1.38)	53	-1.22	50	-0.21	1.01 (0.63 1.38)	47	-1.35	42	0.00	1.35 (0.90 1.81)
14	13	-1.57	10	-0.41	1.16 (0.27 2.06)	47	-1.45	43	-0.28	1.16 (0.74 1.58)	39	-1.61	35	-0.22	1.39 (0.87 1.92)
15	8	-1.48	9	-0.08	1.39 (0.68 2.10)	36	-1.61	37	-0.21	1.40 (0.91 1.89)	31	-1.79	27	-0.28	1.50 (0.88 2.13)
16	7	-1.80	6	-0.33	1.47 (-0.03 2.98)	28	-1.68	27	-0.36	1.33 (0.68 1.98)	23	-1.84	23	-0.38	1.46 (0.68 2.24)
17	6	-1.90	5	0.34	2.25 (1.49 3.00)	23	-1.59	17	0.08	1.67 (1.03 2.32)	19	-2.00	16	-0.40	1.59 (0.68 2.51)
18	5	-1.95	5	0.33	2.29 (1.13 3.45)	21	-1.81	12	0.25	2.06 (1.27 2.84)	15	-2.12	12	-0.45	1.67 (0.57 2.76)
19	4	-1.96	5	-0.23	1.73 (-0.58 4.04)	16	-2.06	9	0.21	2.28 (1.39 3.16)	12	-2.00	9	-0.43	1.58 (0.19 2.97)
20	2	-2.53	3	0.68	3.21 (0.24 6.18)	15	-2.14	7	0.29	2.43 (1.42 3.44)	9	-1.80	6	-0.85	0.96 (-0.98 2.89)

*** 95% CI based on two sample t-test**
Source: statistical reviewer's analysis.

5.3 Conclusions and Recommendations

In conclusion, OMS302 is effective in maintaining pupil dilution during the intraocular lens replacement surgery compared to KE and placebo; and in reducing ocular pain during the first 12 hours postoperatively compared to PE and placebo.

5.4 Labeling Recommendations

The statistical reviewer has the following labeling recommendations based on the applicant proposed draft label on March 24th, 2014:

- Including the (b) (4)
- (b) (4)

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

/s/

YUNFAN DENG
04/25/2014

YAN WANG
04/25/2014
I concur.