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 #:** | 006 |
| **Drug Name:** | Omidria™ (Phenylephrine HCL/Ketoroloc Tromethamine) |
| **Indication(s):** | Maintaining pupil size by preventing intraoperative miosis<br>Reducing postoperative pain |
| **Applicant:** | Omeros Corporation |
| **Date(s):** | Submission Date: June 09, 2017<br>Receipt Date: June 09, 2017<br>PDUFA goal date: December 09, 2017 |
| **Review Priority:** | Pediatric supplement priority |
| **Biometrics Division:** | DBIV |
| **Statistical Reviewer:** | Yunfan Deng, Ph.D. |
| **Concurring Reviewers:** | Yan Wang, Ph.D. |
| **Medical Division:** | Division of Transplant and Ophthalmology Products |
| **Clinical Team:** | William Boyd, MD, Team Leader |
| **Project Manager:** | Jacquelyn Smith |

**Keywords:** mydriasis, reduction of postoperative ocular pain, active-control, pediatric

## Table of Contents

## LIST OF TABLES



## LIST OF FIGURES

# 1 EXECUTIVE SUMMARY

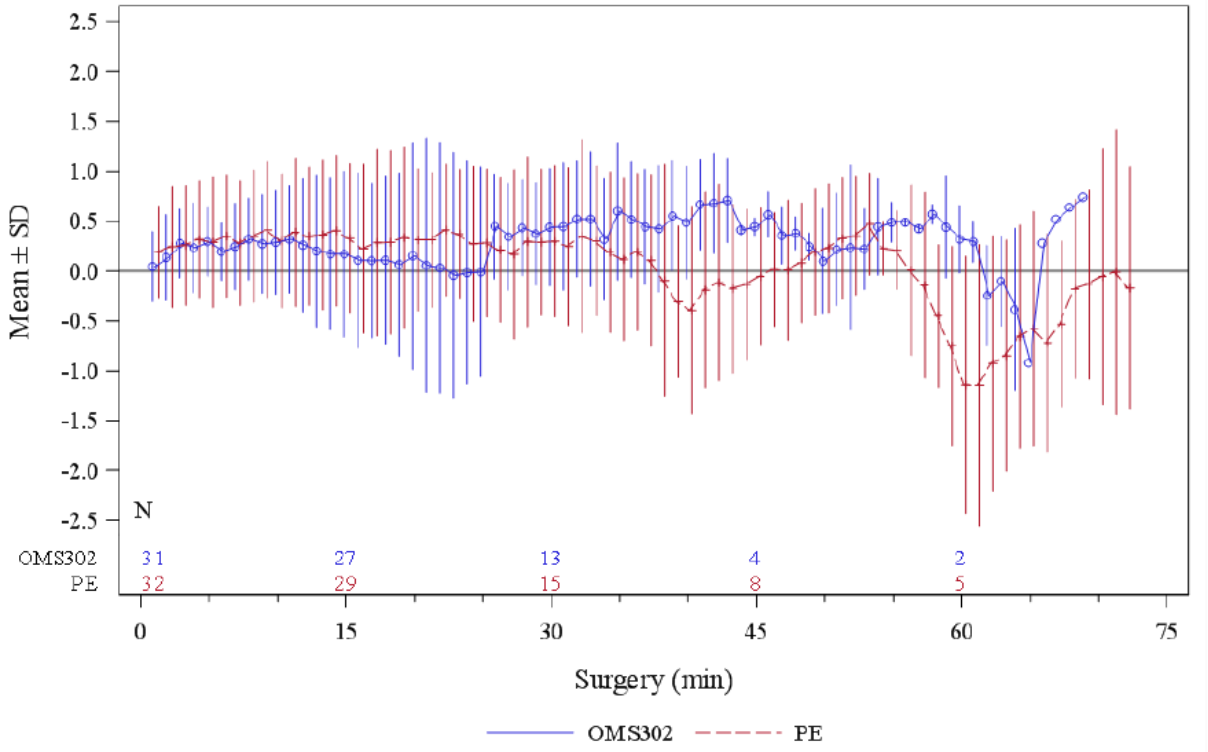
This NDA supplement was a pediatric use supplement. Omidria® (phenylephrine and ketorolac (b) (4) 1% / 0.3% (also refer to as OMS302 throughout this review) was approved in May 2014 for maintaining pupil size by preventing intraoperative miosis and for reducing postoperative pain **in adults** as an irrigation solution used during cataract surgery or intraocular lens replacement. In the approval letter of 2014, the Agency required the applicant to submit a pediatric assessment study before September 30, 2017 under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). The applicant conducted the required pediatric study (Study OMS302-ILR-007) and submitted the study report in this supplement. The supplement was also intended to support a Pediatric Exclusivity requirement and the corresponding labeling change for Omidria®.

The safety and efficacy of Omidria® in pediatric patients was evaluated in one active-controlled clinical trial: OMS302-ILR-007 (referred to as Study 007 throughout this review). Study 007 was a randomized, parallel-group, double-masked, phenylephrine(PE)-controlled study of OMS302 in young children aged birth through 3 years undergoing unilateral cataract extraction with or without lens replacement. Prior to surgery, all subjects received standard of care to dilate their pupils. Study treatment was administered as irrigation solution to the anterior chamber of the eye during surgery to maintain mydriasis throughout the surgery. Postoperatively, all subjects received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic as prescribed by the subject's surgeon. The protocol-defined primary efficacy 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 cataract surgery.
- Postoperative ocular pain as measured by the Alder Hey Triage Pain Score at 3, 6, 9, and 24 hours after surgery.

The mean duration of surgery was 35 minutes for OMS302 group and 40 minutes for PE group; the median duration of surgery was 37 minutes and 39 minutes for OMS302 and PE respectively. Approximately 80% subjects completed the surgical procedure by 40 minutes. Mydriasis was maintained throughout surgery in both treatment groups (Figure 1). At the baseline, the mean pupil diameter was about 7 mm in both OMS302 and PE groups. During the surgery, the mean change from baseline of pupil diameter ranged from -0.92 to 0.74 mm in the OMS302 group, and from -1.14 to 0.47 mm in the PE group. The mean area-under-the curve was 0.16 mm for the OMS302 group and 0.22 mm for the PE group (Table 1); the treatment difference was -0.07 mm with a 95% confidence interval (CI) of (-0.33, 0.19).

**Figure 1: Study OMS302-ILR-007 Mean Change-from-Baseline in Intraoperative Pupil Diameter (mm)**




Source: Figure 3 of Study 007 Report.

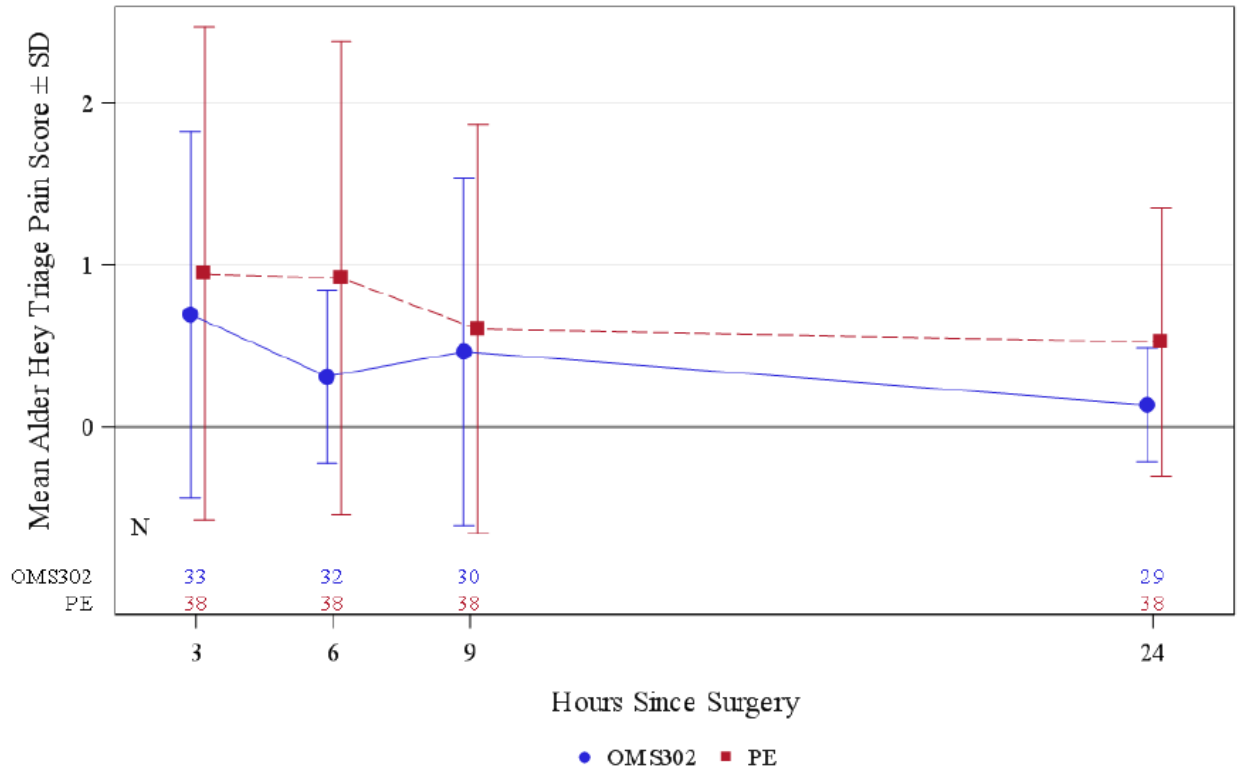
**Table 1: Mean Area-under-the-Curve (AUC) Analysis of Change from Baseline in Pupil Diameter (mm) during Surgery**

| | OMS302 (N=33) | PE (N=39) |
|---|---|---|
| Mean AUC[a] | | |
| Mean (SD) | 0.16 (0.48) | 0.22 (0.601) |
| Median | 0.18 | 0.15 |
| Min, Max | -0.94, 1.40 | -0.88, 2.36 |
| Difference in Mean AUC | | |
| CMH weighted mean difference (SE)[b] | -0.071 (0.131) | – |
| 95% confidence interval | -0.33, 0.19 | – |

[a] AUC is calculated by the trapezoidal rule from the baseline to the last post-baseline value. Mean AUC is calculated by dividing the AUC by the duration from the baseline to the post-baseline value.
[b] CMH weighted mean difference (OMS302 – PE) is adjusted for the randomized intraocular lens (IOL) implant status.
Source: Table 13 of Study 007 Report.

Subjects in both treatment groups had comparable average postoperative ocular Alder Hey Triage pain score; the average scores were low, less than one at 3, 6, 9, and 24 hours after surgery for both groups on a 10-point scale (Figure 2). However, since all subjects received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic post-surgery, the treatment effect of OMS302 or PE for postoperative pain was confounded with that of these concomitant medications. In addition, Alder Hey Triage Pain Score was not an Agency-validated scale for measuring pain in young children. Therefore, the statistical reviewer considered the results for pain to be exploratory in nature.

**Figure 2: Postoperative Alder Hey Triage Pain Score**




Source: Figure 3 of Study 007 Report.

In conclusion, OMS302 is effective in maintaining mydriasis during cataract surgery for pediatric subjects aged 0 to 3.

# 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 few 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.

- PE 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

On May 30, 2014, Omidria® (phenylephrine and ketorolac injection) 1% / 0.3% was approved for maintaining pupil size by preventing intraoperative miosis and for reducing postoperative pain **in adults** as an irrigation solution used during cataract surgery or intraocular lens replacement. In the approval letter of 2014, the Agency required the applicant to submit a pediatric assessment study before September 30, 2017 under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). The applicant conducted the required pediatric study and submitted the study report in this supplement.

The first pediatric study plan (b) (4) . Based on discussion with the Agency, the applicant (b) (4) young children aged birth through three years. The revised pediatric study plan for young children aged birth through three years who undergoing unilateral cataract extraction was submitted on 8/27/2013. The statistical reviewer raised the concern that Alder Hey Triage pain score was not an Agency-validated scale for measuring pain in young children in the review for both plans. On the letter dated 09/13/2013 signed by Dr. Wiley Chambers, it stated that "We acknowledge your plan to study OMS302 in pediatric patients aged birth to three years who are undergoing primary cataract extraction. We have completed our review of the submission, and we confirm our agreement to your PSP."

### 2.1.3 Studies Reviewed

The safety and efficacy of Omidria® in pediatric patients was evaluated in one active-controlled clinical trial: OMS302-ILR-007. Study 007 was a randomized, parallel-group, double-masked, PE-controlled study of OMS302 in young children aged birth through 3 years undergoing unilateral cataract extraction with or without lens replacement.

**Table 2: Summary of Study to be Assessed in the Statistical Review**

| Study No | Design | Objective | Treatment Groups Randomized/Completed | Study Population |
|---|---|---|---|---|
| OMS302-ILR-007 | Multi-center, randomized, double-masked, parallel group, active-control 2-arm | To evaluate the effect of OMS302 compared to phenylephrine only (PE) when administered in irrigation solution during cataract extraction with or without lens replacement (cataract extraction) on:<br>• Intraoperative pupil diameter<br>• Acute postoperative pain | OMS302 / 33<br>Phenylephrine / 39 | pediatric subjects (0 to 3 years of age) underwent unilateral primary cataract extraction with or without lens replacement |

| | | | | |
|---|---|---|---|---|
| | | • Safety as measured by adverse events (AEs) | | |

Source: Statistical Reviewer's Summary

### 2.2 Data Sources

The data sources for this review mainly came from the applicant's study report for Study 007. The study report is available at: \\Cdsesub1\evsprod\NDA205388\0054\m5\53-clin-stud-rep\535-rep-effic-safety-stud\intraocular-lens-replacement\5351-stud-rep-contr\oms302-ilr-007

The applicant submitted SAS datasets electronically; the datasets are available at: \\cdsesub1\evsprod\NDA205388\0054\m5\datasets\oms302-ilr-007

The pupil diameter assessments at each minute during the surgery were included in the "adxp.xpt" dataset with variable names "AVAL". The mean area under curve (AUC) of pupil diameter change from baseline was included in the "adsl.xpt" dataset with variable names "MAUCPD". The treatment variable named "TRTP" was included in both above datasets. The adverse events were included in the "adae.xpt" dataset.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

Overall, the submitted data were in good quality with definition of each variable. Results of the primary efficacy endpoint can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plan (SAP) for the study was submitted.

### 3.2 Evaluation of Efficacy

#### 3.2.1 Study Design and Endpoints

Study 007 was a multi-center, randomized, double-masked, active (PE)-controlled clinical study to investigate the safety and efficacy of OMS302 added to standard irrigation solution on intraoperative pupil diameter and acute postoperative pain in children ages birth through three years undergoing unilateral cataract extraction with or without lens replacement. The OMS302 treatment group received the combination of PE and KE; while the PE treatment group received the same amount of PE as the OMS302 treatment group without the additional KE.

Eligible pediatric subjects were randomized to receive OMS302 or PE in a 1:1 ratio. Randomization was stratified within sites by whether intraocular lens was to be implanted during the surgery or not. Study treatment was administered as irrigation solution to the anterior chamber of the eye during surgery. Prior to surgery, all subjects received topical ophthalmic atropine and

Cyclomydril® or cyclopentolate HCI 1% and phenylephrine 2.5% depending on subject's age to dilate their pupils. Post-surgery, all subjects received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic prescribed by the subject's surgeon.

The protocol-defined primary efficacy 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 cataract surgery.
- Postoperative ocular pain as measured by the Alder Hey Triage Pain Score at 3, 6, 9, and 24 hours after surgery.

The surgical procedure was video recorded. Intraoperative pupil size was determined by measurement of pupil diameter from still photos captured from video recordings of the procedure. Pupil diameter measurements were performed on images from immediately prior to the initial incision and at one-minute intervals until the end of the procedure (wound closure).

Pain was assessed via subject diary at 3, 6, 9, and 24 hours following wound closure by the Alder Hey Triage Pain Score. The Alder Hey Triage Pain Score identifies five categories of observations: voice/cry, facial expression, posture, movement, and color. Each of these has a possible score of 0, 1, or 2, resulting in a total score ranging between 0 and 10 (Steward, 2004). The score was recorded by subject's parent/legal guardian; the parent or legal guardian was trained on its completion by study personnel. It is noted that the Alder Hey Triage Pain score is not an Agency-validated scale for measuring pain in young children.

Eye images were captured at 1-minute intervals from the time of surgical incision. Because the actual times of the images may not have been exactly 1 minute apart, the images were binned into the following analytic windows.

**Table 3: Pupil Diameter Analytic Window**

| Analytic Timepoint (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 5 of Study 007 Report.

If there were more than one pupil diameter measurement in the same timepoint window, the closest one to the scheduled timepoint was used in the summary by timepoint. If there were two pupil diameters that were equally spaced from the scheduled timepoint, the smaller diameter was used.

For the postoperative ocular pain measured by the Alder Hey Triage Pain Score, the actual date and time of collection for postoperative timepoints was binned into the following analytic windows.

**Table 4: Alder Hey Triage Pain Score Analytic Window**

| Analytic Timepoint | Actual Time from End of Surgery |
|---|---|
| 3 hours post-surgery | > 0 to ≤ 4.5 hours |
| 6 hours post-surgery | > 4.5 to ≤ 7.5 hours |

| | |
|---|---|
| 9 hours post-surgery | > 7.5 to ≤ 16.5 hours |
| 24 hours post-surgery | > 16.5 hours |

Source: Table 6 of Study 007 Report.

If there was more than one score in the same timepoint window, the closest one to the scheduled timepoint was used in the summary by timepoint. If there were two scores that were equally spaced from the scheduled timepoint, the larger score was used. All available scores were included in the AUC analysis.

Since all subjects received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic post-surgery, the treatment effect of OMS302 or PE for postoperative pain was confounded with that of these concomitant medications. Therefore, the statistical reviewer considered the results for pain to be exploratory in nature.

The protocol-defined safety endpoints were safety as assessed by the incidence of AEs and serious adverse events (SAEs), vital signs, postoperative visual acuity, and postoperative intraocular pressure (IOP).

The schedule of assessment is presented in the following table.

**Table 5: Schedule of Assessments**

| OMS302-ILR-007 Schedule of Events | Day -28 to -1 | Day1 | | | Day 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Screening | Baseline | Surgery | Post Surgery 3, 6 and 9 hours[1] | Post Surgery 24 hours | Day 8[1] | Day 22-29[1] | Day 90[1] or Early Termination |
| Informed Consent/HIPAA | X | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | |
| Medical & Surgical History | X | X | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X |
| Ophthalmological Exam[2] | X[5] | | | | X | X | X | X[5] |
| Slit Lamp Examination[2] | X[5] | | | | X | X | X | X[5] |
| Visual Acuity Assessment | X[5] | | | | X | X | X | X[5] |
| Intraocular Pressure (IOP) | X[5] | | | | X | X | X | X[5] |
| Adverse Events | | X | X | | X | X | X | X |
| Randomization | | X | | | | | | |
| Treatment with Study Solution | | | X | | | | | |
| Cataract Extraction with or without lens replacement | | | X | | | | | |
| Vital Signs[3] | | | X | | | | | |
| Video Capture | | | X | | | | | |
| Ocular Pain (Alder Hey Triage Pain Score)[4] | | | | X | X | | | |
| Removal of eye patch | | | | | X | | | |
| Collection and review of pain diary | | | | | X | | | |

[1] Visit windows for subject contact were as follows: ±30 minutes for subject diary entries at 3, 6, 9 and 24 hours for the postoperative Alder Hey Triage Pain Score, ± 1 day for Day 8 postoperative visits, ±2 days for Day 22-29 postoperative visits and ± 7 days for the Day 90 postoperative visits.
[2] (1) Examination of the lid, lashes and lacrimal apparatus, (2) Pupillary function, (3) Examination of the fundus, (4) Slit lamp examination of lids, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous. Dilation with phenylephrine was allowed at all study-required timepoints for fundal examination.
[3] Vital Signs: Intra-operative (blood pressure and heart rate after subject under anesthesia and every 10 minutes during procedure); Postoperative (blood pressure and heart rate every 15 minutes in recovery room).
[4] Parent or legal guardian completed pain diary at approximately 3, 6, 9 and 24 hours after surgery.
[5] Ophthalmic procedures required at Screening and Day 90 were to be performed on both eyes. Ophthalmic procedures performed at other visits were to be performed on the study eye only.

Source: Table 3 of applicant's Study 007 report.

Steward, B. (2004, Jul). Validation of the Alder Hey Triage Pain Score. *Arch Dis Child, 89*(7), 625-30.

### 3.2.2 Statistical Methodologies

Per the protocol, the objectives of the study were to estimate the treatment effect of OMS302 relative to PE, and evaluate the safety of OMS302 in young children. The applicant stated that no formal statistical comparisons were performed; and the following analysis strategy was proposed in the study protocol.

Change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure) was summarized using descriptive statistics by treatment group and timepoint (every minute). Analyses of the primary efficacy endpoints were based on the full analysis set (FAS), which included all randomized subjects who received any amount of study treatment. Subjects were grouped per their randomized treatment in the FAS analysis.

The primary analysis of the change in pupil diameter was based on the mean AUC pupil diameter change from baseline. First, the AUC of the pupil diameter from surgical baseline to wound closure was calculated using the trapezoidal rule using the actual time (minutes) from baseline. Second, the mean AUC was obtained by dividing the AUC by the total time for surgery. Third, the mean AUC of change from baseline was calculated by subtracting the baseline pupil diameter from the mean AUC. All available pupil diameters were used to calculate the mean AUC.

Summary statistics of the mean AUC of change from baseline were provided by intraocular lens (IOL) implant status and treatment group. A generalized Cochran-Mantel-Haenszel (CMH) analysis stratified by the IOL implant status was used. In this procedure, the difference in the means within each stratification factor is calculated and then these stratum-specific estimates are combined using weights proportionate to the stratum-specific sample sizes. The CMH weighted mean difference and its 95% confidence interval (CI) were provided.

As a supportive analysis, a repeated-measures analysis of variance (ANOVA) was used to estimate the mean pupil diameter change from baseline for each treatment group. The repeated-measures model included the treatment group (OMS302 and PE), timepoint (as a categorical variable), and the IOL implant status (yes and no) as fixed-effect covariates. A generalized estimating equation (GEE) approach with a first-order autoregression [AR(1)] working correlation structure was used. Least-squares mean difference between the treatment arms (OMS302 – PE) was provided based on the repeated-measures model.

Per the applicant, the sample size of 30 per arm provided a probability of 95% for observing at least one occurrence of an AE with an incidence rate of at least 10% in the study population.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Seventy-eight subjects were randomized in this study. Among these 78 subjects, seventy-two subjects who received any amount of study treatment were included in the FAS set: 33 to the OMS302 group and 39 to the PE group. One subject was randomized to OMS302, but received

PE. This subject was included in the OMS302 group in all efficacy analyses, and in the PE group in all safety analyses. Therefore, the safety analysis set had 32 subjects in the OMS302 group and 40 subjects in the PE group.

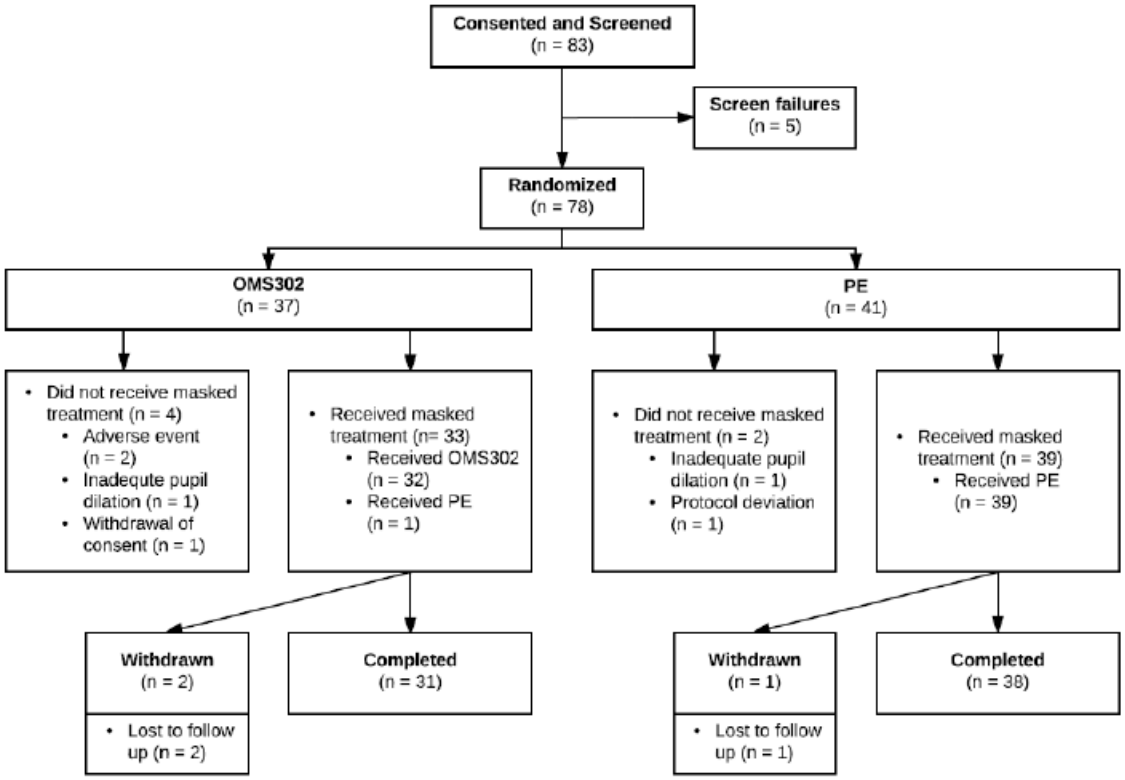
**Table 6: Study 007 Subject Disposition**

| | **OMS302 (N=37) n (%)** | **PE (N=41) n (%)** | **Total (N=78) n (%)** |
|---|---|---|---|
| Number of Subjects Randomized | 37 (100.0%) | 41 (100.0%) | 78 (100.0%) |
| | | | |
| Number of Subjects Receiving Study Treatment | 33 (89.2%) | 39 (95.1%) | 72 (92.3%) |
| | | | |
| Number of Subjects Completed Study | 31 (83.8%) | 38 (92.7%) | 69 (88.5%) |
| | | | |
| Reason for Study Discontinuation | | | |
| Lost to follow-up | 2 (5.4%) | 1 (2.4%) | 3 (3.8%) |
| Other | 4 (10.8%) | 2 (4.9%) | 6 (7.7%) |

Source: Table 9 of Study 007 report.

The applicant also provided the following flow chart to depict the subjects disposition status.

**Figure 3: Subjects Disposition Status**




Source: Figure 2 of Study 007 report.

As presented in the following table, other than the PE group had 10 subjects (26%) who were Hispanic or Latino while there were no Hispanic or Latino in the OMS302 group; demographics characteristics were generally consistent between the two treatment groups.

**Table 7: Study 007 Demographic Characteristics**

| Characteristics | OMS302 (N=33) | PE (N=39) | Total (N=72) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| **Gender** | | | |
| Male | 17 (52%) | 20 (51%) | 37 (51%) |
| Female | 16 (48%) | 19 (49%) | 35 (49%) |
| **Age (year)** | | | |
| Mean (Std) | 1.0 (1.1) | 1.4 (1.2) | 1.2 (1.2) |
| Median | 0.5 | 0.9 | 0.7 |
| Min, Max | 0.1, 3.9 | 0.1, 3.6 | 0.1, 3.9 |
| **Ethnicity** | | | |
| Hispanic or Latino | 0 | 10 (26%) | 10 (14%) |
| Not Hispanic or Latino | 33 (100%) | 29 (74%) | 62 (86%) |
| **Race** | | | |
| White/Caucasian | 26 (79%) | 30 (77%) | 56 (78%) |
| Black/African American | 5 (15%) | 3 (8%) | 8 (11%) |
| Asian | 1 (3%) | 0 | 1 (1%) |
| Other | 1 (3%) | 6 (15%) | 7 (10%) |
| **Planned Intraocular Lens (IOL) Implant** | | | |
| Yes | 16 (48%) | 20 (51%) | 36 (50%) |
| No | 17 (52%) | 19 (49%) | 36 (50%) |

Source: Table 12 of Study 007 report and statistical reviewer's summary for IOL implant.

### 3.2.4 Results and Conclusions

#### 3.2.4.1 Pupil Diameter

Sixty-three subjects were included in the pupil diameter analyses. Video recordings of nine subjects (two randomized to OMS302 [2/33, 6.1%] and seven randomized to PE [7/39, 17.9%]) were excluded. According to the applicant, the exclusion was due to protocol deviations in the recording process (video image capture requirements not met, e.g., ruler image not captured or had incomplete identification so subject identity could not be determined). These videos were identified as uninterpretable for these nine subjects before study unmasking. Therefore, the applicant concluded that it was unlikely that the exclusion of these subjects would introduce a bias in a masked study. The statistical reviewer concurred with the applicant's conclusion since those exclusions were not likely to be treatment-related.

About 80% subjects had completed the surgical procedure by 40 minutes; at the 60-minute time point, two (2) OMS302-treated subjects, and five (5) PE-treated subjects were still undergoing surgery. Mean duration of surgery for OMS302 arm was 35 minutes and 40 minutes for PE arm; the median duration of surgery was 37 minutes and 39 minutes for OMS302 and PE respectively.

Mydriasis was maintained throughout surgery in both the OMS302 and PE groups (Table 8 and Figure 4). At the baseline, the mean pupil diameter was about 7 mm in both OMS302 and PE groups. During the surgery, the mean change from baseline of pupil diameter ranged from -0.92 to 0.74 mm in the OMS302 group, and from -1.14 to 0.47 mm in the PE group.

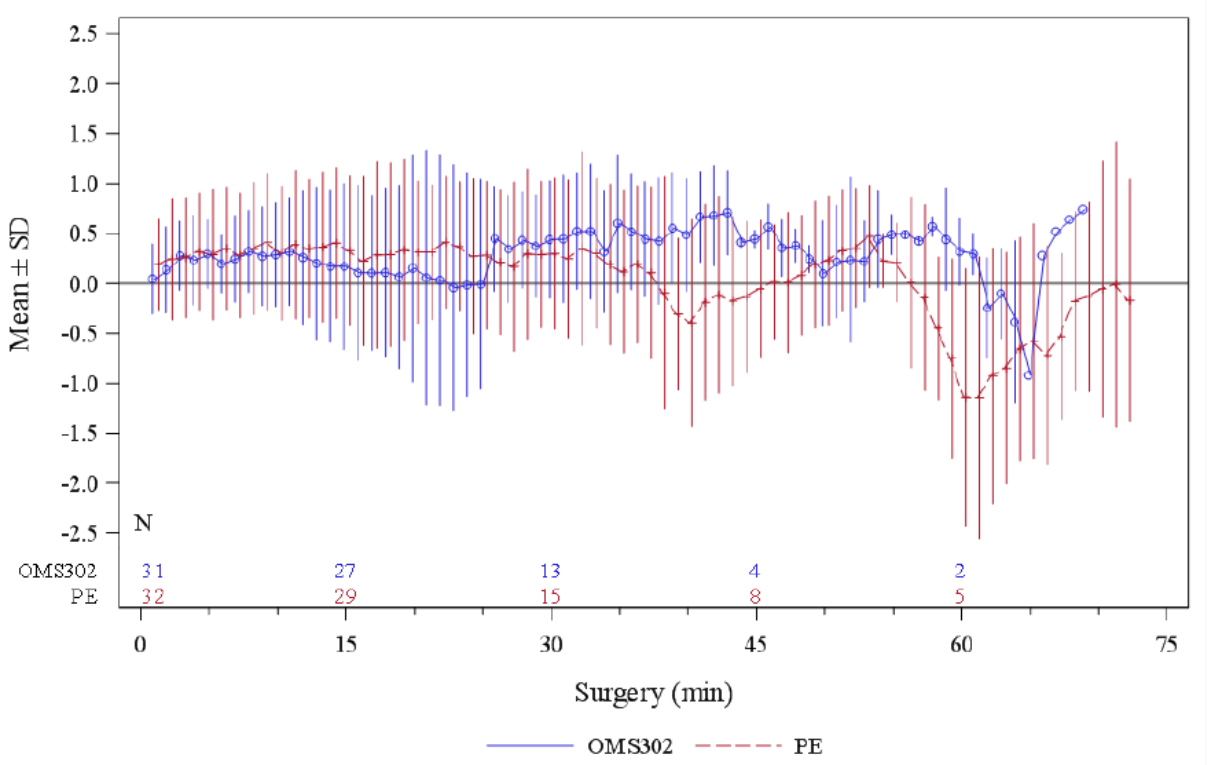
**Table 8: Study 007 Summary for Mean Change from Baseline of Pupil Diameter (mm) at Each Time Point during Cataract Surgery (Subjects with Readable Video Recording)**

| | OMS302 | | PE | | OMS302 vs. PE |
|---|---|---|---|---|---|
| **Time** | **n** | **Mean** | **n** | **Mean** | **Difference (95% CI)*** |
| **Baseline** | 31 | 6.97 | 32 | 7.21 | |
| **1 minute** | 31 | 0.05 | 32 | 0.19 | -0.14 (-0.35, 0.06) |
| **2 minute** | 29 | 0.14 | 31 | 0.24 | -0.11 (-0.37, 0.16) |
| **3 minute** | 29 | 0.28 | 30 | 0.26 | 0.02 (-0.23, 0.27) |
| **4 minute** | 31 | 0.23 | 31 | 0.32 | -0.01 (-0.34, 0.18) |
| **5 minute** | 30 | 0.30 | 32 | 0.29 | 0.01 (-0.25, 0.27) |
| **6 minute** | 31 | 0.20 | 32 | 0.35 | -0.16 (-0.39, 0.08) |
| **7 minute** | 31 | 0.25 | 32 | 0.41 | -0.03 (-0.30, 0.23) |
| **8 minute** | 30 | 0.32 | 32 | 0.35 | -0.03 (-0.30, 0.24) |
| **9 minute** | 30 | 0.27 | 32 | 0.41 | -0.14 (-0.44, 0.15) |
| **10 minute** | 30 | 0.29 | 32 | 0.31 | -0.02 (-0.31, 0.28) |
| **11 minute** | 29 | 0.32 | 31 | 0.39 | -0.07 (-0.40, 0.26) |
| **12 minute** | 28 | 0.26 | 30 | 0.35 | -0.09 (-0.44, 0.26) |
| **13 minute** | 28 | 0.20 | 30 | 0.36 | -0.16 (-0.55, 0.23) |
| **14 minute** | 28 | 0.17 | 29 | 0.41 | -0.24 (-0.63, 0.16) |
| **15 minute** | 27 | 0.17 | 29 | 0.33 | -0.16 (-0.57, 0.26) |
| **16 minute** | 27 | 0.11 | 29 | 0.22 | -0.12 (-0.57, 0.33) |
| **17 minute** | 26 | 0.11 | 26 | 0.29 | -0.18 (-0.65, 0.30) |
| **18 minute** | 25 | 0.11 | 26 | 0.29 | -0.18 (-0.66, 0.30) |
| **19 minute** | 21 | 0.07 | 26 | 0.29 | -0.27 (-0.79, 0.26) |
| **20 minute** | 18 | 0.15 | 22 | 0.31 | -0.16 (-0.77, 0.44) |
| **21 minute** | 16 | 0.06 | 21 | 0.31 | -0.26 (-0.95, 0.43) |
| **22 minute** | 16 | 0.03 | 20 | 0.41 | -0.38 (-1.06, 0.30) |
| **23 minute** | 15 | -0.04 | 18 | 0.37 | -0.41 (-1.11, 0.28) |
| **24 minute** | 15 | -0.01 | 16 | 0.27 | -0.28 (-0.97, 0.39) |
| **25 minute** | 15 | -0.01 | 16 | 0.28 | -0.29 (-0.93, 0.36) |
| **26 minute** | 11 | 0.45 | 16 | 0.21 | 0.24 (-0.23, 0.71) |
| **27 minute** | 13 | 0.34 | 16 | 0.17 | 0.18 (-0.33, 0.68) |
| **28 minute** | 12 | 0.43 | 16 | 0.30 | 0.14 (-0.36, 0.64) |
| **29 minute** | 12 | 0.37 | 16 | 0.29 | 0.08 (-0.38, 0.55) |
| **30 minute** | 13 | 0.44 | 15 | 0.30 | 0.14 (-0.36, 0.64) |
| **31 minute** | 13 | 0.45 | 14 | 0.25 | 0.20 (-0.34, 0.74) |
| **32 minute** | 13 | 0.52 | 13 | 0.35 | 0.17 (-0.44, 0.79) |
| **33 minute** | 11 | 0.52 | 12 | 0.30 | 0.22 (-0.36, 0.80) |
| **34 minute** | 11 | 0.32 | 12 | 0.19 | 0.13 (-0.45, 0.71) |
| **35 minute** | 10 | 0.60 | 12 | 0.12 | 0.48 (-0.14, 1.11) |
| **36 minute** | 9 | 0.52 | 12 | 0.19 | 0.32 (-0.26, 0.91) |

| | | | | | |
|---|---|---|---|---|---|
| **37 minute** | 8 | 0.44 | 10 | 0.11 | 0.34 (-0.33, 1.00) |
| **38 minute** | 8 | 0.42 | 10 | -0.10 | 0.52 (-0.33, 1.36) |
| **39 minute** | 8 | 0.55 | 9 | -0.31 | 0.86 (0.24, 1.49) |
| **40 minute** | 8 | 0.49 | 8 | -0.39 | 0.88 (0.06, 1.70) |
| **41 minute** | 7 | 0.69 | 9 | -0.19 | 0.86 (0.13, 1.58) |
| **42 minute** | 7 | 0.68 | 9 | -0.11 | 0.79 (0.05, 1.54) |
| **43 minute** | 6 | 0.68 | 9 | -0.18 | 0.89 (0.24, 1.53) |
| **44 minute** | 4 | 0.41 | 8 | -0.13 | 0.55 (0.05, 1.04) |
| **45 minute** | 4 | 0.45 | 8 | -0.05 | 0.50 (0.01, 0.98) |
| **46 minute** | 4 | 0.57 | 8 | 0.02 | 0.55 (0.10, 1.00) |
| **47 minute** | 3 | 0.36 | 8 | 0.01 | 0.35 (-0.24, 0.93) |
| **48 minute** | 3 | 0.38 | 7 | 0.08 | 0.30 (-0.19, 0.78) |
| **49 minute** | 3 | 0.25 | 7 | 0.19 | 0.06 (-0.44, 0.55) |
| **50 minute** | 3 | 0.10 | 7 | 0.23 | -0.13 (-0.89, 0.63) |
| **51 minute** | 3 | 0.22 | 7 | 0.33 | -0.11 (-0.89, 0.67) |
| **52 minute** | 2 | 0.24 | 6 | 0.35 | -0.12 (-1.36, 1.12) |
| **53 minute** | 3 | 0.22 | 6 | 0.47 | -0.25 (-0.87, 0.36) |
| **54 minute** | 3 | 0.44 | 5 | 0.23 | 0.22 (-0.38, 0.81) |
| **55 minute** | 3 | 0.49 | 5 | 0.21 | 0.28 (-0.13, 0.69) |
| **56 minute** | 3 | 0.49 | 5 | 0.01 | 0.48 (-0.27, 1.23) |
| **57 minute** | 2 | 0.43 | 5 | -0.14 | 0.57 (-0.25, 1.39) |
| **58 minute** | 2 | 0.57 | 5 | -0.45 | 1.02 (0.38, 1.66) |
| **59 minute** | 2 | 0.44 | 5 | -0.75 | 1.19 (0.07, 2.31) |
| **60 minute** | 2 | 0.32 | 5 | -1.14 | 1.46 (0.24, 2.68) |

Source: Adapted from Table 29 of the clinical study report. * 95% CI was calculated by the statistical reviewer based on two sample t-test.

**Figure 4: Study 007 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline**




Source: Figure 3 of Study 007 Report.

As shown in Table 9, the mean AUC of the pupil diameter was 0.16 mm for the OMS302 group and 0.22 mm for the PE group, with a treatment difference of -0.07 mm [95% CI: (-0.33, 0.19)].

**Table 9: Mean Area-under-the-Curve (AUC) Analysis of Change from Baseline in Pupil Diameter (mm) during Surgery (Subjects with Readable Video Recording)**

| | OMS302 (N=33) | PE (N=39) |
|---|---|---|
| Mean AUC[a] | | |
| n with video data | 31 | 32 |
| Mean (SD) | 0.16 (0.48) | 0.22 (0.601) |
| Median | 0.18 | 0.15 |
| Min, Max | -0.94, 1.40 | -0.88, 2.36 |
| Difference in Mean AUC | | |
| CMH weighted mean difference (SE)[b] | -0.071 (0.131) | – |
| 95% confidence interval | -0.33, 0.19 | – |

[a] AUC is calculated by the trapezoidal rule from the baseline to the last post-baseline value. Mean AUC is calculated by dividing the AUC by the duration from the baseline to the post-baseline value.
[b] CMH weighted mean difference (OMS302 – PE) is adjusted for the randomized IOL implant status.
Source: Table 13 of Study 007 Report.

Supportive analysis using repeated-measures analysis of variance (ANOVA) was conducted to estimate the mean pupil diameter change from baseline for each treatment group. The result also demonstrated that mydriasis was consistently maintained throughout surgery in both the PE and the OMS302 treatment groups

**Table 10: Repeated Measures Analysis[a] of Change from Baseline in Pupil Diameter (mm) During Surgery (Subjects with Readable Video Recording)**

| | OMS302 (N=33) | PE (N=39) |
|---|---|---|
| Mean | | |
| n with video data | 31 | 32 |
| Mean (SD) | 0.03 (0.12) | 0.07 (0.13) |
| Difference in Mean with 95% CI | -0.04 (-0.30, 0.23) | – |

[a] The repeated-measures model included the treatment group (OMS302 and PE), timepoint (as a categorical variable), and the IOL implant status (yes and no) as fixed-effect covariates.
Source: Statistical Reviewer's Analysis.

### 3.2.4.2 Postoperative Pain

Postoperative ocular pain was measured by the Alder Hey Triage Pain Score at 3, 6, 9, and 24 hours after surgery. The summary of postoperative pain scores is presented in the following table. Subjects in both treatment groups appear to have comparable average postoperative ocular Alder Hey Triage pain score; the average scores were low, less than one at 3, 6, 9, and 24 hours after surgery for both groups on a 10-point scale (Table 11 and Figure 2).

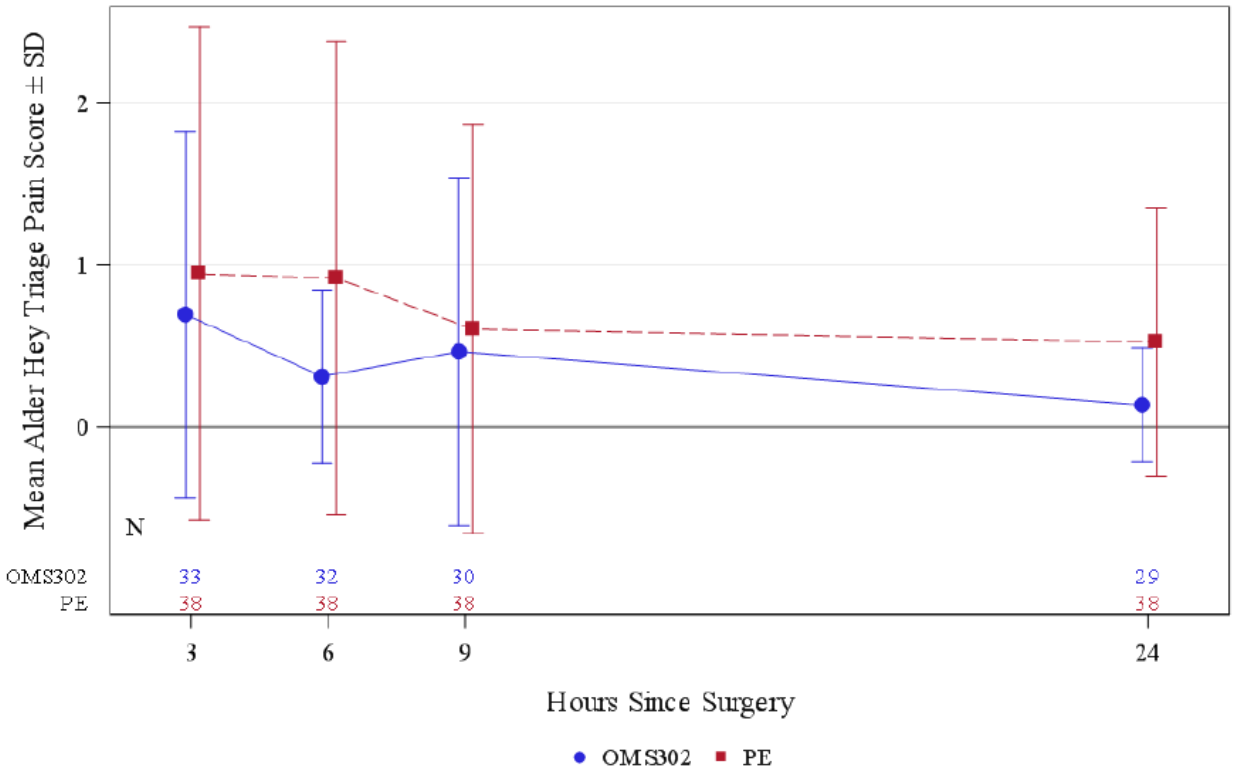
**Table 11: Study 007 Summary for Postoperative Alder Hey Triage Pain Score (Subjects with Readable Video Recording)**

| | OMS302 | | PE | | OMS302 vs. PE |
|---|---|---|---|---|---|
| **Time** | **n** | **Mean** | **n** | **Mean** | **Difference (95% CI)*** |
| **3 Hours** | 33 | 0.70 | 38 | 0.95 | -0.25 (-0.87, 0.37) |
| **6 Hours** | 32 | 0.31 | 38 | 0.92 | -0.61 (-1.11, -0.11) |
| **9 Hours** | 30 | 0.47 | 38 | 0.61 | -0.14 (-0.70, 0.42) |

| | | | | | |
|---|---|---|---|---|---|
| **24 Hours** | 29 | 0.14 | 38 | 0.53 | -0.39 (-0.68, -0.10) |

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

**Figure 5:Postoperative Alder Hey Triage Pain Score**




Source: Figure 4 of Study 007 Report.

As mentioned previously, due to the confounding effect from concomitant topical ophthalmic dexamethasone and antibiotics, and the exploratory nature of the Alder Hey Triage Pain Score, the statistical reviewer considered the results for pain to be exploratory.

## 3.3 Evaluation of Safety

Study drug administration was summarized by treatment group in the following table.

**Table 12: Study Drug Administration (Safety Population)**

| | **OMS302 (N=32)** | **PE (N=40)** |
|---|---|---|
| Total Volume of Test Irrigation Solution (mL) | | |
| n | 32 | 39 |
| Mean (SD) | 250.0 (93.2) | 279.4 (98.1) |
| Median | 237.5 | 285.0 |
| Min, Max | 110, 455 | 123, 500 |
| Study Drug Administration Duration (minutes) | | |
| n | 32 | 40 |
| Mean (SD) | 27.9 (15.4) | 30.6 (15.9) |
| Median | 22.0 | 27.5 |

| | | |
|---|---|---|
| Min, Max | 9, 55 | 9, 65 |

Source: Table 15 of Study 007 Report.

For the OMS302 group, 47% (15/32) subjects had at least one treatment-emergent adverse event (AE) reported; and for the PE group, 45% (18/40) subjects had at least one treatment-emergent adverse event reported. Among these treatment-emergent AEs, the investigators reported that 3% (1/32) was treatment-related in the OMS302 group; and 0% was treatment-related in the PE group.

There were no severe AEs reported in the PE treatment group. Three severe AEs were reported in three subjects (9% [3/32]) in the OMS302 treatment group: bronchiolitis, respiratory syncytial virus infection, and vesicoureteric reflux. All three events were considered by the investigators to be not related to study drug. There was no death during the study.

Please refer to the review of the medical reviewer for details of the safety evaluation.

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Age, Gender, Race, and Baseline GEA Score

The following table presents the mean AUC of change from baseline in intraoperative pupil diameter based on gender, race (white or non-white), and whether IOL was planned or not. In general, there were no marked differences in the efficacy results among the various subpopulations.

**Table 13: Mean AUC of Change from Baseline in Pupil Diameter Based on Gender, Race, and Planned IOL**

| | **OMS302** | | **PE** | | **OMS302 vs. PE** |
|---|---|---|---|---|---|
| | n | Mean | n | Mean | Difference (95% CI) |
| Male | 16 | 0.19 | 15 | 0.38 | -0.19 (-0.65, 0.27) |
| Female | 15 | 0.12 | 17 | 0.08 | 0.03 (-0.26, 0.33) |
| | | | | | |
| White | 24 | 0.05 | 24 | 0.25 | -0.19 (-0.21, 0.93) |
| Non-White | 7 | 0.51 | 8 | 0.14 | 0.36 (-0.49, 0.10) |
| | | | | | |
| Planned IOL (Yes) | 15 | 0.41 | 15 | 0.20 | -0.33 (-0.69, 0.04) |
| Planned IOL (No) | 16 | -0.09 | 17 | 0.24 | -0.33 (-0.15, 0.57) |

Source: statistical reviewer's analysis.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

There are no major statistical issues identified for Study 007.

In this study, nine (12.5%) subjects were excluded from the pupil diameter analyses because their video recordings during the surgery were not readable (two randomized to OMS302 [2/33, 6.1%] and seven randomized to PE [7/39, 17.9%]). The specific reasons included ruler image not captured or had incomplete identification so subject identity could not be determined. These subjects were excluded from the pupil diameter analysis because of technical issues related with video recording and not treatment-related. Therefore, the statistical reviewer concluded that excluding these subjects was unlikely to introduce any bias to the efficacy results.

Subjects in both treatment groups appeared to have comparable average postoperative ocular Alder Hey Triage pain score; the average scores were low, less than one at 3, 6, 9, and 24 hours after surgery for both groups on a 10-point scale. Since all subjects received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic post-surgery, the treatment effect of OMS302 or PE for postoperative pain was confounded with that of these concomitant medications. In addition, Alder Hey Triage Pain Score was not an Agency-validated scale for measuring pain in young children. Therefore, the statistical reviewer considered the results for pain to be exploratory in nature.

## 5.2 Collective Evidence

Both OMS302 and PE maintained mydriasis during the surgical procedures. At the baseline, the mean pupil diameter was about 7 mm in both OMS302 and PE groups. During the surgery, the mean change from baseline of pupil diameter ranged from -0.92 to 0.74 mm in the OMS302 group, and from -1.14 to 0.47 mm in the PE group. The mean AUC of the pupil diameter was 0.16 mm for the OMS302 group and 0.22mm for the PE group, with a treatment difference of -0.07 mm [95% CI: (-0.33, 0.19)].

## 5.3 Conclusions and Recommendations

In conclusion, OMS302 is effective in maintaining pupil dilution during the cataract surgery for pediatric subjects aged 0 to 3.

## 5.4 Labeling Recommendations

The applicant proposed to revise the package insert by adding the following paragraphs regarding this pediatric study to the clinical studies section in the proposed label:

> *"Study in Pediatric* (b) (4) (b) (4) *evaluated in a single, randomized, multicenter, double-masked, active-controlled clinical study in 72 pediatric* (b) (4) *undergoing cataract surgery with or without intraocular lens replacement.*
>
> (b) (4) *were randomized to either Omidria or phenylephrine.* (b) (4) *were treated with preoperative topical mydriatic and anesthetic agents.* (b) (4)

(b) (4)

(b) (4) *As in the adult studies, mydriasis was maintained in the Omidria-treated group."*

Since (b) (4) the statistical reviewer recommended to revise the two paragraphs as follows:

*"Study in Pediatric Subjects*
*The efficacy and safety of Omidria were evaluated in a single, randomized, multicenter, double-masked, active-controlled clinical study in 72 pediatric subjects aged birth through three years undergoing cataract surgery with or without intraocular lens replacement.*

*Subjects were randomized to either Omidria or phenylephrine. Subjects were treated with preoperative topical mydriatic and anesthetic agents. Pupil diameter was measured throughout the surgical procedure. As in the adult studies, mydriasis was maintained in the Omidria-treated group."*

---

**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
11/21/2017

YAN WANG
11/21/2017
I concur.