21 May 2015
EMA/CHMP/289528/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Omidria

International non-proprietary name: phenylephrine / ketorolac

Procedure No. EMEA/H/C/003702/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Omidria
Applicant:	Omeros London Limited 2nd Floor Berkley Square House London W1J 6BD UNITED KINGDOM
Active substances:	phenylephrine hydrochloride / ketorolac trometamol
International Nonproprietary Name:	phenylephrine / ketorolac
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication(s):	Omidria is indicated in adults for maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement surgery.
Pharmaceutical form(s):	Concentrate for solution for intraocular irrigation.
Strength(s):	10.2 mg/ml / 2.88 mg/ml
Route(s) of administration:	Intraocular use
Packaging:	vial (glass)
Package size(s):	10 (1 x 10) vial (multipack)

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List of abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
BCVA	Best corrected visual acuity
CELR	Cataract extraction and lens replacement
CMH	Cochran-Mantel-Haenszel
FAS	Full analysis set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ILR	Intraocular Lens Replacement
IOP	Intraocular pressure
ITT	Intention to treat
KE	Ketorolac tromethamine
LOCS II	Lens Opacities Classification System II
MedDRA	Medical Dictionary for Regulatory Affairs
NRS	Numerical Rating System
NSAID	Non-steroidal anti-inflammatory drug
PE	Phenylephrine HCl
RLE	Refractive lens exchange (i.e. no cataract present)
SAE	Serious adverse event
SOIS	Summed Ocular Inflammation Score
TEAE	Treatment-emergent adverse event
VAS	Visual Analogue Scale
BSS	Balanced salt solution
CEP	Certification of suitability of European Pharmacopoeia monographs
EDQM	European Directorate for the Quality of Medicines
CHMP	Committee for Medicinal Products for Human use
GC	Gas chromatography

GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
NMR	Nuclear magnetic resonance
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
SmPC	Summary of product characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Omeros London Limited submitted on 6 September 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Omidria, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication: maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement (ILR) in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that phenylephrine hydrochloride and ketorolac trometamol were considered to be known active substances.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0136/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0136/2013) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

At the time of submission of the application, a new application was filed in the following countries: United States of America.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Almac Sciences Limited
20 Seagoe industrial estate,
Craigavon,
BT63 5QD,
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: David Lyons Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 6 September 2013.
- The procedure started on 25 September 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 December 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 24 December 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2014.
- During the meeting on 22 January 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 March 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 April 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 8 May 2014.
- During the CHMP meeting on 22 May 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2014.
- Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 2 September 2014.
- PRAC RMP Advice and assessment overview, adopted on 11 September 2014.
- During the CHMP meeting on 24 September 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 November 2014.
- During a meeting of SAG/ ad hoc expert group meeting on 4 December 2014, experts were convened to address questions raised by the CHMP.
- Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 11 December 2014.
- PRAC RMP Advice and assessment overview, adopted on 4 December 2014.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 January 2015.
- During the CHMP meeting on 22 April 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21 May 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Omidria.

2. Scientific discussion

2.1. Introduction

Problem statement

Intraocular lens replacement (ILR) is a common surgical procedure that has a high success rate. An adequately dilated pupil is important for safe and successful procedures. Small pupils are associated with an increased risk of complications. Although complications are rare, they can impair postoperative visual acuity and threaten sight. Therefore, it is important to maintain mydriasis and prevent miosis during the procedure.

Reducing postoperative pain is an important goal. In addition, pain may cause patients anxiety about potential sight-threatening complications. Omidria was developed to address these aspects of ILR through combining into one drug product a mydriatic agent and an anti-inflammatory agent for intracameral irrigation during the procedure.

About the product

Omidria is a fixed dose combination of phenylephrine and ketorolac presented as a four mL liquid formulation to be diluted in 500 mL balanced salt solution and used as irrigation during ocular lens replacement surgery. Omidria is not a substitution therapy but is intended for use in conjunction with standard preoperative treatments.

Omidria added to standard irrigation solution provides constant concentrations of PE and KE at the target receptors and enzymes within the eye during ILR. Unlike preoperatively administered drugs (i.e. eye drops), which are washed out of the eye by the irrigation solution used during ILR, Omidria continually bathes the intraocular structures throughout surgery.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for intraocular irrigation containing phenylephrine hydrochloride equivalent to 10.2 mg/ml of phenylephrine and ketorolac trometamol equivalent to 2.88 mg/ml of ketorolac as active substances.

After dilution of 4 ml of concentrate for solution for intraocular irrigation in 500ml of irrigation solution, the solution contains 0.081 mg/ml of phenylephrine and 0.023 mg/ml ketorolac.

Other ingredients are: citric acid monohydrate, sodium citrate dihydrate, sodium hydroxide and/or hydrochloric acid and water for injection.

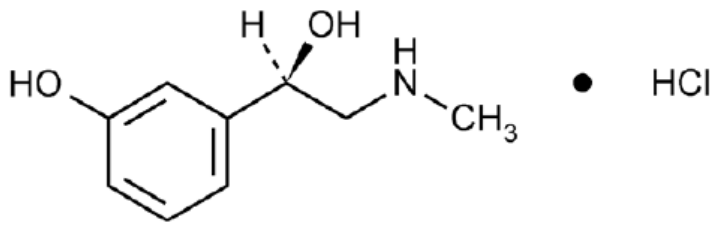
The product is available in a colourless 5-ml type-I glass vial closed with a butyl rubber stopper and a polypropylene flip-off cap.

2.2.2. Active Substance

Phenylephrine hydrochloride

General information

The chemical name of phenylephrine hydrochloride is 3-[(1*R*)-1-hydroxy-2-(methylamino) ethyl] phenol hydrochloride and it has the following structure:



Phenylephrine hydrochloride is a white or almost white, crystalline powder, freely soluble in water and ethanol. It exhibits stereoisomerism due to the presence of one chiral centre.

As there is a monograph of phenylephrine hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes the requirements of Ph. Eur. monograph for phenylephrine hydrochloride and also includes an additional test and limit for the relevant solvents used in its manufacture.

The active substance specification includes tests for: colour, appearance, clarity (Ph. Eur.), colour of solution (Ph. Eur.), identification (IR, specific optical rotation, melting point, chloride reaction) (Ph. Eur.), phenylephrine hydrochloride assay (titration), acidity or alkalinity, related substances (HPLC), residual solvents (GC), inorganic impurities (sulphated ash), sulphates (Ph. Eur.), loss on drying (Ph. Eur.), total aerobic microbial count and total combined molds and yeast count (Ph. Eur.).

The analytical methods used have been adequately described and are compendial or part of the EDQM CEP.

Batch analysis data on five batches of the active substance tested by both the active substance supplier and the finished product manufacturer are provided. The results are within the specifications and consistent from batch to batch.

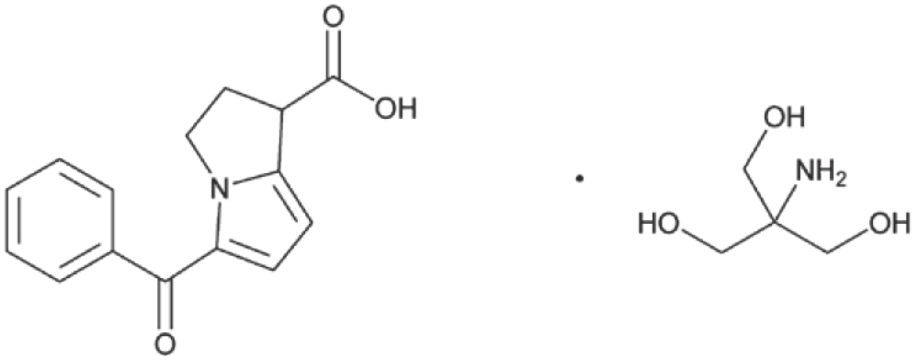
Stability

Reference is made to the CEP which described the proposed retest period in the proposed container.

Ketorolac trometamol

General information

The chemical name of ketorolac trometamol is 2-amino-2-(hydroxymethyl) propane-1,3-diol; 5-benzoyl-2, 3-dihydro-1H-Pyrrolizine-1-carboxylic acid and it has the following structure:



Ketorolac trometamol is a white to off-white, crystalline powder, freely soluble in water and methanol, slightly soluble in alcohol and tetrahydrofuran and practically insoluble in acetone, dichloromethane, toluene, ethyl acetate, dioxane, hexane, butyl alcohol and acetonitrile.

As there is a monograph of ketorolac trometamol in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes the requirements of Ph.Eur. monograph for Ketorolac trometamol and also includes additional tests and limits for the relevant solvents used in its manufacture.

The active substance specification includes tests for: colour, appearance, clarity of solution (Ph. Eur.), colour of solution, identification (IR, UV) (Ph. Eur.), assay (titration) , related substances (HPLC), residual solvents (GC), inorganic impurities (sulphated ash) (Ph. Eur.), heavy metals (Ph. Eur.), pH of solution (Ph. Eur.), loss on drying(Ph. Eur.), , total aerobic microbial count and total combined molds and yeast count. (Ph. Eur.)

The analytical methods used have been adequately described and are compendial or part of the EDQM CEP.

Batch analysis data on four batches of the active substance tested by both the active substance supplier and the finished product manufacturer are provided. The results are within the specifications and consistent from batch to batch.

Stability

Reference is made to the CEP which described the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The development section of the drug product presented is extensive, and all aspects of the drug product development have been well covered. It describes the rationale for the use of two well-known active substances not previously used in fixed dose combination, and includes drug-drug interaction studies, a justification of the container closure system selected and compatibility studies with the proposed diluents: balanced salt solution (BSS) and balanced salt solution plus (BSS Plus). Critical product quality attributes that are likely to affect product safety and efficacy are identified and all are common for this type of product, i.e. identification, assay, purity, sterility, bacterial endotoxins.

Since the product is intended to be used as irrigation solution during ocular surgery, sterility of the finished product was considered critical and the use of a sterilisation method providing the highest SAL possible was considered necessary. The originally proposed manufacturing process involved sterilising filtration and aseptic filling. However the CHMP considered that the choice of the sterilisation method was not in accordance with the Note for guidance "Decision trees for the selection of sterilisation methods" CPMP/QWP/054/98. As a result, the feasibility of terminal sterilisation was further investigated by the applicant with particular focus on the product stability, potency and impurity profile. Based on the results from this study and on a computational toxicology evaluation, a terminal sterilisation method was considered feasible, and was therefore implemented in the proposed manufacturing process.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A 10% overfilled is used in the manufacturing process and is considered justified to ensure target extractable volume of minimum 4 ml.

The primary packaging is a colourless 5-ml type-1 glass vial closed with a butyl rubber stopper and a polypropylene flip-off cap. The materials of the components comply with Ph.Eur. requirements. The choice of

the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of a sterile filtration of the compounded bulk formulation, aseptic filling into a pre-sterilized container closure system, followed by terminal sterilization using a validated steam sterilisation cycle (15 minutes at 121°C) in accordance with Ph. Eur. 5.1.1. The process is considered to be a standard manufacturing process. Filtration and filling are defined as critical steps.

Major steps of the manufacturing process have been validated by a number of studies. Three full scale batches were used to validate the manufacturing process up to the point of terminal sterilisation and two batches were used to validate the terminal sterilisation. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The release finished product specifications include appropriate tests for this kind of dosage form. It includes tests for colour (Ph. Eur.), appearance, volume (Ph. Eur.), subvisible particulate matter (Ph. Eur.), identification (HPLC and diode array), phenylephrine HCl assay (HPLC), ketorolac trometamol assay (HPLC), related substances (HPLC), pH of solution (Ph. Eur.), osmolality (Ph. Eur.), sterility (Ph. Eur.), container closure integrity (helium leak-vacuum mode) and bacterial endotoxins (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guideline.

Batch analysis results are provided for three full scale production batches, two clinical batches and three primary stability batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three production scale batches of finished product sterilised by filtration and stored under long term (25 ºC / 60% RH) and intermediate conditions (30 °C / 75% RH) for 24 months and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Stability data of two pilot scale batches of finished product terminally sterilised using a Ph. Eur. steam sterilisation cycle (15 minutes at 121°C) and stored under long term (25 ºC / 60% RH), intermediate (30 °C / 75% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Samples were tested for description, assay, degradation products, pH of solution, osmolality, subvisible particulate matter, sterility, container closure integrity, and bacterial endotoxin. The analytical procedures used are stability indicating.

Stability results comply with the specifications. Based on the long term stability data of both aseptically manufactured and autoclaved finished product batches, the levels of impurities observed for autoclaved stability batches are not expected to exceed the shelf-life specification limit and it is expected that the stability of autoclaved batches will be similar to the stability of aseptically manufactured finished product batches.

In addition, one primary stability batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study concluded that the drug product is subject to photodegradation and requires protection from light.

The product is a concentrate so a dilution is required. Dilution should be performed immediately after opening so no stability data on the opened concentrate vial is required.

In-use shelf-life after dilution was validated by compatibility studies with the proposed diluents: balanced salt solution (BSS) and balanced salt solution plus (BSS Plus). Results showed that the diluted solution is chemically stable for up to 24 hours under ambient temperature and light and, for up to one hour in stainless steel reservoir and syringe administration aids under ambient temperature and light conditions. The following statement is included in the SmPC : "After dilution, chemical and physical in-use stability has been demonstrated for 6 hours at 25°C. Use within 6 hours of dilution. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user."

Based on available stability data and the applicant commitments to continue the stability studies on the two pilot scale batches of finished product terminally sterilised using Ph. Eur. steam sterilisation cycle (15 minutes at 121°C) and, to provide updated stability data, as well as to immediately inform competent authorities in case of any out-of-specifications results, the shelf-life of 18 months and the storage conditions "Do not store above 25°C. , Keep the vial in the outer carton in order to protect from light. , Following dilution do not store above 25°C" are acceptable and included in the SmPC .

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Since the product is intended to be used as irrigation solution during ocular surgery, sterility of the finished product was considered critical and the use of a sterilisation method providing the highest SAL possible was considered necessary. The originally proposed manufacturing process involved sterilising filtration and aseptic filling. However the CHMP considered that the choice of the sterilisation method was not in accordance with the Note for guidance "Decision trees for the selection of sterilisation methods" CPMP/QWP/054/98. As a result, the feasibility of terminal sterilisation was further investigated by the applicant with particular focus on the product stability, potency and impurity profile. Based on the results from this study and on a computational toxicology evaluation, a terminal sterilisation method was considered feasible, and was therefore implemented in the proposed manufacturing process. Based on available stability data and the applicant commitments to continue the stability studies on the two pilot scale batches of finished product terminally sterilised using Ph. Eur. steam sterilisation cycle (15 minutes at 121°C) and, to provide updated stability data by the agreed timeframe, as well as to immediately inform the Competent Authorities in case of any out-of-specifications results, the shelf-life and the storage conditions as stated in the SmPC are considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant should complete the stability studies on the two pilot scale batches of finished product sterilized by steam sterilisation cycle (15 minutes at 121°C) and submit updated stability data by the agreed timeframe. In addition, the applicant should immediately inform the Competent Authorities in case of any out-of-specification result.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development programme for Omidria was abridged and focused on the investigation of the systemic exposure and primary pharmacodynamics following administration during ILR surgery and the examination of the topical effects in toxicology testing.

Both components have been on the market for several years and have well established profiles. Phenylephrine (PE) and ketorolac trometamol (KE) both have a long history of use as topical agents in ophthalmology and there is a significant body of literature on their individual clinical pharmacology. The applicant's non-clinical program of studies in this application relied on the historical data as well as nonclinical studies conducted with Omidria. Four main nonclinical studies were conducted including a GLP study of Omidria in African green monkeys to evaluate safety and toxicity of the combination of PE and KE in irrigation solution.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics of Omidria was evaluated in three *in vivo* studies performed in African green monkeys undergoing ILR surgery that closely mimics the procedure that is performed in humans. Pharmacodynamic endpoints were also measured as part of the single dose GLP toxicity study. The primary endpoints measured were the degree of mydriasis and flare count measured by laser photometry (a measure of anterior chamber inflammation) following the addition of PE and KE to the irrigation solution used during the surgical procedure. These studies resulted in rapid pupil dilation which exceeded that obtained by preoperative topical 1% tropicamide where the PE concentrations achieved were between 268 µM and 1165 µM. KE alone had no effect on the induction of mydriasis. KE alone reduced postoperative flare counts at concentrations between 10 and 30 µM. These studies provide evidence of efficacy for the use of PE and KE in combination.

Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were not performed. In view of the minimal and transient systemic exposure observed under treatment with Omidria, the risk of secondary pharmacodynamic effects is considered to be negligible. This was accepted by the CHMP.

Safety pharmacology programme

According to ICH S7A guideline 'safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low'. As these conditions were met for Omidria, no safety pharmacology studies were conducted.

Pharmacodynamic drug interactions

Based upon their known pharmacological properties, a pharmacodynamics drug interaction between PE and KE is not anticipated.

2.3.3. Pharmacokinetics

Systemic exposure of PE and KE was examined in African green monkeys following anterior chamber irrigation in two pharmacology studies (Study RX06.02 & Study RX07.03) and in one GLP single dose toxicity study (Study RX07.07). The systemic exposure for both compounds was generally low and transient if measurable at all in the case of PE. The highest plasma concentration of 14.9-38.3 ng/ml PE and 72.2-198.3 ng/ml KE were measured in the high dose group (7200 µM PE and 900 µM KE) in the single dose GLP toxicity study (Study RX07.07) after immediate completion of the irrigation of the eye.

No distribution, metabolism, excretion or other pharmacokinetic studies were conducted and their absence was considered acceptable by the CHMP as the systemic exposure to PE and KE observed following anterior chamber irrigation is minimal.

2.3.4. Toxicology

Single dose toxicity

Administration of solutions containing PE and KE into the anterior chamber of the eye in African green monkeys showed no adverse treatment effects per se. Higher flare values observed in the mid-dose group (2160 µM PE; 270 µM KE) were considered related to the greater degree of surgical trauma. Flare values were comparable between all other groups, vehicle, low-dose (720 µM PE; 90 µM KE) and high-dose (7200 µM PE; 900 µM KE). AST elevations were considered related to surgical intervention and repeated ketamine sedation as they were found in both sexes in all treatment groups including vehicle group and returned to baseline by 11-14 days. No test article-related gross abnormalities or histopathological findings were observed following necropsy in the tissues collected (heart, lungs, spleen, liver, kidneys, brain, eyes, and optic nerves) and other organs and tissues inspected. Histopathological findings observed in the eye were consistent with lens replacement surgery. The NOAEL was established at the highest dose tested (7200 µM PE; 900 µM KE). This represent a 6.2 safety margin of clinical PE exposure and a 4.2 safety margin of clinical KE exposure based on a maximum anticipated clinical dose of OMS302 diluted in 500 mL irrigation solution (480 µM PE; 89 µM KE).

Electrocardiograms (ECGs), heart rate, respiratory rate, oxygen partial pressure and rectal temperature were measured during the surgical procedure. There were no significant changes in intraoperative respiratory rate and oxygen partial pressure. Intraoperative heart rate and rectal temperature decreased in all groups. Since these effects were also observed in the control group, the drop in heart rate and body temperature was likely to be due to the surgery and anaesthesia. Cardiac rhythm was normal during surgery.

Repeat dose toxicity

Repeat dose toxicity studies were not performed.

Genotoxicity

While no genotoxicity studies were performed with OMS302, data presented for PE and KE alone shows a very low genotoxic potential for both active ingredients.

Carcinogenicity

Carcinogenicity studies were not performed with Omidria as they are not required for a medicinal product intended for single use. The CHMP accepted this justification.

Reproduction Toxicity

No repeat dose toxicity or reproductive and developmental toxicity studies were conducted and their absence was considered acceptable by the CHMP given the low systemic exposure of Omidria. Given the limited reproductive and developmental data, Omidria is not recommended during pregnancy and in women of childbearing potential not using contraception and should not be used during breast-feeding. These warnings have been adequately highlighted in section 4.6 of the SmPC.

Toxicokinetic data

Study RX07.07 was GLP compliant toxicokinetic study. Five out of 48 measurements had non-zero plasma level at baseline and an unacceptably high PE concentration was observed at 24h.

Local Tolerance

The local tolerance of OMS302 was assessed in the single-dose toxicology study (Study RX07.07). There were no drug-related adverse local tolerance findings.

Other toxicity studies

An additional GLP-compliant rabbit ocular toxicity study was conducted to evaluate the effect on corneal endothelium. In this study Omidria was diluted in balanced salt solution to the diluted clinical concentration and administered by intracameral injection into one eye, and vehicle control was injected into the contralateral eye. In this study, eight female New Zealand White rabbits were evaluated by a board-certified veterinary ophthalmologist every four weeks during a 12-week post-dose observation period. At the end of the 12-week post-dose observation period, the ocular tissues were collected for microscopic evaluation by a board-certified veterinary pathologist. No treatment-related effects on the cornea were observed.

2.3.5. Ecotoxicity/environmental risk assessment

The predicted environmental concentration in the surface water (PECsurfacewater) of PE and KE was calculated based on a dose of 49.5mg and 17 mg, respectively, to be below the action limit of 0.01 µg/L. For this calculation, the Fpen was refined based on the estimated number cataract surgeries from a recent OECD

analysis evaluating data for European countries in 2010. Furthermore, PE and KE are not PBT (persistent, bioaccumulative and toxic) substances as log Kow does not exceed 4.5. Therefore, the CHMP concluded that Omidria was not expected to pose a risk to the environment.

Table 1. Summary of main study results

Substance (INN/Invented Name): Phenylephrine HCl (PE), Ketorolac trometanol (KE)			
CAS-number (if available): PE:61-76-7 KE: 74103-07-4			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	KE: -0.27; PE: -0.31	not B
	BCF	-	
Persistence	DT50 or ready biodegradability	-	not P
Toxicity	NOEC or CMR	-	not T
PBT-statement :	The compound is not considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)		KE: 0.0013 μg/L PE: 0.00044 μg/L	below 0.01 μg/L threshold

2.3.6. Discussion on non-clinical aspects

Non-clinical pharmacology studies show that use of Omidria results in rapid pupil dilation that exceeded that obtained by preoperative topical 1% tropicamide, where the PE concentration achieved concentrations between 268 μM and 1165 μM. KE alone had no effect on the induction of mydriasis. KE alone reduced postoperative flare at concentrations between 10 and 30 μM, and a trend towards reduced flare was seen in study RX07.03 but did not reach statistical significance when KE and PE were added in combination (OMS302). Conclusions on flare reduction and reduction on postoperative inflammation could not be made in study RX07.07 given the lack of concentration dependent effects. The applicant considered that these findings possibly reflected greater surgery-associated trauma that occurred in the mid dose group, where no effects on flare measures were seen.

These studies provide some evidence of efficacy for the use of PE and KE in combination and further enhance the well characterised pharmacological profiles of both the individual components within an ophthalmic setting.

The absence of secondary and safety pharmacology studies was considered acceptable by the CHMP owing to the low and transient systemic exposure of PE and KE during irrigation with Omidria. Furthermore, no adverse effects on vital functions were seen in the GLP single dose toxicity study. Pharmacodynamic drug interactions are not expected due to low and transient systemic exposure.

The PK and TK results of were considered difficult to interpret given the insensitive nature of the PE analytical assay, the unexplainable and aberrant spurious observations (e.g. high concentrations at baseline) and lack of consensus of results between studies. The reported pharmacokinetic concentrations fluctuated in a very wide range and did not show any reasonable pattern. The CHMP has requested the Applicant to discuss the probable causes of these errors. The applicant has provided results of a reanalysis of samples drawn in study RX07.06 and RX07.07 but the root cause of the high pharmacokinetic concentrations fluctuations observed in these studies have not been resolved. However, the lack of overt toxicities seen with within these studies alleviated the CHMP concerns surrounding PK anomalies.

Maximum plasma concentrations of PE observed in the pharmacokinetic studies performed with Omidria showed comparable exposures with other ophthalmological formulations. However when compared to oral formulations, it appeared that the systemic exposure of the low dose PE in monkeys (Study RX07.07) was approximately 5-fold and 4- fold higher than exposures observed in fed and fasted patients with a 10 mg oral dose. Following the CHMP request, the applicant discussed these results in more detail and provided IV data to qualify the low intraocular systemic exposures for PE. While the systemic concentration of PE appear to be higher in monkeys compared to exposure in fed and fasted patients with a 10 mg dose and with healthy volunteers administered a short IV infusion (albeit at the high dose only), this was found by the CHMP to not to be a cause for concern due to absence of overt toxicities seen in this single dose toxicity study.

The CHMP also noted that Omidria is a fixed-dose combination product with well-known active substances. Therefore the requirements set by the Guideline on Clinical Development of Fixed Combination Medicinal Products (Doc. Ref. CHMP/EWP/240/95 Rev. 1) are applicable. This Guideline does not require per se carrying out toxicological studies provided that reasonable justification is given for waving safety concerns. The CHMP was of the opinion that there are no safety concerns in this regard because clinical studies confirmed that systematic absorption of the active substances is minimal. A comparison of the maximal plasma concentrations observed in non-clinical studies with levels determined in the clinical pharmacokinetic study demonstrated that the values in human subjects were considerably below those noted in monkeys at the NOAEL (7200 µM PE and 900 µM KE). The NOAEL represents a 6.2-fold multiple of clinical PE exposure and a 4.2-fold multiple of clinical KE exposure based on a maximum anticipated clinical dose of OMS302 diluted in 500 mL irrigation solution (480 µM PE; 89 µM KE). Relative to the concentrations of PE and KE in OMS302 for clinical use, the concentrations at the NOAEL represent 15-fold and 10-fold higher multiples for PE and KE, respectively.

The absence of any overt adverse effects related to the test article at any dose in the single dose toxicity study supports the local safety and tolerability of Omidria. Systemic exposure to PE and KE in the single-dose toxicity study increased with increasing PE/KE concentrations in the irrigation solution, but was generally low and transient. Based on this data, the CHMP considered risk of systemic side effects due to circulating PE and or KE levels to be negligible.

The CHMP accepted the lack of any further toxicity studies because the intended clinical use of the drug product is limited to a single surgical intervention. Both active ingredients are well-known thus it was accepted by the CHMP that publicly available data was used to summarize the toxicological profile of both active ingredients.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data were considered appropriate to support the proposed clinical use of Omidria.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Four clinical studies were performed in the OMS302 clinical development program (Table 1). These studies included one Phase 1/2 exploratory study designed to evaluate safety and potential efficacy endpoints for future studies (Study C07-005), one factorial study designed to evaluate the separate contributions of PE and KE to the proposed indication (Study C09-001), and two confirmatory Phase 3 safety and efficacy studies (Studies OMS302-ILR-003 and OMS302-ILR-004). Study OMS302-ILR-004 included a pharmacokinetics substudy.

- Tabular overview of clinical studies

Table 2: Study Design of Clinical Efficacy and Safety Studies

Study No. (Location)	**Design**	**Treatment Regimen**	**No. Patients**
C07-005 (U.S.)	Phase 1/2, randomized, controlled, double-masked, multicentre, exploratory study of the clinical benefit and safety of OMS302 in subjects undergoing unilateral CELR.	Subjects were randomized 1:1:1 to: • OMS302 (483 µM PE and 60 µM KE changed from 714 µM PE and 89 µM KE by amendment) • PE (483 µM changed from 714 µM by amendment) or • Vehicle (BSS). Administered in irrigation solution during CELR; the follow-up period was 28 days.	60
C09-001 (U.S.)	Phase 2, randomized, parallel-group, double-masked, vehicle-controlled factorial study in subjects undergoing CELR.	Subjects were randomized 1:1:1:1 to: • OMS302 (483 µM PE, 89 µM KE) • PE (483 µM) • KE (89 µM) • Vehicle (BSS). Administered in irrigation solution during CELR; the follow-up period was 30 days.	222
OMS302-ILR-003 (U.S.)	Phase 3, randomized, parallel-group, double-masked, placebo-controlled study in subjects undergoing CELR or RLE.	Subjects were randomized 1:1 to: • OMS302 (483 µM PE, 89 µM KE) or • Placebo (BSS containing sodium citrate). Administered in irrigation solution during ILR; the follow-up period was 14 days.	402
OMS302-ILR-004 (U.S. and the Netherlands)	Phase 3, randomized, parallel-group, double-masked, placebo-controlled study in subjects undergoing CELR or RLE.	Subjects were randomized 1:1 to: • OMS302 (483 µM PE, 89 µM KE) or • Placebo (BSS containing sodium citrate). Administered in irrigation solution during ILR; the follow-up period was 90 days.	406

Patient base: Patients who received at least one application of study medication. BSS: balanced salt solution; CELR: cataract extraction with lens replacement; ILR: intraocular lens replacement; RLE: refractive or clear lens exchange; PE: phenylephrine hydrochloride; KE: ketorolac trometamol.

2.4.2. Pharmacokinetics

Absorption

In the pharmacokinetic sub-study of Study OMS302-ILR-004, 1 of 14 patients had detectable PE: this patient (190063) was assigned to OMS302. The patient's pre-treatment sample, immediately following instillation of topical PE pre-medication had a phenylephrine concentration of 1.7 ng/mL decreasing after Omidria administration to 1.3 ng/mL during the first two hours and undetectable at later time points. Since the highest PE concentration was observed prior to OMS302 administration, it presumably has been due to absorption of the preoperative PE 2.5% eye drops.

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

Distribution and elimination

As there is no or minimal systemic absorption, distribution and elimination have not been studied.

Pharmacokinetic interaction studies

No interaction studies were performed.

Pharmacokinetics using human biomaterials

Not applicable

2.4.3. Pharmacodynamics

No specific pharmacology studies were conducted with Omidria since both phenylephrine and ketorolac are well-known active substance for which the mechanism of actions has already been well-described in the scientific literature.

Mechanism of action

The phenylephrine and ketorolac in Omidria act by distinct mechanisms, to maintain intraoperative mydriasis, to prevent intraoperative miosis, and to reduce acute postoperative pain. Phenylephrine is an α1-adrenergic receptor agonist and acts as a mydriatic agent by contracting the radial muscle of the iris, dilating the pupil with little or no cycloplegia. Vasoconstriction occurs in the conjunctival circulation and in other ocular vessels to the extent that they are exposed to drug.

Ketorolac is an NSAID that inhibits both cyclooxygenase enzymes (COX1 and COX2), reducing pain and inflammation by decreasing tissue concentrations of prostaglandins resulting from surgical trauma. Ketorolac, by inhibiting prostaglandin synthesis secondary to ocular surgical insult or direct mechanical stimulation of the iris, may also contribute to the prevention of surgically induced miosis.

Primary and Secondary pharmacology

No specific pharmacology studies were conducted with Omidria since both phenylephrine and ketorolac are well-known active substance for which the mechanism of actions has already been well-described in the scientific literature.

When administered systemically, the cardiovascular pharmacology of PE is characterized by increased blood pressure secondary to increased vascular resistance, and a concomitant reflex reduction in heart rate (Hoffman, 2001).

A meta-analysis of nine clinical studies indicated that increases in systolic pressure of up to 20 mmHg, increases in diastolic pressure of up to 15 mmHg; and decreases in heart rate of up to 10-15 beats per minute (bpm) could occur at plasma levels of 10 ng/mL, but that the predicted changes in blood pressure and heart rate at plasma levels below 2 ng/mL was close to zero (FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee, 2012).

The PD effects of topical ophthalmic PE were assessed by blood pressure monitoring in two studies. In the first study (Kumar, 1985) of 24 patients undergoing vitreoretinal surgery randomised to receive two drops of either 2.5% aqueous or 10% viscous ophthalmic solutions of PE, the maximal mean increase in systolic blood pressure (SBP) was 6 mmHg in the 2.5% solution group and 19 mmHg in the 10% solution group. The maximal mean increase in diastolic blood pressure (DBP) was 10 mmHg in the 2.5% solution group and 18 mmHg in the 10% solution group; the difference between groups was not statistically significant. There was no correlation between the plasma PE level and change in blood pressure.

In the second study (Kumar, 1986) 30 patients undergoing vitreoretinal surgery were randomised to receive two drops of either 2.5% aqueous or 2.5% viscous ophthalmic solutions of PE. The hemodynamic results showed that mean SBP and DBP were increased by approximately 10 mmHg (range 8 to 13) compared to preoperative values at ten minutes after PE application in both treatment groups, and these values returned to near baseline by 30 minutes. There was no correlation between the plasma PE level and change in blood pressure in this study.

2.4.4. Discussion on clinical pharmacology

The systemic absorption of phenylephrine following administration of OMS302 is minimal to non-existent. Ketorolac does appear to be absorbed in detectable quantities. The CHMP was of the opinion that the applicant's explanation for the unexpectedly high levels of ketorolac in two patients was plausible.

The CHMP concluded that the data from patient 179011 were anomalous and the data from the patient with the next highest Cmax should be included instead in the SmPC section 5.2.

Following a request from the CHMP, the applicant has provided a discussion of the effect of phaco fluid dynamic settings and phaco time on the exposure to PE and KE.

As only one subject had detectable PE plasma concentrations, there were not sufficient data to analyse the effect of phaco fluid dynamic settings or phaco time on the systemic exposure to PE. The effect of surgical variables on the systemic exposure to ketorolac was evaluated.

Data on the fluid dynamic settings of the phacoemulsification machine were not collected. Therefore, the effect of the fluid dynamic settings on the exposure to KE cannot be analysed. However, data are available on the total volume of irrigation solution used during the procedure and the total duration of irrigation solution administration. The effect of both of these variables on systemic KE exposure was evaluated. The available data indicate a wide scatter between ketorolac exposure and volume of irrigation fluid, duration of irrigation, and phaecoemulsification time and no firm conclusions can be made on this basis.

The CHMP noted that the published studies which compared the PK and hemodynamic effects of different formulations of PE were not designed to address the potential haemodynamic effects of PE since the difference in pre- and post-administration blood pressure may have been due to other factors, such as other medications or the surgical procedure.

As this is a class effect of sympaticomimetics, a warning about elevations of blood pressure has been included in Section 4.4 of the SmPC. Further discussion of potential risks associated with systemically absorbed phenylephrine can be found in Discussion on clinical safety section of this report.

The CHMP asked the Applicant to discuss the potential for PK and PD interaction with other topical medications used perioperatively.

Both components of OMS302 (phenylephrine and ketorolac) have been used topically for decades in ILR surgery. Despite this widespread use drug interactions have not been reported between either PE or KE and any ophthalmological medications. Therefore the potential for unwanted pharmacokinetic or pharmacodynamic interactions between OMS302 and topical medications used perioperatively is small.

It was also noted that OMS302 was used in the clinical trial programme as an addition to other medications used during eye surgery. Concomitant medications actually used on the eye on the day of surgery in the non-clinical and clinical studies (in the OMS302 treatment group) included local anesthetics, α1-adrenergic receptor agonists, anticholinergics, NSAIDs, corticosteroids, glaucoma medication and antimicrobial agents and cholinergic miotic agents.

The CHMP agreed that although unexpected drug-drug interactions are theoretically possible from the use of a novel combination they appear to be highly unlikely given the well-known nature of the active substances.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the view that the available information in the scientific literature as well the PK data collected in the clinical trials were sufficient to support the application for Omidria from a clinical pharmacology perspective. Given the local route of administration and that no significant systemic exposure was observed, the CHMP considered that the lack of specific pharmacodynamics or pharmacokinetic studies was acceptable.

2.5. Clinical efficacy

The Applicant has conducted four clinical studies in support of the authorisation of OMS302. Study CO9-001 evaluated the safety and efficacy of OMS302 against vehicle and against PE alone and KE alone (in

compliance with the EMA/CHMP fixed combination regulatory guidance). Studies OMS302-ILR-003 and OMS302-ILR-004 were Phase III safety and efficacy comparisons to vehicle (placebo).

2.5.1. Dose response study

The optimal concentrations of PE and KE in the OMS302 irrigation solution were determined on the basis of nonclinical and clinical data. Three nonclinical studies evaluated the effect of PE on pupil diameter in African green monkeys. The no observed adverse effect level (NOAEL) values were 7200 µM PE and 900 µM KE. The data concluded that the maximally effective PE concentration is at least 268 µM (Study RX07.06) and no more than 720 µM (Study RX07.07).

The Phase 1/2 exploratory study C07-005 was a pilot study of Omidria without ocular pre-medication at concentrations of 714 µM PE and 89 µM KE. This did not give acceptable mydriasis and the study protocol was revised to provide ocular pre-medication and a less concentrated irrigation fluid of PE and KE of 483 µM and 60 µM, respectively. The amended protocol KE concentration of 60 µM was ineffective on ocular pain in the early postoperative period so 89 µM was used in the remainder of the clinical programme.

Concentrations of PE above and below this have not been explored which is acceptable in view of the likelihood of a flat dose response curve and the invasive nature of the surgery required for the dose-response evaluation.

2.5.2. Main studies

Study OMS302 ILR-003: Phase III Randomised, Double-Masked, Placebo-Controlled Study of the Effect of OMS302 on Intraoperative Pupil Diameter and Early Postoperative Pain in Patients Undergoing Intraocular Lens Replacement with Phacoemulsification

Methods

Study Participants

Eligible patients fulfilled the following principal inclusion criteria; were 18 years of age or older at the time of surgery, were to undergo unilateral primary CELR or RLE, under topical anaesthesia, with a coaxial phacoemulsification device with insertion of an acrylic lens, BCVA of 20/400 or better in the non-study eye, have an intraocular pressure (IOP) between 5 mm Hg and 22 mm Hg, in the study eye. For women of childbearing potential, have a negative urine pregnancy test and use a specified in the trial forms of contraception.

The principal exclusion criteria were the presence of hypersensitivity (including cross-sensitivity) to relevant medications and the presence of significant ocular or general medical conditions.

Treatments

Omidria was supplied as a sterile, clear solution containing 60.75 mM phenylephrine HCl (12.37 mg/mL) and 11.25 mM ketorolac tromethamine (4.24 mg/mL) formulated in a 20 mM sodium citrate buffer. Placebo was a sterile, clear solution containing 20 mM sodium citrate buffer.

Objectives

Primary:

- Evaluate the effect of OMS302 compared to placebo when administered in irrigation solution during phacoemulsification and intraocular lens replacement on intraoperative pupil diameter.

Secondary:

Evaluate the effect of OMS302 compared to placebo when administered in irrigation solution during phacoemulsification and intraocular lens replacement on:

- Pain during the early postoperative period as measured by Visual Analog Scale (VAS)
- Postoperative photophobia as measured by the photophobia subscale of the Numerical Rating System (NRS)
- Postoperative best-corrected visual acuity (BCVA)
- Postoperative inflammation as measured by Summed Ocular Inflammation Score (SOIS)
- Pain after the early postoperative period
- Safety as measured by adverse events (AEs).

Outcomes/endpoints

Primary:

• To evaluate the effect of OMS302 compared to placebo on the change in pupil diameter over time from surgical baseline to the end of surgery when administered in irrigation solution during phacoemulsification and intraocular lens replacement.

Secondary:

- Postoperative pain at 2, 4, 6, 8, and 10 to 12 hours as measured by Visual Analogue Scale (VAS)
- Postoperative photophobia as measured by the photophobia subscale of the Numerical Rating Scale (NRS)
- Postoperative best-corrected visual acuity (BCVA)
- Postoperative inflammation as measured by Summed Ocular Inflammation Score (SOIS) at 24, 48 hours, and at seven and fourteen days.
- Pain after the early postoperative period (up to fourteen days).
- Safety as measured by adverse events (AEs).

Sample size

The sample size to support the ocular pain endpoint was 200 patients per treatment arm, based on a t-test at the 0.05 two-sided level of significance, a difference between the treatment arms [in VAS] of 5.0 mm with s.d. 13.3 mm, gave a 96% power to detect the treatment difference. The sample size to support the pupil diameter was based on a t-test at a 0.05 two-sided level of significance an treatment difference of 0.6 mm

with s.d. 0.7 mm; this gives > 99% power to detect the treatment difference. The mean treatment differences and standard deviations for the sample size were taken from Study C09-001.

Randomisation

Patients were randomised 1:1 to OMS302 or placebo; randomisation was stratified within site by Cataract Lens Opacities Classification System II.

Blinding (masking)

A masked central reader performed the pupil size measurements.

To maintain masking, the bottles of irrigation solution were prepared by an unmasked pharmacist or designee who was not otherwise involved in the study. An unmasked pharmacy clinical research associate monitored the pharmacy. All other study personnel remained masked throughout the study. No subjects were unmasked during the study.

Statistical methods

All statistical analyses were performed using SAS version 9.2 or later. Study endpoints were summarised with descriptive statistics for continuous variables, and frequencies and percentages for categorical variables. All statistical tests were performed at the two-sided 5% significance level. All confidence intervals were constructed at the two-sided 95% confidence level.

Analysis Populations

Enrolled Population All patients who completed the informed consent. The Full Analysis Set (FAS) included all randomised patients who received study medication. It was expected that all randomised patients were to be included in the FAS but, consistent with the intention-to-treat principle patients not starting treatment were excluded from the FAS.

The Safety Population All randomised patients who received study medication. Patients were grouped by the actual treatment received. Should a patient receive two or more different treatments, they were summarised within the treatment group for which they received the most treatment.

Per-protocol population All patients in the FAS population who had no significant protocol deviations that could complicate interpretation of the efficacy and/or safety. The analyses of the efficacy endpoints were based on the FAS population. All safety analyses were based on the SP.

Sample size and analysis

The sample size to support the ocular pain endpoint was 200 patients per treatment arm, based on a t-test at the 0.05 two-sided level of significance, a difference between the treatment arms [in VAS] of 5.0 mm with s.d. 13.3 mm, gave a 96% power to detect the treatment difference. The sample size to support the pupil diameter was based on a t-test at a 0.05 two-sided level of significance an treatment difference of 0.6 mm with s.d. 0.7 mm; this gives > 99% power to detect the treatment difference. The mean treatment differences and standard deviations for the sample size were taken from Study C09-001.

The mean change in pupil diameter during surgery was calculated as the area-under-the curve (AUC) divided by the surgery time minus the baseline for each patient. Summary statistics of the mean AUC of change from baseline was provided by stratum and treatment group. A generalised Cochran-Mantel- Haenszel (CMH) test stratified by the randomisation strata was used to compare the two treatment groups.

Early postoperative ocular pain was measured on the day of operation by VAS at 2, 4, 6, 8, and 10 to 12 hours post-surgery. The mean ocular pain VAS was calculated as the AUC divided by the time during the first 12 hours postoperatively. Summary statistics of the mean AUC was provided by stratum and treatment group. A generalized CMH test stratified by the randomisation strata was used to compare the two treatment groups.

To maintain an overall type I error of 0.05 for the secondary endpoints, a step-down approach was used to evaluate statistical significance of the selected secondary endpoints. If the primary efficacy endpoint reached the 0.05 level of significance, the following secondary endpoints were tested sequentially at the 0.05 level: postoperative ocular pain VAS score at 2, 4, 6, 8 and 10-12 hours after ILR surgery, photophobia at 6 hours after surgery, photophobia at day 1, best corrected visual acuity (BCVA) at day 1, mean summed ocular information score (SOIS) at day 1, ocular Pain VAS score at day 1

Results

Participant flow

All patients were to receive standardised preoperative antibiotic treatment (Vigamox® four times daily for three days prior to surgery), mydriatic treatment (one drop of PE 2.5% and one drop of tropicamide 1% at approximately 30, 15, and 5 minutes prior to surgery) and anaesthesia (topical lidocaine or tetracaine administered according to the manufacturer's instructions). Postoperatively, all patients continued Vigamox® for seven days. All patients were discharged with paracetamol and instructed to contact their physician for pain not controlled by paracetamol.

Study procedures were performed at screening, at baseline prior to surgery, the day of surgery intraoperatively, and postoperatively at approximately 2 hours, 4 hours, 6 hours, 8 hours, 10 to 12 hours, 24 hours, 48 hours, 7 days, and 14 days. Daily diaries were to be completed once each morning during the first seven days. The length of time for patient participation was approximately two to six weeks: up to 28 days in the screening process and 14 days in the postoperative period

Recruitment

A total of 444 patients were screened of whom 405 were randomised. Thirty-nine patients were not randomised, primarily because of failure to meet the inclusion and exclusion criteria. The number of patients randomised to placebo was 203 and to OMS302 was 202.

Conduct of the study

The study was conducted from September 2011 to January 2012 at eighteen US investigative sites.

On 17th January 2012 Protocol Amendment No 2 changed pain during the first 12 hours postoperatively from a co-primary efficacy measure to a secondary efficacy measure.

Baseline data

Table 3: Patients' baseline characteristics

Treatment	Placebo	OMS302	Total
n	201	`201	402
Age in years Mean (s.d.)	68.5 (9.9)	68.2 (9.6)	68.4 (9.7)
Male gender (%)	44.8	40.8	172 (42,8)

Numbers analysed

Analyses of the primary efficacy endpoints were based on the FAS, excluding subjects for whom pupil diameter data were not available. Safety analyses were based on the SP. Both of these analyses were based on randomized subjects starting study treatment. All subjects received the treatment to which they were randomized.

The FAS consisted of all 402 subjects enrolled and randomized to treatment in this study who underwent surgery and received study drug.

Three-hundred sixty-four subjects were included in the pupil diameter analyses. Video recordings of 38 subjects were not readable or had incomplete identification so subject identity could not be determined. It is unlikely that the exclusion of these subjects could introduce a bias in a masked study. Also, multiple imputation analyses support the primary analysis of the study with this population.

All 402 subjects in the FAS population provided at least one postoperative VAS pain score and were included in the ocular pain analyses.

The PP population consisted of 332 subjects. This represents the FAS population after excluding 70 subjects because they had significant protocol deviations.

The SP population consisted of 402 subjects; the three subjects who did not receive study treatment were excluded from this analysis set. All subjects received the assigned treatment.

Outcomes and estimation

Pupil diameter

Pupil diameter decreased throughout the surgical procedure in the placebo treatment group, but mydriasis was maintained in the OMS302 treatment group (Table 4 and Figure 1). Data and analysis for postoperative pain following surgery are shown in Table 5.

Table 4: AUC change from baseline in pupil diameter (mm) during surgery

Treatment	Placebo	OMS302
n (with video data)	180	184
Mean (s.d.)	-0.5 (0.58)	0.1 (0.41)
CMH weighted mean difference (s.e.) 0.577 (0.052) 95% CI 0.075, 0.067 p < 0.0001		

Figure 1: Intraoperative change in pupil diameter (mm) by time

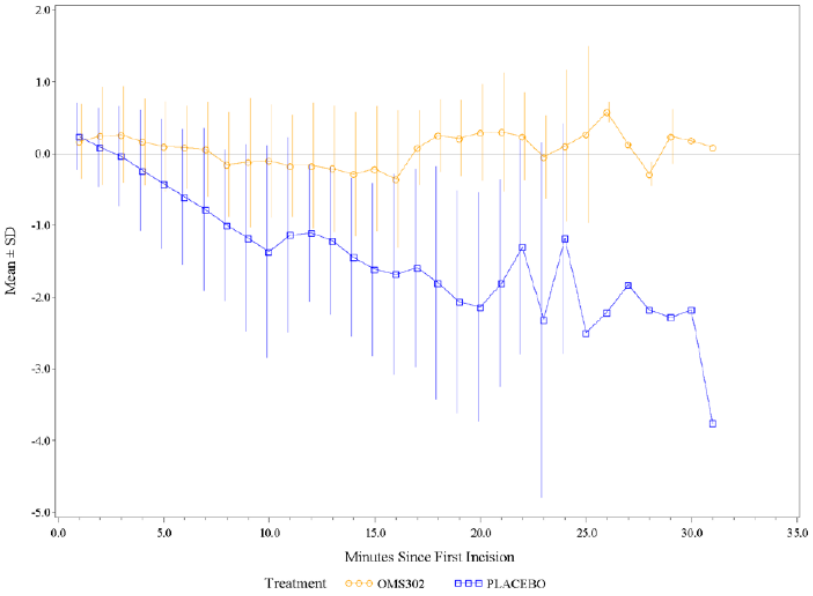


Table 5: Study OMS302-ILR-003 outcomes for secondary endpoints

Treatment	Placebo	OMS302
AUC 12 hour ocular pain VAS score (mean & s.d.)		
n 	201 9.2 (12.9)	201 4.1 (8.07)
CMH weighted mean difference (s.e.) -5.199 (1.076) 95% CI -7.307,-3.091 p < 0.0001		
BCVA log score at baseline (mean & s.d.)		
n 	198 0.3 (0.28)	197 0.3 (0.22)
BCVA log score at Day 1 (mean & s.d.)		
n 	201 0.1 (0.19)	200 0.1 (0.18)
Wilcoxon rank sum score test at Day 1 p = 0.096 there was no significant difference at any time to D 14		
Ocular inflammation SOIS grade baseline (mean & s.d.)		
n 	201 0	201 0
Ocular inflammation SOIS grade Day 1 (mean & s.d.)		
n 	201 2.9 (1.4)	201 2.7 (1.1)
Generalised CMH p = 0.0532 D1 and at Day 14 p = 0.5266		
Photophobia at six hours		
n No photophobia Moderate/severe	198 108 (54.5%) 20 (10.1%)	200 133 (66.5%) 21 (10.5%)
CMH test p = 0.0514		

Study OMS302 ILR-004: Phase III Randomised, Double-Masked, Placebo-Controlled Study of the Effect of OMS302 on Intraoperative Pupil Diameter and Early Postoperative Pain in Patients Undergoing Intraocular Lens Replacement with Phacoemulsification

Methods

Study Participants

Eligible patients fulfilled the following principal inclusion criteria; were 18 years of age or older at the time of surgery, were to undergo unilateral primary CELR or RLE, under topical anaesthesia, with a coaxial phacoemulsification device with insertion of an acrylic lens, BCVA of 20/400 or better in the non-study eye, have an intraocular pressure (IOP) between 5 mm Hg and 22 mm Hg, in the study eye. For women of childbearing potential, have a negative urine pregnancy test and use a [trial specified] form(s) of contraception.

The principal exclusion criteria were the presence of hypersensitivity (including cross-sensitivity) to relevant medications and the presence of significant ocular or general medical conditions.

Treatments

Omidria was supplied as a sterile clear solution containing 60.75 mM phenylephrine HCl (12.37 mg/mL) and 11.25 mM ketorolac tromethamine (4.24 mg/mL) formulated in a 20 mM sodium citrate buffer. Placebo was a sterile clear solution containing 20 mM sodium citrate buffer.

Objectives

Co-Primary:

Evaluate the effect of OMS302 compared to placebo when administered in irrigation solution during phacoemulsification and intraocular lens replacement (ILR) on:

- Intraoperative pupil diameter.
- Pain during the early postoperative period.

Secondary:

Evaluate the effect of OMS302 compared to placebo when administered in irrigation solution during phacoemulsification and intraocular lens replacement on:

- Postoperative photophobia as measured
- Postoperative best-corrected visual acuity
- Postoperative inflammation.
- Pain after the early postoperative period.
- Safety as measured by adverse events.
- Systemic pharmacokinetics (subset of subjects) of phenylephrine HCl (PE) and ketorolac tromethamine (KE).

Outcomes/endpoints

Co-primary:

- To evaluate the effect of OMS302 compared to placebo on the change in pupil diameter over time from surgical baseline to the end of surgery when administered in irrigation solution during phacoemulsification and intraocular lens replacement. Pupil diameter was measured by video capture and read by a masked central reader
- Ocular pain measured in the early postoperative period by VAS 100 mm scale with 0 being no pain and 100 being worst possible pain.

Secondary:

- Postoperative photophobia as measured by the photophobia subscale of the Numerical Rating Scale (NRS)
- Postoperative best-corrected visual acuity (BCVA)
- Postoperative inflammation as measured by Summed Ocular Inflammation Score (SOIS) at 24, 48 hours, and at seven and fourteen days.
- Pain after the early postoperative period (up to fourteen days).
- Systemic pharmacokinetics (measured in a subset of patients)
- Safety as measured by adverse events (AEs).

Sample size

The sample size to support the ocular pain endpoint was 200 patients per treatment arm, based on a t-test at the 0.05 two-sided level of significance, a difference between the treatment arms [in VAS] of 5.0 mm with s.d. 13.3 mm, gave a 96% power to detect the treatment difference. The sample size to support the pupil diameter is on a t-test at a 0.05 two-sided level of significance an treatment difference of 0.6 mm with s.d. 0.7 mm; this gives > 99% power to detect the treatment difference. The mean treatment differences and standard deviations for the sample size were taken from Study C09-001.

Randomisation

Patients were randomised 1:1 to OMS302 or placebo. Randomisation to treatment group was stratified within site by cataract Lens Opacities Classification System II.

Blinding (masking)

A masked central reader performed the pupil size measurements.

To maintain masking, the bottles of irrigation solution were prepared by an unmasked pharmacist or designee who was not otherwise involved in the study. An unmasked pharmacy clinical research associate monitored the pharmacy. All other study personnel remained masked throughout the study. No subjects were unmasked during the study.

Statistical methods

The mean change in pupil diameter during surgery was calculated as the area-under-the curve (AUC) divided by the surgery time minus the baseline for each patient. Summary statistics of the mean AUC of change from

baseline was provided by stratum and treatment group. A generalised Cochran-Mantel- Haenszel (CMH) test stratified by the randomisation strata was used to compare the two treatment groups.

Early postoperative ocular pain was measured on the day of operation by VAS at 2, 4, 6, 8, and 10 to 12 hours post-surgery. The mean ocular pain VAS was calculated as the AUC divided by the time during the first 12 hours postoperatively. Summary statistics of the mean AUC was provided by stratum and treatment group. A generalized CMH test stratified by the randomisation strata was used to compare the two treatment groups.

To maintain an overall type I error of 0.05 for the secondary endpoints, a step-down approach will be used to evaluate statistical significance of the selected secondary endpoints. If the primary efficacy endpoint reaches the 0.05 level of significance, the following secondary endpoints will be tested sequentially at the 0.05 level: postoperative ocular pain VAS score at 2, 4, 6, 8 and 10-12 hours after ILR surgery, photophobia at 6 hours after surgery, photophobia at day 1, best corrected visual acuity (BCVA) at day 1, mean summed ocular information score (SOIS) at day 1, ocular Pain VAS score at day 1

Results

Participant flow

All patients were to receive standardised preoperative antibiotic treatment (Vigamox® four times daily for three days prior to surgery), mydriatic treatment (one drop of PE 2.5% and one drop of tropicamide 1% at approximately 30 minutes, 15 minutes, and 5 minutes prior to surgery), and anaesthesia (topical lidocaine or tetracaine administered according to the manufacturer's instructions). Postoperatively, all patients continued the Vigamox® regimen for seven days. All patients were discharged with acetaminophen (paracetamol) and instructed to contact their physician for pain not controlled by acetaminophen (paracetamol).

Study procedures were performed at screening, at baseline prior to surgery, the day of surgery intraoperatively, and postoperatively at approximately 2 hours, 4 hours, 6 hours, 8 hours, 10 to 12 hours, 24 hours, 48 hours, 7 days, and 14 days. Daily diaries were to be completed once each morning during the first seven days. The length of time for patient participation was approximately two to six weeks: up to 28 days in the screening process and 14 days in the postoperative period.

Recruitment

A total of 451 patients were screened of whom 416 were randomised. Thirty-five patients were not randomised, primarily because of failure to meet inclusion and exclusion criteria. The number of patients randomised to placebo was 204 and to Omidria was 202.

Conduct of the study

The study was conducted from April 2012 to January 2013 at fifteen investigative sites in US and one in Europe. After Amendment 2.0, all patients received topical ophthalmic ketorolac on the first postoperative day. The dose was at the investigator's discretion. All patients were to be treated with topical ketorolac for at least seven days.

Baseline data

Table 6: Patients' baseline characteristics

Treatment	Placebo	OMS302	Total
n	204	202	406
Age in years Mean (s.d.)	67.5 (10.6)	69.2 (9.2)	68.3 (10.0)
Male gender (%)	38.2	42.1	40.1

Numbers analysed

Analyses of the primary efficacy endpoints were based on the full analysis set (FAS). Safety analyses were based on the safety population (SP).

The FAS population consisted of 406 subjects who received study drug. Eleven subjects (seven in the OMS302 group and four in the placebo group) were not included in the analyses of intraoperative pupil diameter because data from the video recording were not available. Two subjects (both in the placebo group) were not included in the analyses of early postoperative pain because they did not provide VAS data on the day of surgery.

The PP population consisted of 374 subjects; 32 subjects (16 subjects in each treatment group) were excluded from the FAS population because they had significant protocol deviations that could confound the interpretation of the results.

The SP consisted of 406 subjects who received study drug. All subjects in the SP received the assigned treatment.

Outcomes and estimation

The statistical analysis for pupil diameter is shown in Table 7 and the time course of intraoperative pupil diameter is in Figure 2. Eleven patients were excluded from analysis as video recordings were incomplete, missing, or of poor technical quality.

The analysis of postoperative pain is shown in Table 8 and Figure 3.

Table 7: Co-primary endpoint AUC change from baseline in pupil diameter (mm) during surgery

Treatment	Placebo	OMS302
n	200	195
Mean (s.d.)	-0.5 (0.57)	0.1 (0.43)
CMH weighted mean difference (s.e.) 0.590 (0.049) 95% CI 0.494, 0.686 p < 0.0001		

Figure 2: Intraoperative change in pupil diameter (mm) by time

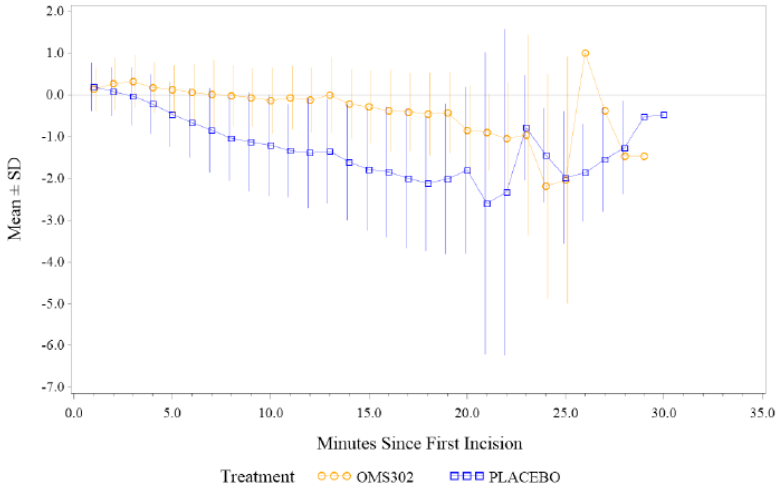


Table 8: Co-primary endpoint AUC VAS score 12 hour postoperative ocular pain

Treatment	Placebo	OMS302
n	202	202
Mean (s.d.)	8.9 (15.19)	4.3 (8.75)
CMH weighted mean difference (s.e.) -4.580 (1.192) 95% CI -6.92, -2.24 p = 0.0002		

Figure 3: Early postoperative ocular pain (VAS) score

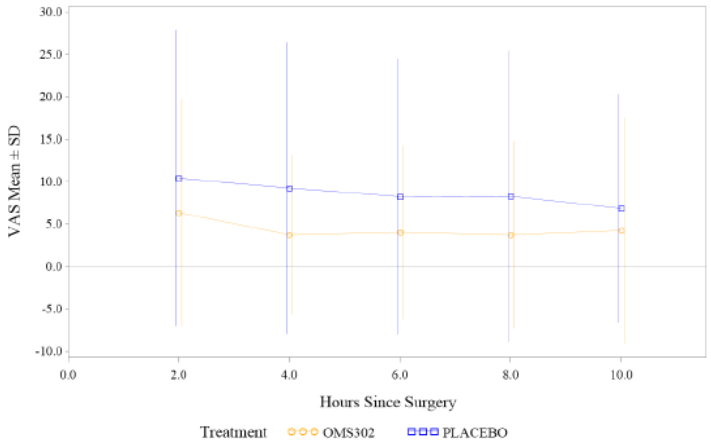


Table 9: Study OMS302-ILR-004 outcomes for secondary endpoints

Treatment	Placebo	OMS302
Photophobia at six hours		
n No photophobia Mod/severe	202 128 (63.4%) 16 (7.92%)	200 140 (70%) 9 (4.5%)
BCVA log score at baseline (mean & s.d.)		
n 	197 0.3 (0.22)	199 0.4 (0.22)
BCVA log score at Day 1 (mean & s.d.)		
n 	203 0.1 (0.18)	201 0.1 (0.20)
Wilcox. rank sum Day 1 p = 0.24 there was no statistically significant difference between treatments at any time to D90		
Ocular inflammation SOIS grade baseline (mean & s.d.)		
n 	204 0	202 0
Ocular inflammation SOIS grade Day 1 (mean & s.d.)		
n 	204 2.9 (1.3)	202 2.8 (1.0)
Generalised CMH Day 1 p = 0.33 there was no statistically significant difference between treatments at any time to D90		

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Phase 3, randomized, parallel-group, double masked, placebo-controlled study in subjects undergoing CELR or RLE.			
Study identifier	**OMS302-ILR-003**		
Design	This Phase 3 study was a randomized, parallel-group, double-masked, placebo-controlled study of OMS302 in subjects undergoing ILR (CELR or RLE		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1st patient enrolled 22/Sept/2011, Last subject completed: 31/Jan/2012 not applicable
Hypothesis	The primary objective of the OMS302-ILR-004 study was to evaluate the effect of OMS302 compared to placebo on intraoperative pupil diameter and ocular pain in the early postoperative period when administered in irrigation solution during phacoemulsification and intraocular lens replacement surgery.--Superiority		
Treatments groups	Placebo		single administration intraoperatively irrigation, n=201 randomized
	OMS302		phenylephrine hydrochloride (PE); ketorolac tromethamine (KE) diluted in balanced salt solution (BSS) and administered as irrigation solution during ILR surgery. OMS302 is the combination of 483 µM PE and 89 µM KE when diluted. n=201 randomized
Endpoints and definitions	Primary endpoint	label	Mean AUC of change in pupil diameter over time from surgical baseline to wound closure
	Principal Secondary	label	Mean AUC of postoperative pain VAS score at 2, 4, 6, 8, and 10-12 hours after surgery
	Secondary	label	• Postoperative photophobia as measured by the photophobia subscale of the Numerical Rating System (NRS) • Postoperative best-corrected visual acuity (BCVA) • Postoperative inflammation as measured by Summed Ocular Inflammation Score (SOIS) • Pain after the early postoperative period • Safety as measured by adverse events (AEs).
Database lock	02/July 2013		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description				
Descriptive statistics and estimate variability	Treatment group	Vehicle	OMS302	
	Number of subject	n=201	n=201	
	Age, y Mean ± SD	69 ± 9.9	68 ± 9.6	
	Median (min-max)	69.0 (39-89)	69.0 (31-88)	
	Age Group (years), n(%)≥ 65	139 (69.2)	143 (71.1)	
	Gender, male (n, %)	90 (44.8%)	82 (40.8%)	
	Race, n(%) White	155 (77.1%)	165 (82.1%)	
	Asian n(%)	19 (9.5%)	12 (6.0%)	
	LOCS II Grade, n(%)			
	Low (N0, N1)	160 (79.6%)	155 (77.1%)	
	High (N2, N3)	41 (20.4%)	46 (22.9%)	

Effect estimate per comparison	Mean Area-under-the-curve Analysis of Change from Baseline in **Pupil Diameter (mm) During Surgery**	Placebo (n=180)	OMS302 (n=184)
		Mean ± SD	Mean ± SD
		- 0.51 ± 0.58	**0.1 ± 0.41**
		Difference b [95% CI] P value	0.577 (0.052) 0.075,0.067 P<0.0001
	Mean AUC in VAS for **Ocular Pain during 12 hours** after Surgery	Placebo (n=201)	OMS3 (n=201)
		9.22 ± 12.93	4.07 ± 8.07
		Difference b [95% CI] P value	-5.20 95% confidence interval -7.307, -3.091 p-value c 0.0001
Notes	OMS302 was superior to placebo in change in pupil diameter (maintenance of mydriasis and prevention of miosis). OMS302 was superior to placebo in prevention of miosis defined as an absolute pupil diameter less than 6 mm at cortical clean-up, an absolute pupil diameter less than 6 mm anytime during the procedure, or pupillary constriction of at least 2.5 mm during the procedure. OMS302 was also superior to placebo in reduction of early postoperative pain. The decrease in mean VAS score was approximately 50%.		
Analysis description			

	Primary analysis: Mean area-under-the curve analysis Mean AUC was calculated as the area of the endpoint over time using the trapezoidal rule divided by the total time. Treatment comparisons were performed by a generalized CMH test stratified by the randomization strata. **Sensitivity analysis:** Repeated measures analysis Repeated measures model included the treatment group, time-point, and the randomization strata as covariates. A generalized estimating equation method with an AR(1) working-correlation structure was used to estimate the model parameters. Treatment comparisons were based on least-squares mean difference between treatment groups.

A Phase 3 Randomized, Double-Masked, Placebo-Controlled Study of the Pharmacokinetics of OMS302 and the Effect of OMS302 on Intraoperative Pupil Diameter and Early Postoperative Pain in Subjects Undergoing Intraocular Lens Replacement (ILR) with Phacoemulsification		
Study identifier	**OMS302-ILR-004**	
Design	A Phase 3 study was a randomized, double-masked, placebocontrolled study assessing the safety and efficacy of OMS302 for the maintenance of mydriasis, prevention of intraoperative miosis, and reduction of early postoperative pain in subjects undergoing intraocular lens replacement (ILR) surgery (either CELR or refractive or clear lens exchange (RLE)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Efficacy: Day14, Safety: Day90 Date first subject enrolled: 4 April 2012 Date last subject completed: 9 January 2013 not applicable
Hypothesis	Superiority: OMS302 superior to placebo on the co-primary endpoint of maintenance of mydriasis. • OMS302 superior to placebo on the co-primary endpoint of reduction of ocular pain in the early postoperative period. • OMS302 superior to placebo in prevention of miosis defined as either pupillary constriction ≥ 2.5 mm at any time during the procedure, or absolute pupil diameter ≥ 6 mm at the time of cortical clean-up or at all times during the procedure. • OMS302 superior to placebo in the mean pupil diameter at the time of cortical clean-up.	
Treatments groups 416 randomized /406 treated/	Vehicle	Placebo diluted in BSS and administered as irrigation solution during ILR surgery. The placebo contains 20 mM sodium citrate in the vial that is diluted into 500 mL irrigation solution. , Single administration; for irrigation during ILR surgery

	OMS302		OMS302 diluted in balanced salt solution (BSS) and administered as irrigation solution during ILR surgery. OMS302 is the combination of 483 µM PE and 89 µM KE in the diluted irrigation solution, Single administration; for irrigation during ILR surgery
Endpoints and definitions	CoPrimary endpoint	label	• Mean AUC of change in **pupil diameter** over time from surgical baseline to wound closure • Mean AUC of postoperative **pain VAS score** at 2, 4, 6, 8, and 10-12 hours of the end of surgery
	Secondary endpoint	label	• Pupil diameter ≥ 6mm at cortical clean-up • Pupil diameter < 6mm at any time during surgery • Moderate-to-severe ocular pain (VAS ≥ 40) at any time-point during 12 hours postoperatively • Ocular pain free (VAS = 0) at all time-points during 12 hours postoperatively • Postoperative pain VAS after day of surgery • Photophobia after surgery • BCVA after surgery • SOIS after surgery
Database lock	08/July 2013		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	<Intent to treat> <Per protocol> <other: specify> <time point>		

Descriptive statistics and estimate variability	Treatment group	Vehicle	OMS302	
	Number of subject	n=204	n=202	
	Age(Mean ± SD)	68 ± 10.6	69 ± 9.2	
	Age (median, min-max)	69.0 (26-90)	70.0 (39-87)	
	White n(%)	158 (77.5%)	165 (81.7%)	
	Nuclear color/, n(%) N 0 N 1 N 2 N 3	 10 (4.9%) 23 (11.3%) 93 (45.6%) 78 (38.2%)	 7 (3.5%) 26 (12.9%) 104 (51.5%) 65 (32.2%)	

Effect estimate per comparison	Mean AUC in Change from	Placebo (n=200)	OMS302 (n=195)

	Baseline in Pupil Diameter (mm) a	-0.49 ± 0.57	0.09 ± 0.43
		Difference [b] [95% CI] P value	0.59 95% confidence interval 0.494, 0.686
		P-value	p-value c <.0001
	Mean AUC in VAS for Ocular Pain during 12 hours after Surgery	Placebo (n=202)	OMS302 (n=202)
		8.91 ± 15.19	4.25 ± 8.75
		Difference [b] [95% CI] P value	-4.580 (1.192) 95% confidence interval -6.917, -2.244
		P-value	0.0002
	Subjects with ≥6 mm at cortical clean-up	Placebo (n=204)	OMS302 (n=202)
		154/200 (77.0%)	187/195 (95.9%)
		P-value	.0001

Notes	**CONCLUSIONS** • OMS302 was statistically superior to placebo on the co-primary endpoint of maintenance of mydriasis. • OMS302 was statistically superior to placebo on the co-primary endpoint of reduction of ocular pain in the early postoperative period. • OMS302 was statistically superior to placebo in prevention of miosis defined as either pupillary constriction ≥ 2.5 mm at any time during the procedure or as absolute pupil diameter < 6 mm at the time of cortical clean-up or as < 6 mm at any time during the procedure. • OMS302 was statistically superior to placebo in the mean pupil diameter at the time of cortical clean-up. • No statistically significant treatment effect was observed on moderate-to-severe pain in the early postoperative period (p = 0.08). Since a step-down approach was used to evaluate statistical significance of secondary efficacy endpoints, this meant that the remaining endpoints (ocularly pain free in the early postoperative period, ocular pain on Day 1, photophobia at six hours and one day postoperatively, SOIS, and BCVA) did not achieve statistical significance, even though some of the endpoints had nominal p-values less than 0.05. • All sensitivity analyses were consistent with OMS302 treatment effects observed in the FAS population on both intraoperative pupil diameter and postoperative ocular pain. These sensitivity analyses included per protocol analyses, multiple imputation analyses, repeated measures analyses, and analysis of intraoperative miosis. • Systemic exposure to PE and KE was low or undetectable at all timepoints. • OMS302 was well tolerated. • More placebo-treated subjects (70%) than OMS302-treated subjects (58%) reported at least one treatment-emergent AE (TEAE) across both treatment groups. • The most frequently observed AEs overall were eye pain, headache, posterior capsule opacification, anterior chamber inflammation, vision blurred, ocular discomfort, conjuctival hyperaemia, photophobia, and increased IOP, all anticipated events following ILR surgery. These events occurred at a similar incidence across the treatment groups with the exception of increased intraocular pressure. The adverse event of **increased intraocular pressure was reported more frequently in the OMS302 treatment group than in the placebo treatment group. This finding has not been previously observed.** • Adverse events were generally mild or moderate and not considered to be related to study treatment. • Four subjects (two in each treatment group) experienced SAEs that were not considered related to study drug. No deaths occurred in this study. • No subjects discontinued from the study because of an AE.

Analysis description	**Primary analysis:** Mean area-under-the curve analysis Mean AUC was calculated as the area of the endpoint over time using the trapezoidal rule divided by the total time. Treatment comparisons were performed by a generalized CMH test stratified by the randomization strata. **Sensitivity analysis:** Repeated measures analysis Repeated measures model included the treatment group, time-point, and the randomization strata as covariates. A generalized estimating equation method with an AR(1) working-correlation structure was used to estimate the model parameters. Treatment comparisons were based on least-squares mean difference between treatment groups.

Analysis performed across trials (pooled analyses and meta-analysis)
The applicant has not performed any efficacy meta-analyses. This approach was accepted by the CHMP as the two Phase III studies gave very consistent results.

Additional prospectively defined analyses were performed on the pupil diameter measures. These analyses were the proportion of subjects who experienced an absolute pupil diameter less than 6 mm at any time during the surgical procedure and at the time of cortical clean-up, and the proportion of subjects who experienced pupil constriction of at least 2.5 mm during the surgical procedure.

Pooled data on pupillary size during surgery from Omidria Phase III studies (all comparisons p <0.001 Chi-square)

	Placebo (n = 405)	Omidria (n = 403)
Diameter < 6 mm at any time	161/380 (42.4%)	37/379 (9.8%)
Diameter < 6 mm at cortical clean-up	87/380 (22.9%)	15/379 (4.0%)
≥ 2.5 mm pupillary constriction	103/380 (27.1%)	8/379 (2.1%)

Similar to pupil diameter, additional ocular pain analyses were prospectively defined to provide context to the findings of pain reduction. These analyses were the proportion of subjects who reported no ocular pain (defined as VAS = 0 at each of the postoperative time points) and the proportion of subjects who reported moderate-to-severe ocular pain (defined as a VAS score ≥ 40 at one or more of the postoperative time points).

Pooled data on postoperative pain from Omidria Phase III studies (all comparisons p <0.01 Chi-square)

	Placebo (n = 405)	Omidria (n = 403)
Subjects with VAS = 0 at all times	69/403 (17.1%)	104/403 (25.8%)
Subjects with VAS ≥ 40 at any time	57/403 (14.1%)	29/403 (7.2%)

The use of analgesics on the day of surgery (other than ketorolac in subjects who received as a component of OMS302) was analysed in the Phase 3 clinical trials. All analgesics administered on the day of surgery were included. More placebo-treated subjects received an analgesic on the day of surgery than OMS302-treated subjects (34.7% of placebo-treated subjects and 24.6% of OMS302-treated subjects; $p = 0.002$ (Chi squared test)). Also, more pain was reported by placebo-treated subjects than by OMS302-treated subjects regardless of whether they used analgesics on the day of surgery ($p < 0.001$ in both subgroups).

Clinical studies in special populations

The Applicant has not conducted any specific studies in special populations. This has been found acceptable by the CHMP.

In Studies C09-001, OMS302-ILR-003, and OMS302-ILR-004, approximately 28% of subjects were younger than 65 years of age, approximately 45% were 65-75 years of age, and approximately 27% were older than 75 years of age. The median age range was 23 years to 90 years with median 67 to 70 years. The majority of subjects were female. Approximately 80% of subjects were white, with most other patients being either black or Asian

Elderly population was substantially represented in the studies, reflecting the onset of need for lens replacement therapy due to the nature of pathophysiology.

Hepatic or renal impairment was not a selection point as the active ingredients are applied only once, for 15-40 minutes and their absorption and systemic effect are negligible.

Supportive study

Study C09-001 was a Study of Phenylephrine HCl's and Ketorolac Tromethamine's Ability, Alone and in Combination, to Maintain Mydriasis and Relieve Pain and Inflammation in Patients Undergoing Unilateral Cataract Extraction with Lens Replacement.

Methods

The primary objectives of the study were to evaluate the safety of OMS302 compared to vehicle when administered during cataract extraction and lens replacement surgery (CELR) as measured by adverse events, evaluate the efficacy of OMS302 compared to vehicle on intraoperative mydriasis during CELR surgery as measured by intraoperative pupil diameter and to evaluate the efficacy of OMS302 compared to vehicle on ocular pain during the first 12 hours postoperatively. The remaining objectives were to evaluate the effect of OMS302 compared to ketorolac tromethamine (KE) on mydriasis during CELR surgery as measured by pupil diameter and to evaluate the effect of OMS302 compared to phenylephrine HCl (PE) on ocular pain during the first 12 hours postoperatively.

The study was a randomised, parallel-group, double-masked, vehicle-controlled evaluation of PE, KE, and OMS302 (the fixed combination) in patients undergoing CELR using a coaxial phacoemulsification process with insertion of an acrylic lens. The study evaluated, using a full-factorial design, the effects of OMS302 on intraoperative pupil diameter and ocular pain in the early postoperative period.

Patients were randomised to one of the following four treatment groups in a 1:1:1:1 fashion:

1. Balanced salt solution (BSS) vehicle
2. Single study-drug formulation containing 483 µM PE
3. Single study-drug formulation containing 89 µM KE

4. Combination study-drug formulation containing 483 µM PE/89 µM KE (OMS302).

The study included two co-primary endpoints. The effect of OMS302 was compared to vehicle for the maintenance of mydriasis and for reduction in postoperative ocular pain.

OMS302 was compared to KE for maintenance of mydriasis. (The contribution of PE to maintenance of mydriasis in the indication would be demonstrated if OMS302 was superior to KE on this endpoint. OMS302 was compared to PE for reduction in postoperative ocular pain. (The contribution of KE to reduction in postoperative ocular pain would be demonstrated if OMS302 was superior to PE on this endpoint. Randomisation to treatment group was stratified by cataract Lens Opacities Classification System II (LOCS II) grade (N0 and NI, NII and NIII).

Study Population

For inclusion into the trial, patients were required to fulfil the following criteria within 28 days prior to the day of surgery:

1. Are 18 years of age or older at the time of surgery.
2. Are to undergo unilateral primary CELR, under topical anaesthesia, with a coaxial phacoemulsification device with insertion of an acrylic lens.
3. Have a best corrected visual acuity (BCVA) of 20/400 or better in the non-study eye.
4. Have an intraocular pressure (IOP) between 5 mm Hg and 22 mm Hg, inclusive.
5. For women of child bearing potential, have a negative urine pregnancy test. Women of child bearing potential were to use to use two methods of contraception throughout the study as necessary.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

2. Hypersensitivity to phenylephrine, ketoprofen or named medicinal products with potential cross sensitivity to phenylephrine and/or ketoprofen.
3. Women who are nursing a child or plan to nurse a child during the study.
4. Presence of clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, endocrine, neurological, psychiatric, respiratory or other medical condition as determined by the Investigator. Presence of any connective tissue disorder (e.g., lupus, rheumatoid arthritis, fibromyalgia).
6. Presence of systolic blood pressure of ≥150 mmHg or ≤90 mmHg, or diastolic blood pressure of ≥105 mmHg or ≤40 mmHg.

Sample size

The sample size required for the study was estimated at 192 patients (48 per treatment arm) based on the number of patients needed to demonstrate trends with respect to reduction of ocular pain on the day of operation taking into consideration results from a completed Phase 1/2 study in the same indication. In the completed Phase 1/2 study, the proportion of patients pain-free by 12 hours postoperatively in the treatment arm was 0.92 versus 0.67 in the vehicle arm. The assumed study parameters provide 90% power for a two sided t-test at a significance level of 0.05. To account for patients randomized but who do not qualify for

inclusion in the mydriasis and pain analysis set populations for primary efficacy analyses, a total of 200 patients are anticipated to be randomized in the study.

Results

Disposition of patients and baseline characteristics

A total of 264 patients were screened and 223 randomised at 23 study sites. All but one randomised patients received study treatment: Patient 20097 cancelled surgery before receiving treatment. Two patients received the incorrect treatment. Only one of the 222 patients who received study treatment discontinued from the study before completing all follow-up assessments.

Table 10: Baseline characteristics of safety population

Treatment	Vehicle	PE	KE	OMS302
n	57	54	55	56
Age in years Mean (s.d.)	68.5 (9.6)	67.6 (10.6)	66.8 (8.6)	66.4 (11.2)
Male gender (%)	42.1	37.0	40.0	33.9
LOCS group I (%)	26.3	24.1	23.6	23.1
LOCS group II (%)	73.7	75.9	76.4	76.8

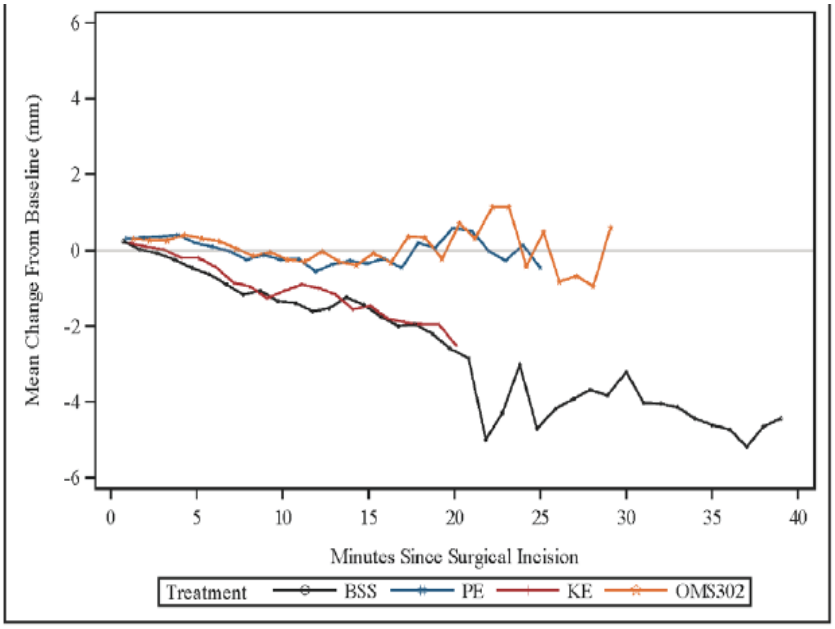
Mydriasis

Pupil diameter measurements were taken at one-minute intervals from the time of incision to wound closure during surgery; a summary of measurements over time is provided for the mydriasis analysis set (n =203) population in Table 11 and graphically represented in Figure 4.

Table 11 Repeated measures analysis change from baseline in pupil diameter (mm) during surgery

	OMS302 vs. vehicle	OMS302 vs. KE
LS mean treatment difference (s.e.)	0.9 (0.1)	0.7 (0.1)
95% C.I	0.6, 1.1	0.5, 0.9
Repeated measures model $p < 0.001$ for both comparisons		

Figure 4: Change from Baseline of Pupil Diameter During Surgery (Mydriasis Analysis Set)



Postoperative pain

Using the repeated measures ANOVA to compare ocular pain based on VAS pain score, OMS302 was statistically superior to vehicle and PE (Table 12 and Figure 5).

Table 12: Repeated measures analysis ocular pain VAS score within 12 hours of surgery

	OMS302 vs. vehicle	OMS302 vs. PE
LS mean treatment difference (s.e.)	-4.6 (2.2)	-5.9 (2.2)
95% C.I	-8.9, -0.2	-10.3, -1.5
Repeated measures model for OMS302 vs. vehicle p = 0.042 vs. KE p = 0.009		

Figure 5: Postoperative Ocular pain VAS score (Pain analysis set)

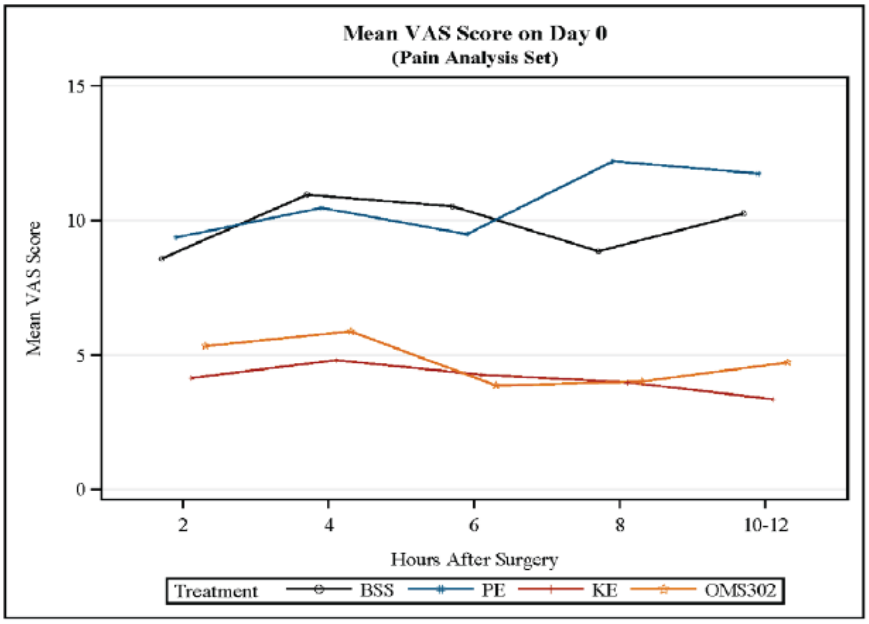


Table 13: Study CO9-001 outcomes for secondary variables

	Vehicle	PE	KE	OMS302
Photophobia at six hours (n & %)				
n No photophobia Mod/severe	53 26 (46.4%) 10 (18.9%)	53 29 (51.8%) 8 (15.1%)	49 33 (60.0%) 0	50 29 (51.8%) 3 (6%)
CMH comparison of OMS302 vs. other groups was not statistically significant at any time point to D 14 except for a isolated values of p = 0.039 vs. KE D 2 and p = 0.029 vs. PE D 3				
Best corrected visual acuity at baseline (mean & s.d.)				
n 	54 0.4 (0.3)	55 0.4 (0.2)	53 0.4 (0.2)	53 0.4 (0.3)
Best corrected visual acuity at D 1 (mean & s.d.)				
n 	56 0.1 (0.2)	55 0.2 (0.3)	55 0.2 (0.2)	54 0.1 (0.2)
CMH comparison of OMS302 vs. other groups was not statistically significant at any time point to D 30				

Ocular inflammation SOIS grade baseline (mean & s.d.)				
n	56 0	56 0	55 0	55 0
Ocular inflammation SOIS grade D 1 (mean & s.d.)				
n	56 2.7 (1.4)	56 2.3 (1.3)	55 2.6 (1.3)	55 2.2 (1.1)
ANOV comparison of OMS302 vs. other groups was not statistically significant at any time point to D 30				

Study C09-001 showed that for the primary endpoints; maintenance of mydriasis during surgery, and ocular pain for twelve hours after surgery, OMS302 was clearly superior to vehicle. For secondary endpoints (see Table 4) such as photophobia, visual acuity, and ocular inflammation no benefit over vehicle was observed and no claim was made in the SmPC on this basis

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Design and conduct of the clinical studies was appropriate to show clinical advantages of adding OMS302 to the intracameral irrigation solution during lens replacement therapy. Inclusion criteria were acceptable.

Overall, the CHMP agreed that studied populations were representative of majority of the target population with respect of demographic and other baseline characteristics. Study OMS302-ILR-004 randomized also patients 18 years of age or older at the time of surgery, however due to the nature of conditions the majority of the patients was >65 years old (Vehicle group 69.2% and OMS302 group 71.1%).

Each of the studies in this application was conducted in the United States. One site in the Netherlands participated in study OMS302-ILR-004; this site randomized 12 subjects. The surgical procedure for ILR in Europe is identical to the surgical procedure in the United States, and there are no identified differences between patients in Europe and the United States in the aetiology or natural history of cataracts. Therefore, the CHMP agreed that population in the studies evaluating Omidria is considered to be representative of ILR patients in both Europe and the United States.

Applicant's claim that study populations represent target populations was only partially endorsed by the CHMP. Exclusion criteria seem to have been set to investigate study drug in basic, safe and uncomplicated circumstances so as to get interpretable results. The involved subjects did not represent those subgroups of patients who are expected to have substantial limitation in their mydriatic ability, namely those who suffer from connective tissue disorders, intraocular inflammation, prior iris trauma, presence of pseudoexfoliation in either eye or intraocular infection.

The applicant provided a theoretical discussion as to why the product could still have a positive B/R ratio in excluded patients with connective tissue disorders and intraocular inflammation. Pharmacological agents can help maintain pupil dilation following surgical dissection, namely as the scarring can anchor the iris to the underlying anterior capsule and cause an anatomical barrier to pupil dilation. Similar effect is most probably true with prior iris trauma.

Neither phenylephrine nor ketorolac are contraindicated for use in these conditions and no specific safety concerns are noted in these patients for either agent. In fact, NSAIDs, including ketorolac, are used in the treatment of uveitis, either primary or caused by connective tissue diseases. Therefore, there is unlikely to be any added risk with the use of Omidria in these patients.

Neither phenylephrine nor ketorolac should increase the risk of infection-related operative complications. Both components of OMS302, by maintaining pupil dilation throughout the surgical procedure, should make ILR easier and less traumatic in the setting of ocular infection, beneficially reducing the inflammatory response secondary to surgical trauma. In addition, it was also noted that ocular infection is a relative contraindication to ILR.

This explanation was in principle accepted by the CHMP. However, as there was no clear evidence to support the efficacy or safety of Omidria in patients with a history of uveitis or iris trauma, the CHMP has not agreed that a positive benefit-risk balance can be assumed in these patients. Likewise in patients at risk of floppy iris syndrome due to alpha-adrenergic antagonist use, it cannot be assumed that Omidria will successfully maintain mydriasis. These considerations have been included in the SmPC.

Study CO9-001 evaluated the safety and efficacy of OMS302 against vehicle and against PE alone and KE alone (in compliance with the EMA/CHMP fixed combination regulatory guidance). The applicant's approach to this guidance was unusual in that each single component was compared to the combination using an endpoint for which the single components are generally considered inactive. For the endpoint of mydriasis OMS302 was compared to ketorolac – which has no mydriatic properties. Likewise for the endpoint ocular pain, OMS302 was compared to phenylephrine which has no known anti-inflammatory or analgesic properties. Although the statistical methodology may be technically correct, the comparisons lead to a predictable result with no evident clinical or regulatory interpretation. A more appropriate analysis was requested by the CHMP. Specifically, OMS302 should be compared to PE for the endpoint pupil diameter during surgery and compared to KE for the endpoint postoperative ocular pain within twelve hours of surgery.

The provided analysis suggested that for pupil diameter Omidria is equivalent to PE and for postoperative pain Omidria is equivalent to ketorolac. As there was no suggestion of inferiority of the combination to the single substances, the CHMP accepted this as a justification for the fixed dose combination.

Efficacy data and additional analyses

For the primary endpoints - maintenance of miosis during surgery and reduction of postoperative pain in the twelve hours post-surgery - Omidria showed clear and consistent benefit in two sizable and well conducted Phase III studies.

The change in pupil diameter over time from surgical baseline was the primary pupil-related efficacy variable in each of the Phase 3 clinical trials. The primary analysis was based on the mean area-under-the-curve (AUC) pupil diameter change from baseline which is a standard methodology. All subjects in each Phase 3 trial received standard-of-care preoperative mydriatic (i.e., phenylephrine and cyclopentolate) topical drops. In the analysis in each trial, OMS302 was superior to placebo ($p < 0.0001$ in both studies). In each trial, pupil diameter remained relatively stable in the OMS302-treatment groups while steadily decreasing in the placebo treatment groups. The variability observed at later time points during the surgery was related to the small number of subjects whose procedure had not been completed by those times. To provide context to the mean AUC analyses described above, additional prospectively defined analyses were performed on the pupil diameter measures. These analyses were the proportion of subjects who experienced an absolute pupil diameter less than 6 mm at any time during the surgical procedure and at the time of cortical clean-up, and the proportion of subjects who experienced pupil constriction of at least 2.5 mm during the surgical

procedure. This is important because the pupil is the viewing portal onto the surgical field, and pupil constriction of 2.5 mm represents an approximately 50% decrease in the total pupil area. This significantly increases the difficulty of the procedure and the risk of surgical complications. When a patient's pupil is inadequately dilated, the full operative field is not visible and instruments must be used blindly. Evidence from the published literature (Menapace, 2005) supports the contention that surgery is more difficult with increasing pupillary constriction and has a higher complication rate and that a papillary diameter of less than 6 mm may act as a 'marker' for difficult surgery.

Fewer than 10% of Omidria-treated subjects experienced a pupil diameter of less than 6 mm at any time during their surgical procedures. In contrast, more than 40% of placebo-treated subjects experienced pupil diameters of less than 6 mm despite receiving standard-of-care preoperative topical mydriatic drops. This demonstrates that more than four times as many subjects collectively in the placebo-treated group than in the Omidria group incurred the increased risk of vitreous loss associated with less than 6-mm pupil diameters. At the time of cortical clean-up, approximately 4% of Omidria-treated subjects had a pupil diameter less than 6 mm compared to 23% of placebo-treated subjects. This demonstrates that more than one in five placebo-treated subjects had small pupils limiting surgeon visualization of the capsular contents during cortical clean-up, making effective lens epithelial cell removal less likely and the risk of complications greater.

The analysis of intra-operative pupil constriction of at least 2.5 mm also supports the clinical importance of the magnitude of the OMS302 treatment effect. More than 25% of placebo-treated subjects experienced this degree of pupil constriction during the surgical procedure compared to approximately 2% of OMS302-treated subjects. In these studies, a loss of 2.5 mm in diameter produces a loss in total pupil area of approximately 50% based on the mean baseline pupil diameters.

In the Phase 3 program, all subjects received standard-of-care pain management: preoperative anaesthetic drops topically and paracetamol, as needed, postoperatively. Ocular pain measured at 2, 4, 6, 8, and 10-12 hours postoperatively using the Visual Analogue Scale (VAS) which was the principal secondary efficacy measure in Study OMS302-ILR-003 and a co-primary efficacy measure in Study OMS302-ILR-004. This duration of the pain assessment period was chosen because it approximates the waking duration of patients following ILR surgery. The primary analysis of the ocular pain VAS was based on the mean AUC. In each trial, OMS302 was superior to placebo in reduction of postoperative ocular pain over the initial 10-12 postoperative hours ($p < 0.001$ in both studies). The magnitude of pain reduction observed in the OMS302-treated groups was consistent over the 12-hour pain assessment period. Although the mean pain scores were relatively modest, in both studies the OMS302-treated subjects reported less than 50% of the pain reported by the placebo-treated subjects. Given that the pain measurements assessed ocular pain, the benefits provided by OMS302 in this Phase 3 program are clinically relevant.

In addition, more placebo-treated subjects received an analgesic on the day of surgery than OMS302-treated subjects (34.7% of placebo-treated subjects and 24.6% of OMS302-treated subjects; $p = 0.002$ (Chi squared test)). Also, more pain was reported by placebo-treated subjects than by OMS302-treated subjects regardless of whether they used analgesics on the day of surgery ($p < 0.001$ in both subgroups). Similar to pupil diameter, mean AUC and additional ocular pain analyses were prospectively defined to provide context to the findings of pain reduction. These analyses were the proportion of subjects who reported no ocular pain (defined as VAS = 0 at each of the postoperative time points) and the proportion of subjects who reported moderate-to-severe ocular pain (defined as a VAS score ≥ 40 at one or more of the postoperative time points). These analyses are important because both surgeons and their patients have a low threshold for concern regarding ocular pain and expect ILRs to result in minimal postoperative pain. Similarly, most

surgeons and their patients do not find acceptable significant postoperative ocular pain (moderate-to-severe pain) following ILR.

The CHMP agreed with the Applicant's argumentation that a pupil diameter of at least six millimetres is a target to facilitate surgery and was achieved by the great majority of patients. The difference in pain score and use of analgesics in the Omidria treated patients supports better pain control in the active treatment group. However, as there was no measurement of overall satisfaction with surgery of either the surgeon or the patient, the CHMP noted that the absolute clinical relevance is difficult to establish.

The CHMP remarked that patients with diabetes may represent a particular efficacy and safety concern as the condition is common, predisposes to the need for cataract surgery, and wound healing is often considerably slower than in non-diabetic patients. This group of patients might develop also neuropathy by the time of development of cataract. The diabetic neuropathy might influence the innervation, thereby reactivity of the iris leading to difficulties to get necessary intraoperative mydriasis. The applicant was asked to provide the number of diabetic patients in the study populations and data on any difference in the efficacy and the safety measurements among them.

The efficacy and safety of OMS302 between subjects with and without diabetes was compared in Studies C09-001, OMS302-ILR-003, and OMS302-ILR-004. Subjects with diabetes were identified by a medical history or use of concomitant medications used to treat diabetes mellitus. The studies included 185 subjects with diabetes (slightly over 20% in the placebo group and slightly under 20% in the Omidria group). Forty-two subjects were using insulin. This included 20 in the placebo groups and 22 in the OMS302 groups. Comparison of the mean AUC analysis of the change from baseline in pupil diameter in subjects with and without diabetes and the mean AUC analysis of the ocular pain VAS score was comparable between subjects with or without diabetes. Therefore, the presence of diabetes does not appear to impact the pupil diameter- or ocular pain-related efficacy of OMS302. The comparison of insulin using diabetics involves only small numbers but the analysis does not suggest any difference between safety and efficacy in those using insulin and those not using insulin. Therefore, CHMP agreed that no specific warnings are warranted for this population.

Additional expert consultation

In the course of the procedure, the CHMP identified the need for expert input and thus an ad-hoc expert meeting was convened on the following questions:

Question 1.

The experts are asked to provide information on the methods used in the current clinical practice if intraoperative mydriasis is not adequate.

The experts noted that there are no medicinal products approved specifically for maintaining mydriasis and preventing miosis during cataract surgery. However, off label use of mydriatic agents (e.g. phenylephrine, adrenaline or tropicamide) either as intracameral bolus injection or by adding them to the irrigation solution is very common and supported by years of experience.

In case pharmaceutical approach is not effective, mechanical methods such as pupil stretching, iris hooks or viscoelastics are used. These methods tend to carry higher risks of infection and iris damage. The choice of method is highly individual and depends on the surgeon's estimation of relative risks of using these tools versus the risks of operating on a small pupil.

The experts reported that the clinical practices and methods used to maintain mydriasis can differ significantly between the hospitals, even within the same country or region.

Question 2.

In the experience of the experts, is use of ad-hoc (magisterial or hospital) preparations rare, occasional or common in current practice of ophthalmic surgery?

The experts stated that use of ad-hoc hospital preparations is common in current practice. They are being prepared either by the hospital pharmacy or by a nurse in the operating theatre, depending on the site's practice and facilities. Intracameral cefuroxime and solution of adrenaline in infusion fluid were given as examples of such preparations.

Question 3.

In the experts' experience, what percentage of patients needs additional (on demand) mydriatic medications during surgery? Is this possible to predict which patients are likely to fall in that group?

The experts reported that approximately 25% of their patients need additional mydriatic intervention during surgery but it is not possible to confidently predict which patients will fall in that group. This is in line with the Chang et al 2014 publication. There are several known risk factors that increase the likelihood of progressive miosis; diabetes, glaucoma, use of alpha-blockers, uveitis, history of trauma etc. However, pupil constriction can happen also in patients without any of the known risk factors.

Question 4.

The experts are asked to comment on the clinical relevance of effect of Omidria on maintenance of intraoperative mydriasis, prevention of intraoperative miosis, and post-operative analgesia.

The experts were of the opinion that the efficacy of Omidria with regards to the effect on pupil size has been clearly demonstrated during clinical trials as Omidria was superior to placebo. However, the pivotal trials lacked direct comparison with the EU standard of care (off label use of mydriatic agents during surgery).

With regards to the effect on pain scores, the experts observed that the clinical relevance of Omidria is rather modest. The experts noted that 95% of patients do not complain of pain after the surgery and the currently administered steroids and NSAIDs provide sufficient level of pain control. The experts also advised that every patient is assessed individually and the need for e.g. retrobulbar anaesthesia is decided on case-by-case basis.

Question 5.

In the experts' view, to what extent is there potential added value of Omidria in the intraocular lens replacement surgery? Can you identify specific groups of patients who could especially benefit from the use of Omidria during the procedure?

The expert group discussed the potential clinical utility of Omidria in the routine procedures and advised that, in their opinion, this product does not provide clear clinical added value over the current EU standard of care.

The experts considered that a product available through a marketing authorization compared with current locally prepared solutions would offer superior guarantee of pharmaceutical quality and benefit:risk follow-up, all other things being equal.

The experts observed that Omidria could potentially have an effect on intraoperative pain levels. However, this was not measured in any of the clinical studies.

The experts debated the potential added value of Omidria in the group of patients mostly at risk of progressive miosis during surgery e.g. patients with pseudoexfoliation or iris abnormalities. One of the experts thought that patients with the history of uveitis could potentially benefit the most. However, these high risk patients were not included in the clinical trials conducted by the Applicant so it is not possible to state this categorically.

The experts also expressed an opinion that there are certain groups of patients for whom Omidria would not be appropriate. For example, Omidria should not be used if cataract surgery is combined with vitrectomy, due to the vasoconstricting effects of phenylephrine. Same precaution may also apply to cases of vitreous loss arising as a complication of cataract surgery.

2.5.4. Conclusions on the clinical efficacy

Overall, the CHMP concluded that the available data demonstrated a clinically relevant effect of Omidria on intraoperative mydriasis and acute postoperative ocular pain in intraocular lens replacement surgery. Thus, the available clinical evidence on efficacy was considered sufficient to support the Marketing Authorisation application.

2.6. Clinical safety

Patient exposure

In the four controlled clinical studies conducted in the development program of Omidria, a total of 1,090 patients received study-drug treatment (Omidria, PE, KE, or placebo/vehicle). In the integrated safety evaluation, patients who were treated with PE or KE alone were not analysed, leaving 960 patients in the safety analysis population, of whom 478 were treated with Omidria (with Study C07-005 using concentrations of PE and KE in test product that differed from the concentrations in Omidria proposed for commercial use) and 482 were treated with placebo/vehicle. Patients from studies C09-001, OMS302-ILR-003, and OMS302-ILR-004 were pooled for safety analyses, with 459 having been treated with Omidria and 462 having been treated with placebo/vehicle. All studies enrolled adults undergoing ILR, primarily CELR, with less than 1% of patients undergoing RLE.

Adverse events

Table 14: Treatment related AE in pooled placebo controlled trial database.

MedDRA SOC preferred term	Placebo n = 462	Omidria n = 459
Any event	65 (14.1)	51 (11.1)
Eye disorders	62 (13.4)	49 (10.7)
Eye pain	32 (6.9)	22 (4.8)
Anterior chamber inflammation	21 (4.5)	18 (3.9)
Conjunctival hyperaemia	8 (1.7)	10 (2.2)

Corneal oedema	4 (0.9)	6 (1.3)
Photophobia	15 (3.2)	8 (1.7)
Ocular discomfort	7 (1.5)	4 (0.9)
Eye inflammation	5 (1.1)	2 (0.5)
Eye irritation	2 (0.4)	2 (0.4)
Conjunctival oedema	0	1 (0.2)
Corneal disorder	2 (0.4)	1 (0.2)
Mydriasis	0	1 (0.2)
Vision blurred	1 (0.2)	0
Visual acuity reduced	0	1 (0.2)
Vitreous floaters	0	1 (0.2)
Eye pruritus	0	1 (0.2)
Eyelid pain	0	1 (0.2)
Foreign body sensation in eye	3 (0.6)	1 (0.2)
Glare	0	1 (0.2)
Abnormal sensation in eye	1 (0.2)	0
Conjunctival haemorrhage	1 (0.2)	0
Iridocele	1 (0.2)	0
Iris disorder	1 (0.2)	0
Lacrimation increased	1 (0.2)	0
Miosis	1 (0.2)	0
Gastrointestinal disorders	0	1 (0.2)
Nusea	0	1 (0.2)
General & administration site disorders	4 (0.9)	6 (1.3)
Inflammation	3 (0.6)	6 (1.3)
Pain	1 (0.2)	1 (0.2)
Investigations	1 (0.2)	1 (0.2)
Intraocular pressure increased	1 (0.2)	1 (0.2)
Nervous system disorders	4 (0.9)	1 (0.2)
Headache	4 (0.9)	1 (0.2)

Respiratory disorders	1 (0.2)	0
Rhinorrhoea	1 (0.2)	0

Serious adverse event/deaths/other significant events

Six SAEs were reported, each occurring in an individual patient. The SAEs in the Omidria group were dehydration, electrocution, and myocardial infarction. The SAEs in the placebo group were malignant lung neoplasm, pleural effusion, and respiratory arrest. All SAEs were considered to be unrelated to study drug.

Laboratory findings

The analysis of laboratory findings including intraoperative heart rate and blood pressure did not show any safety concerns.

Safety in special populations

The safety of Omidria was prospectively evaluated with respect to gender, age, race, iris colour, and lens opacity for pooled studies. Safety measures evaluated by gender and age included AEs, vital signs, and IOP. Only AEs were evaluated by race, iris colour, and lens opacity since vital signs and IOP were not expected to be affected by these variables.

For all age groups, the incidence of individual TEAEs summarized by PT was similar between the treatment groups and across age groups.

The post hoc analysis of cardiovascular adverse events reported by patients with pre-existing hypertension or other cardiovascular disease was also conducted. Blood pressure was reported as increased in 22 (4.8%) of placebo treated patients and 21 (4.6%) of the pooled Omidria patients.

Omidria has not been studied in the paediatric population.

Safety related to drug-drug interactions and other interactions

There were no safety events due to drug interactions.

Discontinuation due to adverse events

One patient discontinued the study prematurely; he was fatally electrocuted in an industrial accident while still in the follow up period of the study.

2.6.1. Discussion on clinical safety

Clinical safety has been evaluated in four well conducted clinical studies, in three of them at the concentrations of PE and PK proposed for clinical use. The database was not large for a common surgical procedure. All three clinical trials gave very similar pictures in terms of safety profile. The CHMP also noted that the adverse events relating to the eye are difficult to evaluate as most of them probably relate to the process of surgery rather than unwanted effects of phenylephrine or ketorolac.

The existing dataset of over four hundred patients treated with Omidria and over four hundred control patients suggests that the product is safe. Complications of surgery were infrequent and there was no suggestion that they were more frequent in the active treatment arm than the control arm. From the safety database all the treatment related adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The CHMP noted that the effect of Omidria on the long term corneal and retinal health may not been sufficiently investigated due to the relatively small number of patients and short follow-up period. The potential risk of postoperative cystoid macular oedema (CMO) was also highlighted.

In response to this question, the applicant provided an in-depth discussion of preclinical and clinical development. In the clinical trials for OMS302, corneal safety was evaluated by analysis of adverse events and best-corrected visual acuity (BVCA). Corneal adverse events and BCVA are relevant measures because injury to corneal endothelial cells is associated with corneal oedema and clouding, both of which impact vision. In the OMS302 safety database, corneal oedema was reported more frequently in placebo-treated subjects than in OMS302-treated subjects. Also, no consistent pattern of corneal oedema was apparent between treatment groups.

Histological examination of corneal endothelium in toxicology studies together with analysis of clinical corneal adverse events and BCVA were deemed sufficient to detect clinically significant corneal endothelial injury. In these measures, no evidence of corneal endothelial injury associated with OMS302 was observed and no consistent OMS302-related treatment effect was observed on the cornea; therefore, the risk of damage to corneal endothelium was judged to be small.

Cystoid macular oedema has many causes including cataract surgery, uveitis, sarcoidosis, retinal dystrophies, retinal vein occlusion, and choroidal nevi. The incidence of cataract surgery-related clinical CMO is 0.1-2.35% [Yonekawa, 2012] and CMO usually occurs 1-3 months postoperatively.

The long-term safety of Omidria was evaluated in Study OMS302-ILR-004. In that study subjects were followed for 90 days postoperatively. One subject in the Omidria group reported cystoid macular oedema (CMO, mild severity) and one subject in the placebo group reported macular oedema (moderate severity). The incidence of each of these adverse events was 0.5%. This is near the lower end of the incidence range of clinical CMO reported in the literature of 0.1-2.35%. The reported incidence of angiographic CMO is 15-30% and CMO detected by optical coherence tomography is 4-11% [Yonekawa, 2012]. The Applicant also noted that ketorolac is a recognized treatment for CMO and the OMS302 clinical studies collectively do not demonstrate an increased risk of CMO associated with OMS302 treatment. Corneal disorders were reported by two subjects in the placebo treatment group (1.0%, both mild severity) and none in the OMS302 treatment group. Corneal oedema was reported by seven subjects in the placebo treatment group (2.9%, six mild and one moderate severity) and four subjects in the OMS302 treatment group (1.5%, three mild and one moderate severity). One subject in the OMS302 reported mild corneal guttatae (Preferred Term of corneal degeneration). This was reported in both eyes and, thus, not considered related to study treatment. No other corneal adverse events were reported.

The absence of toxicology findings related to the retina, the low incidence of CMO in the clinical studies relative to its literature-reported incidence, and the comparability of CMO incidence between the OMS302- and vehicle/placebo-treated groups demonstrate that the risk of CMO with use of OMS302 is low.

CHMP concluded that the CMO does not appear to be a particular concern and the duration of clinical trials follow-up for what is a single short intervention seems acceptable. Nevertheless, as the data are limited and the follow up was shorter than suggested by the convened expert group, these risks cannot be excluded. Consequently, the corneal oedema was added as a Potential Identified Risks in the Risk Management Plan and lack of long-term data on corneal endothelial injury and influence on the incidence of cystoid macular oedema were added as missing information.

The CHMP expressed a concern about the pro-hypertensive effects of phenylephrine which has been contraindicated for use in some authorised mydriatic products in the EU. However, the clinical data showed

that OMS302 does not appear to have a hypertensive effect in the general population. The change from baseline in systolic blood pressure (SBP) was evaluated separately in subjects with and without hypertension. This analysis demonstrated that the SBP changes from baseline are similar between OMS302 and placebo regardless of the presence or absence of hypertension.

A review of the systolic and diastolic blood pressure changes from baseline in the placebo-controlled studies demonstrated variability in blood pressure changes throughout the surgical procedures. The mean and median changes for the OMS302 treatment group were approximately zero and comparable to the changes observed for the placebo treatment group. The frequency of DBP greater than 105 mmHg was similar between treatment groups. Therefore, OMS302 did not have a hypertensive effect on DBP.

Because Omidria did not appear to have a hypertensive effect in subjects either with or without hypertension and the systemic exposure of phenylephrine is very low the Applicant proposed that poorly controlled hypertension be included as a warning or precaution in the Summary of Product Characteristics (SmPC). This is consistent with a recently approved (2009) ophthalmic product that contains phenylephrine, Mydriasert. The CHMP agreed that the problem with sympathomimetics and eye surgery is not a sustained pro-hypertensive effect as the levels are low and the exposure short, but rare, unexpected individual surges in blood pressure. The Applicant's proposal for the warning in the SmPC was found to be appropriate by the CHMP.

An acute attack of angle-closure glaucoma can be triggered by certain drugs with the potential for causing dilation of the pupil, by anatomical changes in the ciliary body and iris, or, by movement of the iris-lens diaphragm. As phenylephrine is a mydriatic agent, narrow-angle glaucoma has been included as contraindication in the SmPC of Omidria as a precautionary measure.

The CHMP noted that administration of cefuroxime (1 mg in 0.1 ml injected in the anterior chamber at the end of surgery) is part of clinical practice for the prevention of postoperative endophthalmitis in a number of EU countries. As there is a significant exposure of phenylephrine and ketorolac in the anterior chamber at the time end of surgery, there may be a risk from the perspective of drug-drug interactions as well as local safety. The applicant was requested to present available data together with an in depth discussion of potential risks with the concomitant use of Omidria and intracameral cefuroxime.

The administration of cefuroxime into the intracameral space at the end of surgery would be anticipated to mix with, and partially displace, any residual irrigation solution containing Omidria. Cefuroxime use should be compatible with the use of Omidria during cataract surgery because no pharmacological interactions are expected and these agents are physically compatible. No drug/drug interactions are reported with systemically administered alpha agonists or nonsteroidal anti-inflammatory drugs.

Cefuroxime is not appreciably metabolised and is excreted by the kidney [Petri, 2011]. Neither PE nor KE will alter the metabolism of cefuroxime nor block its excretion. Cefuroxime is not a monoamine oxidase inhibitor so, therefore, will not interfere with the metabolism of phenylephrine. Ketorolac is metabolized by hydroxylation [Mroszczak, 1990]. Cefuroxime will not interfere with this reaction.

Given the distinct pharmacology for these three active ingredients and the lack of significant toxicity associated with neither of them, their combination is not expected to increase the risk of local toxicity.

The CHMP agreed that in view of the lack of pharmacological interactions, absence of reports of clinical interactions, and the compatibility of Omidria with cefuroxime in a biologically relevant fluid, the risk of concomitant use of Omidria and cefuroxime is negligible.

Additional expert consultations

In the course of the procedure, the CHMP identified the need for expert input and thus an ad-hoc expert meeting was convened on the following question:

Question 6.

The experts are asked if the long-term safety is a potential concern for Omidria, particularly with regards to corneal endothelial cell health and the risk of cystoid macular oedema. If yes, what would be reasonable length of active follow-up after surgery?

The expert panel agreed that the length of the follow-up in Phase 3 clinical trials was not sufficient to assess long-term safety and that the company should have considered performing an endothelial cell count during pre- and post-surgery visits. There is currently not enough data to exclude possible long-term effects on corneal endothelial cell health and the potential risk of cystoid macular oedema.

The experts also noted that there is currently no data in public domain on the intracameral administration of ketorolac so it is not known if it may result in endothelial cell loss or not.

The experts mentioned that cataract surgery can be sometimes combined with a corneal transplant. Due to the doubts on the effects on Omidria on the endothelial cell health, use of Omidria in that setting would not be advisable. There is also not enough reassurance to recommend the use of Omidria in patients with any coexisting endothelial cells impairments.

As macular oedema can develop up to 6 months after surgery, the experts suggested that the expected duration of follow-up should be minimum 6 and ideally 12 months.

2.6.2. Conclusions on the clinical safety

Overall, the CHMP was of the view that the available safety data were sufficient to support the application for Omidria. The CHMP concluded that the safety profile of Omidria was acceptable with the majority of adverse reactions being eye disorders and related to surgical procedure, while the risk of systemic exposure and adverse reactions was considered low. The safety profile was furthermore considered adequately reflected in the product information and all safety concerns were addressed in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 03 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 04 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity or cross sensitivity (to aspirin/NSAIDs, or a past medical history of asthma) Acute attack or exacerbation of narrow-angle glaucoma
Important potential risks	Medication error Cardiovascular reactions in patients with pre-existing cardiovascular disease and/or hyperthyroidism Corneal oedema
Missing information	Paediatric data Use in relevant subgroups not studied in the clinical trial programme - patients with connective tissue disorder - intraocular inflammation - prior iris trauma - intraocular infection Lack of long-term data on corneal endothelial injury Influence on the incidence of cystoid macular oedema

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
OMS302-ILR-007 Phase 3	To evaluate the effect of Omidria	General safety in this population	Planned to start June 2014	September 2017

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Randomized, double-masked, phenylephrine-controlled study of the effect of Omidria (OMS302) in young children (category 3)	(OMS302) on pupil diameter and acute postoperative pain in children ages 0-3 years			
OMS302-ILR-008 Phase 2 Randomized, double-masked, placebo-controlled study of the effect of Omidria (OMS302) in adolescents (category 3)	To evaluate the effect of Omidria (OMS302) on pupil diameter and acute postoperative pain in children ages 13-17 years	General safety in this population	Planned to start Q2 2014	March 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity or cross sensitivity (to aspirin/NSAIDs, or a past medical history of asthma)	Addressed in proposed SmPC section 4.3 and section 4.4. Addressed in proposed PIL section 2. Addressed on outer carton.	None.
Narrow-angle glaucoma	Addressed in proposed SmPC section 4.3. Addressed in proposed PIL section 2.	None.
Medication error	Addressed in proposed SmPC section 4.1, section 4.2, section 4.4 and section 6.6. Addressed in proposed PIL section 1 and section 3. Addressed on outer and inner carton and small immediate packaging units.	None.
Cardiovascular reactions in patients with pre-existing cardiovascular disease and/or hyperthyroidism	Addressed in proposed SmPC section 4.4. Addressed in proposed PIL section 2.	None.
Corneal oedema	No specific information required beyond the general instructions.	None.
Paediatric data	Addressed in proposed SmPC section 4.2.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Addressed in proposed PIL section 2.	
Use in relevant subgroups not studied in the clinical trial programme - patients with connective tissue disorder - intraocular inflammation - prior iris trauma - intraocular infection	Addressed in proposed SmPC section 4.2.	None.
Lack of long-term data on corneal endothelial injury	No specific information required beyond the general instructions.	None.
Influence on the incidence of cystoid macular oedema	No specific information required beyond the general instructions.	None.

2.9. Significance of paediatric studies

Not applicable.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The beneficial effect of Omidria added to the irrigation solution used during lens replacement procedures has been demonstrated in the submitted studies.

The results of the two Phase 3 Studies OMS302-ILR-003 and OMS302-ILR-004 provide robust evidence that Omidria maintains mydriasis as demonstrated by the mean change-from-baseline analysis in which the Omidria-treatment groups maintained the baseline pupil diameter throughout the procedure, while the

placebo group showed constriction of the pupil diameter with statistically significant differences between both groups observed in both studies.

In addition, studies OMS302-ILR-003 and OMS302-ILR-004 showed significantly fewer subjects in the Omidria group than the placebo group who experienced intraoperative miosis defined as absolute pupil diameter less than 6 mm or as a at least 2.5 mm of pupil constriction during ILR.

This effect of Omidria has been found clinically relevant by the CHMP as the intraoperative miosis significantly increases the difficulty of the ILR procedure and the risk of surgical complications. When a patient's pupil is inadequately dilated, the full operative field is not visible and instruments must be used blindly. Evidence from the published literature (Menapace, 2005) supports the contention that surgery is more difficult with increasing pupillary constriction and has a higher complication rate and that a pupillary diameter of less than 6 mm may act as a 'marker' for difficult surgery.

Omidria also reduced postoperative pain, which is mediated through the anti-inflammatory effect of ketorolac. The CMH weighted mean difference for postoperative pain (100-mm VAS) showed a significant difference between treatment groups. The categorical analyses of postoperative pain assessed the frequency of subjects with no ocular pain (VAS = 0) at all times and the frequency of subjects with moderate-to-severe pain (VAS ≥ 40) also showed significant differences between treatment groups.

Uncertainty in the knowledge about the beneficial effects.

Concentrations of phenylephrine and ketorolac above and below the concentrations used for Omidria have not been fully explored which is acceptable in view of the invasive nature of the surgery required for the dose-response evaluation. However, the applicant has selected a dose that was effective and well tolerated. As it is probable that the dose response curve for both active substances is flat, the proposed dose was accepted by the CHMP.

The clinical trial protocols specified exclusion criteria for patients with conditions that could complicate the interpretation of the data such as connective tissue disorders and intraocular disorders. Consequently, the submitted studies did not include subgroups of patients who are expected to have substantial limitation in their mydriatic ability, e.g. those who suffer from connective tissue disorders, intraocular inflammation, prior iris trauma, presence of pseudoexfoliation in either eye or intraocular infection.

The clinical trials did not include any evaluation of the surgeons' satisfaction with the procedure. Although it is acknowledged that there is no validated scale for such an evaluation, a simple scoring system could have been used. Consequently, the benefit to the surgeon and patient in terms of added value over the current best clinical practice was not fully explored.

Ocular lens replacement is typically a short procedure. The great majority of patients in the submitted studies had their surgery completed within thirty minutes so the anti-inflammatory and analgesic benefits of ketorolac are based on twenty to thirty minutes exposure. It is therefore to be expected that any analgesic and anti-inflammatory benefits will be predominantly peri-operative and this is generally what the results of the studies show. Benefits at times subsequent to the day of surgery have ceased to be measurable.

Risks

Unfavourable effects

Omidria appears safe and well tolerated when used at low concentration in eye surgery. The most frequent adverse events observed in clinical trials were eye pain, anterior chamber inflammation, conjunctival hyperaemia, photophobia and corneal oedema.

The limited amount of systemic testing carried out by the applicant suggests that when used as recommended, systemic exposure to PE is below the level of detection in most patients and KE is present in detectable low concentrations for one to two hours post-surgery in most patients. The risk of systemic side effects has been assessed by the CHMP to be very low.

The risk of an acute attack of angle-closure glaucoma or the exacerbation of pre-existing narrow-angle glaucoma is established for phenylephrine. Therefore, use of Omidria has been contraindicated in patients with narrow-angle glaucoma.

Uncertainty in the knowledge about the unfavourable effects

The safety population was generally considered representative for the proposed target population of Omidria. There was some uncertainty regarding the long-term safety of Omidria, as there follow-up period after clinical trials was relatively short. However, overall, the CHMP considered the extent of exposure sufficient to support the application and the long term safety has been addressed as missing information in the Risk Management Plan.

With the exception of eye pain (which was less frequent in Omidria group) the number and nature of adverse events in the active and vehicle group were quite similar. The CHMP also noted that the adverse events relating to the eye are difficult to evaluate as most of them probably relate to the process of surgery rather than unwanted effects of phenylephrine or ketorolac.

The CHMP also noticed that it should be assumed that in some patients and/or when Omidria is not properly used, phenylephrine will be present in higher concentrations than in the submitted studies and may cause systemic side effects. It is recognized that α-adrenergic drugs can cause dangerous dysrthythmias when used in eye-surgery and an appropriate warning has been included in the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

Maintenance of mydriasis and prevention of miosis are important since uncomplicated procedure helps ensure a successful operation, quick recovery, well-functioning new lens and an uncomplicated postoperative period.

The large difference in the proportion of subjects who experienced miosis with a pupil diameter of < 6 mm in the vehicle/placebo groups compared to the active treatment groups is likely to represent a substantial decrease in surgical risk in the Omidria-treated subjects. The frequency of patients with a constriction of ≥ 2.5 mm in pupil diameter confirms this result.

Currently, the benefit to the surgeon in terms of facilitating his/her task and thus benefiting the patient in terms of better outcome was not directly measured. However, mydriasis was better maintained with Omidria than with vehicle alone which is expected to be beneficial. Omidria may also be particularly useful in case of longer surgeries, performed by less experienced or trainee surgeons

With regards to the effect on pain scores, the convened expert panel observed that the clinical relevance of Omidria is rather modest. The experts noted that majority of patients do not complain of pain after the surgery and the currently administered steroids and NSAIDs are likely to provide sufficient level of pain control. Nevertheless, based on the clinical trial results, the CHMP was of the opinion that the observed effect on pain was still clinically relevant.

The CHMP concluded that use of Omidria during lens replacement surgery may be of benefit to the patient and the procedure: both intraoperatively by leading to a better visibility and faster, more precise intervention by maintaining mydriasis, as well as post-operatively, by reducing early post-operative pain.

Benefit-risk balance

In light of the totality of the evidence and taking into account the experts' view, the CHMP concluded that the benefits of Omidria outweighed its risks when used for maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement surgery. Thus, the benefit-risk balance was considered to be favourable.

Discussion on the benefit-risk balance

So far, no medicinal products have been available for intracameral use to maintain preoperatively evoked mydriasis during cataract surgery. Off label use of IV formulations of mydriatic agents (e.g. phenylephrine, adrenaline or tropicamide) either as intracameral bolus injection or by adding them to the irrigation solution is very common. The convened expert group also noted that mechanical methods such as pupil stretching, iris hooks or viscoelastics tend to carry higher risks of infection and iris damage.

Omidria has been developed, formulated and investigated for use in intracameral irrigation solution during lens replacement surgery for the purpose of maintaining mydriasis. Therefore, the CHMP agreed that it covers an unmet need.

The effects of Omidria on intraoperative mydriasis and postoperative pain have been clearly demonstrated. As the global population is aging, lens replacement therapy will be more demanded and optimum intraoperative settings are needed.

Omidria seems well tolerated and as it contains two well-known active substances, there are no unexpected findings in the safety database.

As there was no clear evidence to support the efficacy or safety of Omidria in patients with a history of uveitis, iris trauma or patients using alpha-adrenergic antagonists, the CHMP could not establish that a positive benefit-risk balance can be assumed in these cases. This has been made clear in the SmPC.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Omidria in adults for maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement surgery is favourable and therefore recommends the granting of the marketing authorisation, subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Paediatric Data

No significant studies in the agreed paediatric investigation plan P/0136/2013 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.