EMA/457364/2010
Evaluation of Medicines for Human Use

CHMP Assessment report

Ozurdex

International Nonproprietary Name: dexamethasone

Procedure No. EMEA/H/C/001140

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Allergan Pharmaceuticals Ireland submitted on 24 February 2009 an application for Marketing Authorisation to the European Medicines Agency for Ozurdex, 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 Agency/CHMP on 24 April 2008. 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 legal basis for this application refers to:

A - Centralised / Article 8(3) / Known active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant applied for the following indication: OZURDEX is indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).

1.1.1. Information on paediatric requirements

Pursuant to Article 7, of Regulation (EC) No 1901/2006 the application included an Agency Decision (P/68/2008) for the following condition: Other retinal vascular occlusion on the granting of a (product-specific) waiver.

1.1.2. Licensing status:

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.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **Gonzalo Calvo Rojas**

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 24 February 2009.
- The procedure started on 25 March 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 June 2009.
- During the meeting on 20-23 July 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2009.
- The summary report of the inspection carried out at the following site Allergan Inc, California, USA between 9-12 November 2009 was issued on 8 December 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2010.
- During the CHMP meeting on 15-18 February 2010, 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 9 April 2010.
- During the meeting on 17-20 May 2010, 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 Ozurdex on 20 May 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 May 2010.

2. Scientific discussion

2.1. Introduction

Macular oedema is a nonspecific response of the retina to a variety of insults, and is associated with a number of diseases, including uveitis, retinal vascular abnormalities, sequela of cataract surgery, macular epiretinal membranes, and inherited or acquired retinal degeneration. Macular oedema involves the breakdown of the inner blood-retinal barrier at the level of the capillary endothelium, resulting in abnormal retinal vascular permeability and leakage into the adjacent retinal tissues. The macula becomes thickened due to fluid accumulation resulting in significant disturbances in visual acuity. Prolonged oedema can cause irreversible damage resulting in permanent visual loss.

Depending on the location of the venous blockage, retinal vein occlusion is classified as branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Retinal vein occlusive disease is thought to occur as a consequence of thrombus formation at the lamina cribrosa or by compression of the venous wall by an overlying arteriole. Although the prevalence of retinal vein occlusion is only between 0.7 and 1.6 %, it is the second most common sight-threatening vascular disorder after diabetic retinopathy.

Therapeutic choices for macular oedema depend on the cause and severity of the condition. Currently there are no approved pharmacologic therapies for macular oedema. Argon laser photocoagulation increased the likelihood of vision improvement in patients with macular oedema due to BRVO, but not in patients with macular oedema due to CRVO.

Focal/grid laser photocoagulation has been shown to be efficacious in the prevention of moderate visual loss for macular oedema due to diabetic retinopathy. For central retinal vein occlusion, there are no known effective therapies.

Greater understanding of the pathophysiology of macular oedema has provided a scientific rationale for the use of steroids as a potential treatment. Vascular endothelial growth factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability.

Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema. There is a growing body of clinical evidence supporting the efficacy of intraocular steroids for the treatment of macular oedema.

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. The use of dexamethasone has had limited success in treating retinal disorders including macular oedema, largely due to the inability to deliver and maintain adequate quantities of the drug to the posterior segment. After topical administration of dexamethasone, only about 1% reaches the anterior segment, and only a fraction of that amount moves into the posterior segment. Although intravitreal injections of dexamethasone have been used, the exposure of the drug is very brief as the half-life of the drug within the eye is approximately 3 hours. Periocular and posterior sub-Tenon's injections of dexamethasone also have a short-term treatment effect.

Ozurdex is a sterile, single-use system intended to deliver one biodegradable implant into the vitreous for the treatment of macular oedema. The rationale of the design is to overcome ocular drug delivery barriers and prolong the duration of dexamethasone effect in the eye. This biodegradable implant delivers a 700 micrograms total dose of dexamethasone to the vitreous with gradual release over time allowing for sustained levels of dexamethasone in the target areas. Ozurdex may offer a new

therapeutic option in the treatment of macular oedema while reducing the potential for side effects typically observed from steroid administration through other routes of delivery (e.g. systemic).

The claimed indication reads as follows: Ozurdex is indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).

2.2. Quality aspects

Introduction

Ozurdex is presented as a prolonged release intravitreal implant in applicator containing 700 micrograms of dexamethasone as the active substance. It is a medicinal product-device combination product for implantation into the vitreal chamber of the eye.

The implant is formed into rods (diameter 0.46 mm x 6 mm long). Matrix of the implant is biodegradable, slowly degrading to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water. It consists of two different poly (D, L lactide-co-glycolide) polymers (PLGAs). The only difference between the polymers is that one is terminated with an ester group (50:50 PLGA ester) and the other is terminated with an acid end group (50:50 PLGA acid).

The implant is contained within its own specific applicator, located in the needle (stainless steel) of the disposable device. The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab. The applicator containing the implant is packaged in a sealed foil pouch containing desiccant.

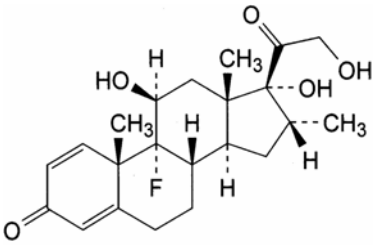
Administration is by needle injection. At the time of use, the patient is typically under a topical or local anaesthetic. The implant is delivered in a controlled manner by depressing the actuator button with the index finger. The needle is subsequently withdrawn as the puncture site self seals. To prevent applicator reuse the actuation lever latches after the dispensing stroke has been completed and the implant has been deployed.

To ensure that air is not introduced into the eye, the applicator has been designed to vent air through a small gap between the implant and the inner needle wall. This allows air to move back through and out of the needle as the implant is being delivered. The small size of this gap prevents fluid from flowing out of the eye through the needle.

The needle is a 22-gauge thin-wall hypodermic needle and is externally lubricated with silicone oil. A silicone rubber sleeve is placed over the needle from the hub to a cut-out in the needle. The sleeve is designed with a small ring at the distal end that fits into a cut-out in the needle to hold the implant in place. The sleeve remains outside the eye and contacts the conjunctiva during insertion.

Active substance

Dexamethasone is chemically designated as pregna-1,4-diene-3,20-dione-9-fluoro-11,17,21-trihydroxy-16-methyl-,(11β,16α) or 9α-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (IUPAC) or (11β, 16α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione (CAS) and has the following structure:



It is white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in anhydrous ethanol, slightly soluble in methylene chloride. Dexamethasone has 8 chiral centers and is optically active, specific rotation values are +75° and +80° (dried substance).

Two polymorphs (form A and form B) and a chloroform solvate are described in the literature. Although form A and form B have equivalent solubility in water, the proposed manufacturing process leads to a single polymorphic form. Chloroform is not used in the manufacturing process utilised by the proposed manufacturer.

- ***Manufacture***

The manufacturer of dexamethasone obtained a Certificate of suitability with requirements of European Pharmacopoeia (CEP). The detailed information on manufacturing process, starting materials, justification of critical steps, process controls and their evaluation, critical process intermediates and acceptance criteria were provided to the EDQM and assessed before granting the CEP.

Since particle size may be considered a critical attribute and because the particle size grade is not within the scope of the CEP the applicant provided satisfactory information concerning the method of micronisation and demonstrated that this process is adequately controlled.

It has been confirmed that no changes in the manufacturing process, specifications and analytical methods, were introduced since the granting of the CEP.

- ***Specification***

Dexamethasone is described in the European Pharmacopoeia and its manufacturer has confirmed that the active substance complies with these requirements. Additional tests for particle size, bacterial endotoxin, microbial contamination and residual solvents have been added to the specification for the active substance. A copy of the CEP has been provided. The CEP includes a test for residual solvents used during the synthesis.

The tests methods are according to the Ph Eur except for the assay and related substances tests were an in-house HPLC method is used. Satisfactory details for this method have been provided. It includes a satisfactory system suitability test.

Satisfactory validation data are provided for the HPLC assay for the active substance and related substances (including demonstration of equivalence with the Ph Eur monograph methods).

The microbiological contamination and endotoxin tests have also been satisfactorily validated.

Batch analysis data were provided for 5 batches of the active substance. All results were consistent from batch to batch and complied with the requirements in the active substance specification.

- ***Stability***

A retest period and storing conditions of the active substance are not mentioned in the CEP. To support the claimed shelf-life and storing conditions stability data from a study in formal conditions (ICH) have been provided.

Results indicate that the active substance is stable when stored according to proposed conditions and confirmed the claimed re-test period.

Finished Medicinal Product

- ***Pharmaceutical Development***

The goal of the formulation development was to obtain a sustained release polymer implant that delivers dexamethasone to posterior segment of the eye.

An extensive formulation development program has been conducted. The implant formulation development proceeded through two major formulation changes that were in response to three process changes, as the implant form changed from a compressed tablet to an extruded filament. The formulation was initially developed as a solid, tablet-shaped implant delivered surgically to the posterior segment of the eye. Since the tablet implant required surgical insertion and the manufacturing process was no viable for large scale manufacturing a hot-melt extruded implant has been developed. The extrusion process is an efficient and accurate method to produce homogeneous dexamethasone-polymer matrices assuring that the consistency and the diameter of the filament could be more precisely controlled, allowing placing inside a 22G hypodermic needle. A single-use applicator was designed with the needle for injecting the implant into the vitreous.

The change from a tablet to an extruded filament required:

1. Change of polymers as the extruded implant needed to be mechanically stronger than the tablet (which was surgically inserted). The polymeric matrix was also changed in order to achieve drug release profile for the extruded filament, equivalent to that observed for the tablet. Many different PLA and PLGA polymer combinations were tested and a combination of two PLGA polymers was selected.

2. Evidence that the extrusion and the sterilization process did not adversely affect the safety, quality or performance of the implant. The effects of extrusion on the active substance were studied. The effect of extrusion on the drug substance was studied comparing the crystallinity, melting point, melting enthalpy and IR spectra of dexamethasone in the implant with the same properties of the pure dexamethasone.

   The effects of gamma sterilization were studied in relation to the polymer matrix. Gamma radiation reduces the molecular weight of PLGA polymers by cleaving the backbone chains, and this could potentially result in faster drug release from gamma irradiated implants than from non-irradiated implants. The studies showed that the drug release rate with the gamma radiation dose selected was not affected.

3. Improve dimensional tolerance and content uniformity to facilitate placement of the implant in a 22 gauge needle, the delivery of the implant from the needle and a guarantee that cut filaments provide a consistent dose of dexamethasone.

The final formulation was established as a combination of two poly D,L-lactide-co-glycolide) polymers to produce a suitable matrix that controls the sustained release of dexamethasone, and ensure a

mechanical strength suitable for use in the applicator. This formulation was established in Phase 2b clinical study and has remained unchanged since then.

- ***Adventitious agents***

None of the excipients used in the medicinal product, including the active substance, is of the animal origin.

- ***Manufacture of the product***

During the development program of the manufacturing process a number of studies were undertaken. Development program included (1) development an extrusion process to assure content uniformity of the drug in the implant, the dimensional tolerances and physical characteristics that would facilitate the reliable delivery of the implant from the applicator, (2) development a cutting process to assure accurate dosing in the implants, (3) development a loading process and vision system to detect the loaded implant in the applicator system and (4) development a sterilization process to assure that the implant with the applicator was not adversely affected by gamma sterilization.

Based on these development studies and manufacturing experience gained during development all critical steps of the manufacturing process have been identified and adequately studied, and appropriate in-process control parameters have been established.

Manufacturing process developed for Phase 3 is essentially the same as the one proposed for commercial product. The Phase 3 equipment is also the same as proposed for commercial product except for improvements that have subsequently been introduced to the commercial process.

The product is terminally sterilised by gamma irradiation. The specified dose is 25 - 40kGy which is in compliance with the Ph Eur standard requirements.

The majority of steps in the Manufacturing process of the medicinal product are performed in a Grade C environment resulting in sealed applicator pouches which are than terminally sterilised by gamma irradiation and packed in its outer carton.

Validation data on three process validation batches manufactured in the proposed manufacturing site have been submitted. Validation reports were provided for all critical steps of the process and considered satisfactory.

- ***Product specification***

The drug product specifications include tests for appearance, identification of dexamethasone (HPLC and TLC), assay of dexamethasone (HPLC), impurities (HPLC), Insoluble Particulate Matter, Actuation Force, Dexamethasone Release, sterility, Bacterial Endotoxin (implant and the device), content uniformity.

The analytical methods have been sufficiently described, some of them are compendial methods described in the Ph Eur.

Single HPLC method is used for dexamethasone content, content uniformity and related substances. The method is specific for dexamethasone, separates dexamethasone from its impurities, and there is no placebo interference. Satisfactory validation data, according to ICH validation guidelines, have been provided. Suitability of the method for routine control and stability has been demonstrated.

The dexamethasone release profile from the implant is determined by using a non-standard dissolution apparatus and HPLC method.This method is intended to determine the amount of dexamethasone released from the polymer matrix over a 21 day period for quality control purposes only. Combined

with the outer and inner blood-retinal barriers as well as a host of retinal pigmented epithelial drug transport mechanisms this makes an a priori in vitro-in vivo correlation in humans impossible. Therefore, for the intravitreal implant, the quality control drug release method is not intended to fully represent the human in-vivo performance of the drug product, but rather to ensure that the implant manufacturing process is reproducible.

Batch analysis results on 5 commercial scale batches of the drug product demonstrated compliance with the proposed specification and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed finished product specification.

- ***Stability of the product***

Stability studies according to the ICH guidelines have been performed on 3 primary stability batches of Ozurdex 700 micrograms. Additional data were generated for 3 primary batches of 350 micrograms implants. This data is considered representative of the 700 micrograms product.

Stability data were generated using the storage conditions listed in the ICH Guidance and contained results for 24 months from long term storage at 25°C/60% RH, 12 months from storage under intermediate conditions at 30°C/65%RH, and 6 months from accelerated conditions at 40°C/75% RH.

Test methods used in "Stability studies" are the same as the one used at release except the test for content uniformity, which is performed only at release.

The container/closure system used in the primary stability study utilizes the same materials as the proposed commercial package.

Photo-stress studies were not conducted as there is brief exposure to light during manufacture and dosing. Additionally, the implant is packaged in an applicator system with an aluminium foil pouch which protects the product from exposure to light until just prior to administration

A package leachable study was performed to evaluate potential volatile leachables which might migrate and adsorb into the implant matrix. The product was monitored after three months of storage at 40°C/75% RH and compared to cut bulk filament stored in glass vials. No leachables were observed, which indicates that the proposed container closure system is suitable for use with implant.

The results generated during the stability studies and statistical analyses support the proposed shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active drug substance, dexamethasone, is a well-known and well-characterized ingredient described in the Ph Eur. The manufacturer is holder of EDQM Chemical Certificate of Suitability (CEP). A copy of this CEP was presented, therefore minimal information on the synthesis and control of the active substance was included in the dossier.

Finished product is a sterile medicinal product-device combination product comprising the drug product that is a biodegradable sustained delivery intravitreal implant and the device component that is a single-use applicator is designed specifically to deliver the rod-shaped implant directly into the posterior segment of eye. The implant is composed of micronized dexamethasone homogeneously dispersed in two biodegradable poly (lactide-co-glycolide) PLGA polymers, and extruded as a filament (0.46 mm diameter/6 mm length) that delivers 700 micrograms of dexamethasone to the vitreous with gradual release over time allowing for sustained drug levels to the target areas despite lower total daily dose, and does not need to be removed since the copolymer dissolves and biodegrades into

carbon dioxide and water over time. The implant is placed in the applicator during the manufacture of the finished product and retained within the needle of the applicator.

The description and composition of the product are properly documented. The application system is packaged in a peelable laminated foil pouch with one packet of desiccant and heat sealed.

The pharmaceutical development of the drug product is adequately and sufficiently described. The information given is very extensive and supports the formula and the pharmaceutical form selected. The final sterilization by gamma radiation is justified

The characteristics and the quality of the applicator are adequately documented.

The method of manufacture is non-standard. Description of the manufacturing process, in-process controls, critical steps and their controls and methods applied are satisfactory. All critical in-process controls parameters are well established and justified.

The control of excipients is satisfactory.

The drug product specification has been correctly discussed and the limits proposed for each test have been established taking into account the data of clinical and stability batches. In general, the specifications are acceptable.

Analytical methods used to control the quality of the finished product are well described and validated according ICH.

The stability studies have been performed in accordance with ICHQ1A guideline on three scale commercial batches. Data from accelerated (6 months), intermediate (12 months) and long-term conditions (24 months) have been submitted. The proposed shelf-life and storage condition are justified.

Conclusions on the chemical, pharmaceutical and biological aspects

The drug substances and the drug product have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that the drug substances and the drug product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1 Introduction

The applicant conducted a partial non-clinical development program. This program is in general agreement with the applicable guidelines.

All definitive toxicology studies were carried out in full compliance with Good Laboratory Practice (GLP) regulations. Investigations undertaken to establish suitable doses for use in the toxicity and pharmacokinetic studies were performed in accordance with the general principles of GLP.

2.3.2. Pharmacology

- ***Primary pharmacodynamic studies***

The applicant provided data from published literature (Nakada, 1987) regarding dexamethasone binding affinity to glucocorticoid receptors in fibroblasts. Data from saturation analysis yielded a K_d of

3.47 ± 0.38 nM and a B_{max} of 50,100 ± 2,200 sites/cell (n=3). The K_d value for [^{3}H] dexamethasone binding correlated very well with the 2.77 nM EC_{50} value for dexamethasone regulation of β-adrenergic receptor subtype. The relevance of these data was initially unclear to the CHMP, but the applicant provided an acceptable justification arguing that the provided references could be extrapolated to the claimed indication as there were no available specific dexamethasone pharmacology data on tissue explants or cell culture models for the blood-retinal barrier at the time of initial submission. In addition, a new reference was submitted by the applicant during the procedure that showed dexamethasone cytokine induction inhibition in human retinal microvascular pericytes in the same range of concentrations (2 nM).

The applicant also provided the results of a 10 week study in the rabbit eye to evaluate the primary pharmacodynamics of the 350 µg and 700 µg DEX PS DDS. The rabbit model used for this study was designed to mimic the pathologies associated with retinal vein occlusion (RVO), demonstrating a breakdown of the blood-retinal and blood-aqueous barriers, and an accumulation of retinal fluid. An intravitreal injection of vascular endothelial growth factor (rHu-VEGF) was used to activate specific endothelial receptors that signal the breakdown of the blood-retinal and blood-aqueous barriers. Glucocorticoids such as dexamethasone and triamcinolone acetonide were previously shown to suppress the expression of VEGF protein and to block nearly all pathological retinal responses elicited by intravitreal VEGF injection. In the study, the 350 µg dose completely blocks VEGF-induced blood-retinal barrier (BRB) breakdown in rabbits two weeks after intravitreal drug injection. This dose also partially inhibits blood-aqueous barrier (BAB; iris) breakdown. Six weeks after injection, the 350 µg dose partially inhibits BRB breakdown but has no effect on BAB breakdown. For the higher 700 µg dose, the efficacy was similar to that of the 350 µg dose, with more pronounced inhibition, and this was still significant six weeks after the injection unlike in the lower dose. There was no pharmacological effect on VEGF-induced responses measured ten weeks after intravitreal injection of either formulation. The doses chosen for this study are the therapeutic doses considered for humans, and it is important to note the relative difference in eye size from the rabbit eye administered intravitreally in this study compared to the larger human eyes. In general, CHMP considered that Ozurdex was effective in the study relevant to the proposed indication.

- ***Secondary pharmacodynamic studies***

No secondary pharmacodynamics studies were performed by the applicant with the 350 µg or 700 µg DEX PS DDS formulations. Considering the low dexamethasone systemic exposure following intravitreal administration of 350 µg or 700 µg DEX PS DDS, systemic effects on glucocorticoid receptors is not expected.

- ***Safety pharmacology programme***

No safety pharmacology studies were conducted with the intravitreal DEX DDS formulations.

The applicant provided literature references regarding peribulbar, intravitreal and anterior chamber injections of dexamethasone (5 mg [peribulbar] and 400 µg [intravitreal and anterior chamber] respectively), as well as topical and oral administration for treatment of different ocular pathologies in humans (endophthalmitis and ocular inflammatory conditions unresponsive to topical corticosteroids). No ocular adverse effects were reported in any of these publications. According to CHMP Guideline on Safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00), considering that DEX PS DDS is administered locally (i.e. ocular, intravitreal), and the systemic exposure is demonstrated to be low, the absence of specific safety pharmacology studies for Ozurdex was acceptable to the CHMP.

- ***Pharmacodynamic drug interactions***

No pharmacodynamic drug interaction studies were performed by the applicant with the 350 or 700 µg DEX PS DDS.

However, as reflected in section 4.2 "Posology and method of administration" of the SPC, adequate anaesthesia and a broad spectrum topical antimicrobial should be given prior to Ozurdex injection. The applicant was therefore requested to discuss potential pharmacodynamic drug interactions between Ozurdex and ophthalmic anaesthetic and antimicrobial agents. The applicant responded by reviewing the results of the repeat-dose toxicity studies in rabbit and primate where gentamicin, tropicamide, proparacaine and benzylalkonium chloride eye drops were administered prior to Ozurdex injection. The applicant highlighted that no increase of infection rates, lack of anaesthetic strength or abnormal pupil dilation were noted. Although the agents included in the repeat-dose toxicity studies are not the same agents that are foreseen to be administered in humans, the CHMP agreed that potential pharmacodynamic interactions do not seem to be likely and that the lack of pharmacodynamic interaction studies between Ozurdex and recommended co-medication has been adequately justified by the applicant.

2.3.3. Pharmacokinetics

To support the safety of Ozurdex (DEX PS DDS Applicator System) in man, the posterior segment pharmacokinetics of dexamethasone has been evaluated in five single-dose ocular absorption and distribution studies in rabbits and in one single-dose study in monkeys. All pivotal single dose pharmacokinetic studies and two repeat dose toxicokinetic studies were conducted in compliance with Good Laboratory Practice (GLP) regulations, using validated analytical methods.

Due to the limited availability of monkey vitreous humour, aqueous humour, retina and iris-ciliary body, rabbit samples were used as a proxy matrix, and the same analytical methods were thus employed for both species. For biological matrices that are difficult to obtain, the use of a physiologically appropriate proxy matrix is scientifically acceptable. For aqueous humour, a cross-validation as described by Bressolle was performed. The applicant considered the results acceptable, although precision results did not satisfy previously established acceptance criteria (< 15%). In addition, for dexamethasone determinations in vitreous humour, retina and iris-ciliary body in monkey samples, no cross-validation was performed to demonstrate the adequacy of the rabbit proxy matrices. The applicant was therefore requested by the CHMP to apply the cross validation criteria to all the analytical methods for the different matrices in rabbit, to warrant the adequacy of the methods validated for rabbit matrices to monkey matrices.

According to the Draft EMEA Guideline on Validation of Bioanalytical Methods (EMEA/CHMP/EWP/192217/2009) more flexible approaches are admitted when validating methods for rare matrices. In addition, the applicant submitted the summaries of two new cross-validation studies for monkey vitreous humour and retina using rabbit proxy matrices. According to these results, analytical methods for monkey VH and retina appear to be adequately validated. However, these reports were not considered fully adequate as final study validation reports since original raw data were not included to allow an accurate assessment of the results presented. The applicant was therefore requested to submit complete study reports including original raw data to the CHMP as a follow-up measure (see section 2.7 of this report).

Absorption

The ocular absorption of DEX PS DDS was studied in New Zealand White (NZW) rabbits and cynomolgus monkeys following a single dose administration for different observation periods. Tablet,

single and double extruded dosage forms were tested, and two different implantation methods were used, sclerotomy and implantation via Ozurdex applicator. The extruded implants generally released dexamethasone more gradually and with less variability than the tablet implants, and the extruded form showed greater uniformity of dexamethasone release compared to the tablet implant.

In the repeat-dose toxicology studies, the plasma C_{max} in rabbit and monkey at the highest DEX PS DDS dose (1400 µg) administered were 1.60 and 0.555 ng/ml, respectively. The repeat-dose toxicokinetic profiles were similar to the single-dose, and this suggests that there is no potential for ocular or systemic drug accumulation following repeat dosing of DEX PS DDS. Based on body weight differences between human (~60 kg) and monkey (~3 kg) the systemic exposure of dexamethasone in human is expected to be ~20-fold lower than in monkey.

The applicant also provided literature references regarding the mean peak plasma concentration following a single (IV or oral) or multiple (topical ocular) administration of dexamethasone or dexamethasone disodium in humans. These plasma concentration varies from 10.5 ± 2.8 (IV), 8.4 ± 3.6 (oral) and 0.7 ± 0.4 mg/ml (topical ocular). The oral and IV doses range from 6 mg up to 8 mg more than ocular administration, leading to subsequently higher human exposure.

Distribution

Following intravitreal implantation, both radiolabel solution and non-radiolabel implant studies showed a similar pattern of distribution and indicate that ocular distribution does not change. There is delivery to the posterior of the eye and distribution to the retina following implantation of DEX PS DDS. As a result of the observations in the 6-month pharmacokinetic study in rabbits, CHMP concluded that the location of the implant in the posterior segment of the eye has a direct effect in the duration of the drug release. The applicant was further requested by the CHMP to discuss the relevance for the healthy/untreated eye of the dexamethasone exposure via contralateral diffusion observed in the 6 months study in rabbits. Taking into account the low systemic levels of dexamethasone following intravenous administration, exposure in the untreated eye due to systemic exposure does not seem to be likely. In addition, as stated by Sigurdsson et al, 2007, the contribution of systemic drug return to the ocular tissues would probably be lower in humans as the apparent volume of distribution is much greater in 70 kg humans than in 2 kg rabbit. Therefore, the CHMP acknowledged that minimal biological effect of DEX PS DDS on the contralateral eye in humans would be expected. However, the route of exposure in the untreated eye following administration of DEX PS DDS in the contralateral eye has not been fully clarified. Section 5.3 of the SPC therefore includes information to reflect the potential contralateral exposure in the untreated eye, as observed in rabbits, as a warning for eventual findings in clinical practice.

No new studies regarding the systemic distribution of dexamethasone have been submitted. The data provided by the applicant from literature references included data from dexamethasone binding to plasma protein. This study revealed that 85, 73, 74 and 77% was bound in rat, dog, cow and human plasma, respectively. Results submitted also suggest that the binding of dexamethasone is linear and occurs primarily to albumin, with little or no binding to corticosteroid-binding globulin (transcortin); endogenous cortisol does not compete with dexamethasone for protein binding sites. Considering the low systemic dexamethasone concentrations following intravitreal administration of DEX PS DDS, no relevant systemic effects are expected in renally impaired patients.

The applicant was requested by the CHMP in the Scientific Advice (EMEA/CHMP/SAWP/340437/2005) to provide in the MAA data on melanin binding (especially intraocular) in a specific study in a pigmented species or from literature. The in vivo results submitted by the applicant instead, adequately reflect the absence of dexamethasone binding to melanin in Dutch-Belted rabbits. In addition, dexamethasone showed rapid clearance from all ocular tissues in NZW rabbits and

Cynomolgus monkeys. Dexamethasone is therefore not expected to accumulate in human pigmented ocular tissue.

Metabolism

The applicant provided literature references regarding dexamethasone metabolism. Dexamethasone metabolism has been extensively examined. Liver metabolism via CYP3A4 enzymes has been shown previously. Ocular metabolism studies were conducted by the applicant and both *in vitro* and *in-vivo* studies have shown no or minimal evidence of metabolism in the rabbit, monkey or human ocular tissue. The use of poly (D,L-lactide-co-glycolide) biodegradable polymer (PLGA) has also been examined previously with humanised monoclonal antibody, rhuMAb HER2 in rabbits, and has been shown to be well tolerated and with slow vitreous clearance. Though the metabolism of the poly (D,L-lactide) polymer (PLA) and PLGA vehicle of the implant is well established and recognised in other drug formulations, this is not established for intravitreal administration, although it can be assumed that they are degraded in a similar way.

Excretion

The elimination of dexamethasone from the systemic circulation following administration of Ozurdex is considered to be similar to that of oral, intravenous or topical ocular administration. Following a single intravitreal injection of dexamethasone in rabbit and monkey, dexamethasone was rapidly cleared from the vitreous humour. Estimation of human vitreal clearance can further be made from the literature (Gan et al, 2005). This study suggests that vitreal clearance in humans to be approximately 12 ml/day, and this is in line with both the rabbit and monkey, implying a similarity in elimination. Influence of a disease state may however have an effect on dexamethasone clearance, but this has not been explored.

Dexamethasone is known to cross the placenta and be excreted in milk. This information is accurately reflected in section 4.6 of the SPC.

Pharmacokinetic drug interactions

No ocular drug-drug interaction studies have been conducted for DEX PS DDS and no systemic pharmacokinetic drug interactions are expected following intravitreal administration of Ozurdex since only very low dexamethasone concentrations will be reached at systemic level.

Regarding potential pharmacokinetic interactions, the CHMP initially highlighted, as stated above in the section on pharmacodynamic drug interactions, that adequate anaesthesia and a broad spectrum topical antimicrobial will be given prior to Ozurdex injection. Following assessment of further data from the applicant the CHMP agreed that systemic pharmacokinetic interactions between Ozurdex and other co-administered medication are not expected due to the low systemic exposure to dexamethasone following Ozurdex intravitreal administration, not high enough to induce hepatic enzymes.

Local interactions were not observed in the repeat-dose toxicity studies conducted in rabbits and monkeys. No abnormal or unexpected pharmacokinetic findings were noted. Potential pharmacokinetic interactions do not seem to be likely. However, it should be noted that co-administered medication in these studies was not exactly the same that is foreseen to be administered in clinical practice.

2.3.4. Toxicology

Toxicity studies were conducted to evaluate the ocular and systemic effects of DEX PS DDS following administration in NZW rabbits. Repeat-dose intravitreal ocular toxicity studies were also conducted in NZW rabbits and cynomolgus monkeys using the DEX PS DDS and the Ozurdex applicator system. No

new studies were performed to investigate the mutagenicity, carcinogenicity, or reproductive effects due to the well established clinical use of dexamethasone and the low systemic exposure following intravitreal administration. All toxicology studies with the DEX PS DDS were conducted according to Good Laboratory Practice (GLP) guidelines and procedures.

Table 1 - Ozurdex Toxicology Program

Study Type/Number	Study Type	GLP	Dosing Duration/ Study Status
Single Dose			
X7I062G	Toxicity study of intraocular dexamethasone drug delivery system (DDS) in the posterior segment of the rabbit eye	Yes	Single dose/ Completed
X8I310G	Toxicity of dexamethasone drug delivery system (DEX PS DDS®)	Yes	Single dose/ Completed
P0701002	90-day ocular and systemic toxicity evaluation of DEX PS DDS® 114, 0.7 mg implanted into the posterior segment of the eyes of New Zealand White rabbits	Yes	Single dose/ Completed
Repeat Dose			
TX05030	POSURDEX®: chronic intravitreal ocular toxicity study in rabbits	Yes	2 injections at 3 months apart/ Completed
TX05029	POSURDEX®: chronic intravitreal ocular toxicity study in monkeys	Yes	2 injections at 3 months apart/ Completed
Other Toxicity			
P0902001	Evaluation of the DDS applicator functionality and safety for insertion and dispensability in the eyes of New Zealand White rabbits	Yes	Single dose/ Completed

- ***Single dose toxicity***

A number of single-dose toxicity studies in rabbits were conducted to evaluate the ocular and systemic effects of DEX PS DDS following sclerotomy implantation of the implant. Rabbits were surgically (sclerotomy) implanted with 700 µg (1 implant), 1400 µg (2 implants), or 2100 µg (3 implants) dexamethasone into the posterior segment of the right and left eyes. Unlike standard single-dose toxicity studies, animals in DEX PS DDS studies were not sacrificed 14 days post-dosing, as the single-dose effects extend beyond this time period and ocular effects were observed up to 23 weeks post-implantation. This was considered as an acceptable approach by the CHMP, in the context of the treatment and administration of the implant.

Sclerotomy implantation to the posterior segment of both eyes showed no evidence of intravitreal ocular toxicity. A number of surgical-related effects were observed, including cataract formation, squinting, decreases in intraocular pressure (IOP), focal granulomatous or chronic inflammation in the sclera and/or conjunctiva associated with silk sutures. These ocular changes were observed in both the test and placebo groups and was believed to be attributed to the surgical procedure and the reduced amount of vitreous volume for the rabbit eye (1.5 ml rabbit compared to 3.6 ml in human). By using relative vitreous volumes to normalise doses between species the applicant demonstrated that it is possible to overcome the effects due to differences in vitreous volume between species.

Lymphotoxicity and decreased body weight was observed, this was most evident up to 30 days post-implantation and considered a dexamethasone-related systemic effect. These effects were reduced at two months and disappeared thereafter. The intravitreal dose of dexamethasone administered in each 700 µg DEX PS DDS implant is equivalent to approximately 0.2 mg/kg body weight in rabbits, which is

roughly 20 times higher than the expected therapeutic dose for man (assuming 60 kg body weight). In more detail, the safety margins relating to the exposure to dexamethasone range from 3.8 to 17 fold in animal studies with use of the applicator, and from 7 to 100 fold following topical and intravenous dexamethasone.

- ***Repeat dose toxicity***

Two repeated-dose toxicity studies were conducted in rabbits and monkeys using the clinical Ozurdex applicator system. In both studies, two intravitreal injections were followed by an observation period up to 9 months post the second injection. Both studies were performed in accordance with GLP standards.

Parameters evaluated in the studies included detailed observations, body weights and food consumption. Serum chemistry and haematology evaluations, urianalysis, organ weights, macroscopic and microscopic pathologic evaluations, gross ocular observations, ophthalmology, electroretinography and tonometry were also conducted in these studies.

As stated earlier, the repeat-dose toxicity studies were conducted in rabbits and monkeys. The Ozurdex implants were tolerated adequately in both species following two intravitreal implantations. In the rabbit there was evidence of cortical lens opacity following the second dose. Of these three incidences, one showed opacity regression after 12 months, which is in line with what has been shown previously to occur following topical administration of corticosteroids.

The duration of the repeat-dose studies was considered adequate by the CHMP. There were expected procedure-related effects of transient conjunctival irritation, vitreal implant remnants, and fibrosis (foreign body reaction) that was localised to the implant (injection) sites and this was observed in both species and in all treated animals and controls. The doses these animals were administered are the human therapeutic doses of 350 µg or 700 µg DEX PS DDS. Considering the relatively small size of the rabbit/monkey eye compared to the human, the doses administered in these repeat-dose studies are higher than would be expected to be exposed to human.

The applicant has, as described earlier, developed an applicator to deliver the DEX PS DDS implant to the posterior segment of the eye, and following administration in the repeat-dose studies, there was no incidence of injection-related cataract observed.

The applicant also provided literature references regarding the lack of toxicity of PLGA microspheres, administered intravitreally, to the ocular tissues. Whereas the implantation of PLGA fibres in a rabbit cornea pouch (cornea micropocket assay) resulted in vascular invasion into the cornea, although it could be caused by leachables from the implanted materials. This bibliographic data was considered sufficient by the CHMP to satisfy the requirements given in the CHMP Scientific Advice (EMEA/CHMP/SAWP/340437/2005) of providing appropriate toxicological studies or other justifications to demonstrate the safety of PLGA by the intravitreal route of administration. In addition, there were no observable findings in the two studies referenced that could be attributable to PLGA in placebo treated animals (i.e. PLGA implant).

The studies into repeated-dose toxicity of DEX PS DDS are considered to be generally acceptable to the CHMP.

- ***Genotoxicity***

Previous studies to evaluate the mutagenic potential of dexamethasone in bacteria and mammalian cells in vitro have been negative. Given the long history of safe use of dexamethasone and with the

low levels of patient exposure, genotoxicity studies have not been performed and this was considered acceptable to the CHMP.

- ***Carcinogenicity***

Given the long history of safe use of dexamethasone and with the low levels of patient exposure, no carcinogenicity studies on dexamethasone or DEX PS DDS have been performed. Inactive components of DEX PS DDS have been shown to metabolise into substances normally found in the body and therefore are not considered to increase the risk of carcinogenicity. This was considered acceptable to the CHMP.

- ***Reproduction Toxicity***

No new studies on fertility and general reproduction, embryo-fetal development, or pre-/post-natal development have been performed for Ozurdex. However, there are published data on the teratogenicity of dexamethasone in mice, rabbits and rhesus monkeys following topical ophthalmic and intramuscular administration. The teratogenic dose in rhesus monkeys (1.0 mg/kg/day dose) is 85-fold higher than a 700 µg DEX PS DDS implant in humans. It should also be considered the low systemic exposures observed following intravitreal implantation of DEX PS DDS in absorption studies (7.40 ng.day/mL and 16.8 ng.day/mL, in rabbits and cynomolgus monkeys, respectively). However, adequate warnings regarding the potential risk in pregnant or nursing women is included in sections 4.6 and 5.3 of the SPC.

- ***Toxicokinetic data***

Mean plasma C_{max} values increased with dose in monkeys between 350 and 700 µg DEX PS DDS, and similarly between 700 and 1400 µg DEX PS DDS treatment groups in rabbits. The extent of systemic exposure appeared to be dose proportional in rabbits and more than dose proportional in monkeys. Duration of plasma drug concentrations was longer for the high dose group compared to the low dose group in both species. No gender-related differences were observed in monkeys where animals of both sexes were included.

- ***Local Tolerance***

The applicant has not performed specific local tolerance studies, but considered based on the Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00) that local tolerance was assessed in the ocular single and repeat dose toxicity studies in rabbits and monkeys.

The CHMP accepted the applicant's strategy, but requested the applicant to discussion in detail the histopathology of the eye in those studies. It should be highlighted that retina and choroid are the target tissues for DEX PS DDS action. In response the applicant provided a discussion on histopathology data from repeat dose toxicity studies, including local tolerance endpoints and based on the conclusion that there were no abnormal findings on the retina or choroids outside the injection site in either rabbit or monkey repeated dose studies, the CHMP subsequently considered that there are no safety concerns regarding the local tolerance of Ozurdex.

- ***Other toxicity studies***

<u>Ozurdex applicator system safety and performance</u>

To evaluate the performance of the DEX PS DDS applicator, a special study in NZW rabbits was conducted. The Ozurdex applicator system was used to implant DEX PS DDS into the posterior segment of rabbit eyes. The study found that the applicator system was easy to use. Traumatic

cataracts and other reactions were observed in this study, but these are thought to be likely related to the dimensions of the rabbit eye and not a problem associated with the Ozurdex applicator.

Phototoxicity

As dexamethasone absorbs outside the visible and UVA/B light spectrum (290-700 nm), phototoxicity testing was not performed. Dexamethasone has a long history of safe use following topical ocular administration.

Studies on impurities

All starting materials were USP grade and met USP specifications. According to the applicant, impurities in the drug product were tested at levels that exceeded current specifications and exceeded what will be used clinically.

Dexamethasone ketone, degradation product, was tested up to 1% in batches used in non-clinical studies according to drug product specifications provided. However, proposed release and shelf-life specification for dexamethasone ketone was NMT 1.4%. The CHMP highlighted that this specification is above the qualification threshold for degradation products in new drug products (Maximum daily dose: < 1 mg; threshold: 1.0% or 5 µg TDI, whichever is lower) according to Note for guidance on impurities in new drug products (CPMP/ICH/2738/99). Therefore, this impurity (degradation product), dexamethasone ketone, was not initially considered by the CHMP as qualified.

In response the applicant argued that as DEX PS DDS is a slow release delivery system, patients are not expected to be exposed to daily amounts of dexamethasone ketone exceeding the qualification threshold, in this case: 1.0% or 5 µg TDI, whichever is lower, for a Maximum daily dose: < 1 mg (Note for guidance on impurities in new drug products (CPMP/ICH/2738/99)). Therefore, as qualification of dexamethasone ketone was considered by the applicant to be required. The CHMP acknowledged the applicants argument and considered that further qualification of the degradation product was not needed.

2.3.5. Ecotoxicity/environmental risk assessment

An environment risk assessment for dexamethasone was performed. The dexamethasone $PEC_{surface\ water}$ value is 0.007 µg/L, below the action limit of 0.01 µg/L and dexamethasone is not a PBT substance as log Kow does not exceed 4.5 (2.06 ± 0.58). It is concluded that Ozurdex intravitreal implant is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has conducted several studies (phase I-III) to evaluate the use of DEX PS DDS. Two of those studies (206207-008 and 206207-009) have utilised the formulation intended for marketing in the proposed indication. The dose ranging study DC103-06 included patients with the intended indication (macular oedema), however, this study was performed with the tableted formulation. The release characteristics of the tablet appear to be very different to the final product, therefore all studies performed with the tablet could only be considered as supportive.

2.4.2. 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.

A routine GCP inspection has been performed on the request from the CHMP In the GCP inspection no critical findings were identified by the GCP inspectors.

Table 2 - Overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Status, Type of Report
safety efficacy	DC103-06	5.3.5.1.1 report DC103-06	compare safety and effectiveness in treatment of macular edema	randomized, examiner-masked, multicenter, observation control	DEX PS DDS (350 or 700 µg dexamethasone) inserted through the pars plana Observation	315	patients with persistent macular edema	6 months (plus every 3 months until exit if DDS at Day 180)	study complete full report
safety efficacy	206207-008	5.3.5.1.1 6-month report 206207-008	compare safety and efficacy	initial treatment randomized, examiner-masked, multicenter, sham control	DEX PS DDS (350 or 700 µg dexamethasone) Sham (needleless DDS applicator without study medication) inserted thru the pars plana using applicator system	599	patients with macular edema due to branch or central retinal vein occlusion	6-month masked initial treatment	study complete full 6-month report
safety	206207-008	5.3.5.1.1 12-month report 206207-008	assess safety of 700 µg dose for additional 6 months	initial treatment randomized, examiner-masked, multicenter, sham control extension non-randomized open-label, multicenter, no control	DEX PS DDS (350 or 700 µg dexamethasone) Sham (needleless DDS applicator without study medication) inserted thru the pars plana using applicator system Eligible patients received a second treatment of DEX PS DDS 700 µg at month 6	599 477 in the re-treated population 118 in the single-treatment population 4 randomized but did not receive treatment	patients with macular edema due to branch or central retinal vein occlusion	6-month masked initial treatment followed by 6-month open-label extension	study complete full 12-month report
safety efficacy	206207-009	5.3.5.1.1 6-month report 206207-009	compare safety and efficacy	initial treatment randomized, examiner-masked, multicenter, sham control	DEX PS DDS (350 or 700 µg dexamethasone) Sham (needleless DDS applicator without study medication) inserted thru the pars plana using applicator system	668	patients with macular edema due to branch or central retinal vein occlusion	6-month masked initial treatment	study complete full 6-month report
safety	206207-009	5.3.5.1.1 12-month report 206207-009	assess safety of 700 µg dose for additional 6 months	initial treatment randomized, examiner-masked, multicenter, sham control extension non-randomized open-label, multicenter, no control	DEX PS DDS (350 or 700 µg dexamethasone) Sham (needleless DDS applicator without study medication) inserted thru the pars plana using applicator system Eligible patients received a second treatment of DEX PS DDS 700 µg at month 6	668 520 in the re-treated population 141 in the single-treatment population 7 randomized but did not receive treatment	patients with macular edema due to branch or central retinal vein occlusion	6-month masked initial treatment followed by 6-month open-label extension	study complete full 12-month report

2.4.3. Pharmacokinetics

No formal pharmacokinetic studies were conducted. Systemic exposure was however measured within the two pivotal phase III studies (206207-009 and 206207-008).

The results indicated that exposure is low. No ocular pharmacokinetic evaluations were conducted. In both studies, the majority of plasma dexamethasone concentrations were below the level of quantitation (BLQ). In the pooled studies, plasma dexamethasone concentrations from 10 of 73

samples in the DEX 700 group and from 2 of 42 samples in the DEX 350 group were above the LLOQ, and ranged from 0.0521 ng/mL to 0.0940 ng/mL. There were no apparent correlations between plasma dexamethasone concentration and age, body weight, or sex. The single highest plasma dexamethasone concentration observed in the phase 3 studies was 0.0940 ng/mL which is only 13.4% of that reported following multiple ocular applications of 1 drop of dexamethasone disodium phosphate (0.1%) to one eye every 1.5 hours.

2.4.4. Pharmacodynamics

No pharmacodynamic studies were conducted and therefore PK/PD relationships could not be ascertained. Pharmacodynamic data were collected from a phase II dose-ranging exploratory study (DC103-06) in which a dose-response improvement in visual acuity was observed. The maintenance of the effect over time was studied in the two confirmatory trials.

2.4.5. Clinical efficacy

- ***Dose response study***

One dose-finding phase II study (DC103-06) was conducted.

Study DC103-06

This dose-ranging study was a randomised, examiner blinded, parallel group, three arms comparative trial (DEX 350 tablets, DEX 700 tablets, both inserted through the pars plana vs. observation) in patients with persistent macular oedema (PME) following treatment and associated with diabetic retinopathy, uveitis, retinal vein occlusion, and Irvine-Gass syndrome. Safety was evaluated for 6 months and efficacy through day 90.

Eligible patients were aged 12 years and older with persistent macular oedema defined as clinically observable macular oedema persisting at least 90 days after laser treatment or after 90 days of medical management. Macular oedema was defined as retinal thickening at the centre of the fovea, visual acuity equal to or worse than 20/40 attributable to PME and angiographic evidence of leakage in the perifoveal capillary net.

The primary endpoint was the proportion of patients with ≥ 2 lines improvement in best-corrected visual acuity (BCVA) at day 90.

Statistical significance for the primary endpoint, an improvement of 2 or more lines in the last observation carried forward (LOCF) analysis of best-corrected visual acuity (BCVA) at day 90, was observed for the DEX PS DDS 700 µg group (36.7%) versus the Observation group (19.0%), p = 0.005. The improvement rate was likewise numerically higher with DEX PS DDS 350 µg (26.1%) than with Observation, although the difference was not statistically significant. The improvement was with DEX PS DDS 350 µg was also lower than with DEX PS DDS 700 µg thus indicating a dose-response effect.

- ***Main studies***

This application is based on two pivotal phase III studies to support the efficacy and safety of DEX PS DDS in the treatment of macular oedema: Study 206207-009 and Study 206207-008. The studies which were identical in design, were six-month randomised, sham-controlled studies with a 6-month open label extension, assessing the safety and efficacy of 700 µg and 350 µg dexamethasone posterior segment drug delivery system, in patients with macular oedema due to Branch or Central Retinal Vein Occlusion. Results of the open label extension were provided during the procedure. In the extension

phase, patients in all three groups received a second DEX 700 implant and were followed up for a further 6 months (re-treated population). A number of patients who received only one treatment at baseline were followed up to 12 months (single treatment population).

STUDY 206207-009 and STUDY 206207-008

- **Methods**

- **Study Participants**

Inclusion criteria

Key inclusion criteria were male or female, at least 18 years of age, macular oedema due to CRVO at least 6 weeks to 9 months prior to study entry; and macular oedema due to BRVO at least 6 weeks to 12 months prior to study entry, best-corrected visual acuity (BCVA) score between 34 and 68 letters by Early Treatment of Diabetic Retinopathy Study (ETDRS), retinal thickness of ≥ 300 µm by optical coherence tomography (OCT). If both eyes were eligible for the study, the eligible eye with the shorter duration of disease was used as the study eye.

Exclusion criteria

Key exclusion criteria were ocular condition that would prevent a 15-letter improvement in VA, epiretinal membrane, ocular hypertension, aphakia or anterior chamber intraocular lens, diabetic retinopathy, retinal or disc or choroidal neovascularization, rubeosis iridis, active ocular infection, toxoplasmosis, visible scleral thinning or ectasia, media opacity, intraocular surgery, need for ocular surgery or laser, hemodilution, periocular depot or systemic steroids, carbonic anhydrase inhibitors, immunosuppressants/modulators, antimetabolites, alkylating agents, topical ophthalmic steroids or topical non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, heparin, enoxaparin, history of intraocular pressure (IOP) elevation in response to steroids.

Therapy considered necessary for the patient's welfare could be given at the discretion of the investigator. Dosages were to remain constant throughout the course of the trial for those concurrent medications that may have affected the study outcomes (e.g. treatment of elevated IOP, if systemic NSAIDs were regularly used prior to enrolment, these medications may have continued during the study, carbonic anhydrase inhibitors were not prohibited if they needed to be used to treat elevated IOP that developed during the course of the study.

- **Treatments**

Patients received DEX 700, DEX 350, or Sham on the randomisation day 0 visit. In addition, qualified patients received open-label DEX 700 at the initial treatment day 180 visit. Only one eye was treated with study drug.

The study treatment procedure was performed by the treating investigator in a surgical suite or office setting using a standard, sterile technique. A combination of topical and subconjunctival anesthetics was used. Patients randomized to active treatment had the study drug placed into the vitreous through the pars plana using the DEX PS DDS applicator system. Patients randomised to Sham treatment had the needleless applicator pressed against the conjunctiva.

- **Objectives**

The study objectives were to evaluate the safety and efficacy of the 700 µg DEX PS DDS applicator system (700 µg dexamethasone) and 350 µg DEX PS DDS applicator system (350 µg dexamethasone) compared with a Sham DEX PS DDS applicator system (needleless applicator).

Secondary objectives were to evaluate the safety and efficacy of the 700 µg compared with the 350 µg DEX PS DDS applicator systems in patients with macular oedema due to BRVO or CRVO as well as to assess the safety of the 700 µg DEX PS DDS applicator system for an additional 6 months in patients who qualify for treatment in an open-label extension.

- **Outcomes/endpoints**

Primary efficacy endpoint

- Efficacy was evaluated by the proportion of patients with a BCVA improvement of 15 or more letters from baseline at D180 (Study -009) and D90 (Study -008), using the Early Treatment of Diabetic Retinopathy Study (ETDRS) method. Visual acuity testing was to be performed at 4 meters, and for participants with sufficiently reduced vision, at 1 meter.

The primary efficacy variable was considered appropriate by the CHMP as improvement in visual acuity is paramount for the patient and improvement by more that 15 letters is considered a clinically relevant outcome.

Secondary key endpoints of efficacy

Secondary analyses include comparisons of DEX 700 versus Sham or DEX 350 versus Sham for specific variables such as:

- Changes from baseline in contrast sensitivity using the Pelli-Robson chart, optical coherence tomography (OCT is a laser-based noninvasive, diagnostic system providing high-resolution images of the retina, which analyzes retinal cystoid spaces and the thickness of the central 1 mm macular subfield), fundus photography (for quality assessment of OCT images), and fluorescein angiography (to analyze leakage improvement).
- Health related quality of life questionnaires (National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25); SF-36™ Health Survey version 1 (SF-36v1); EuroQol5 Dimensions Health Questionnaire (EQ-5D)).
- Safety measurements (AEs, BCVA, IOP, biomicroscopy examination, indirect ophtalmoscopic examination for vitreous and fondus, retroillumination photography, vital signs and DEX PS DDS residual assessment by indirect ophthalmoscopy with scleral depression).

Blood sample(s) of approximately 15 patients were to be collected at selected sites to determine plasma dexamethasone concentrations at each of the following visits: predose, days 1, 7, 30, 60, and 90, and early exit when applicable.

- **Sample size**

The sample size calculation was based on the primary efficacy analyses of the proportion of patients with BCVA improvement from baseline of 15 or more letters in the study eye, comparing between DEX 700 and Sham and between DEX 350 and Sham. Assuming a 9% improvement rate for Sham and α = 0.05, with 165 patients per group the power was 81% to detect a between-group absolute difference of 11 percentage points in the improvement rate.

For this 3-arm study with a 1:1:1 ratio for treatment allocation, a total of 495 patients was needed.

Accounting for approximately 10% dropout rate, approximately 550 patients were to be enrolled.

- **Randomisation**

Patients were randomised in a 1:1:1 ratio to DEX 700, DEX 350 and Sham.

- **Blinding (masking)**

Masking was maintained through the use of a treating investigator who performed the study treatment procedure, and a follow-up investigator who did not participate in study treatment procedures. Individuals collecting efficacy data (BCVA, contrast sensitivity, fluorescein angiography, OCT, and fundus photography) and the central reading facility remained unaware of patient treatment assignments. Patients remained masked from the initial study treatment assignment and for the whole duration of the trial.

- **Statistical methods**

There were 4 analysis populations: intent-to-treat (ITT), per protocol (PP), safety, and re-treated populations. The ITT population includes all randomized patients. The PP population includes patients who had no major protocol violations determined prior to database lock. The safety population includes all randomized and treated patients. The retreated population includes all patients who enter the open-label extension and receive the second treatment.

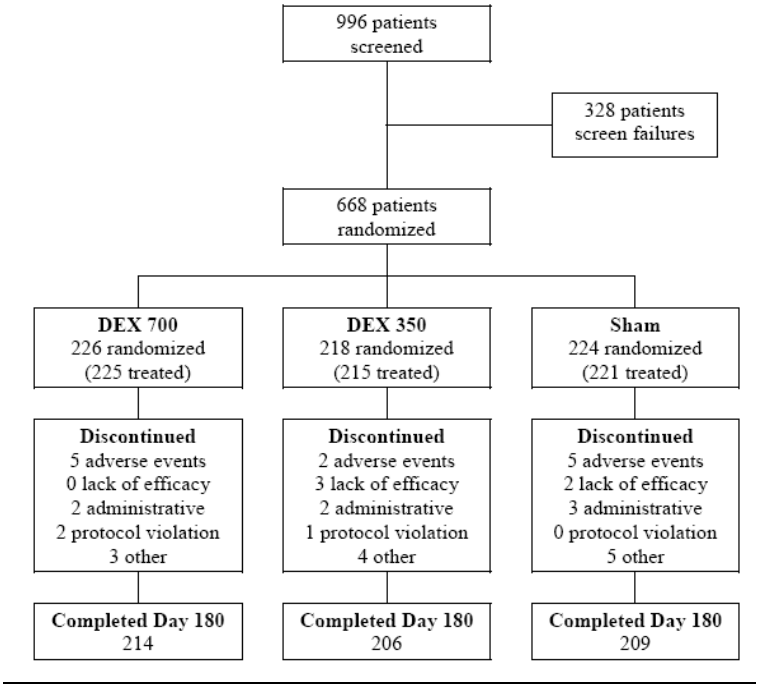
The primary efficacy variable was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. This included a comparison between DEX 700 and Sham and a comparison between DEX 350 and Sham at initial treatment day 180 in the ITT population.

However, for Study 008 the protocol was amended to update the definition and analysis of the primary endpoint after having analysed the results from Study 009: the comparison between DEX 700 versus Sham for the time to achieve a treatment response of BCVA improvement of 15 or more letters from baseline in the study eye during the initial treatment period was designated as the primary efficacy analysis. However, for the European Medicines Agency (EMA) submission, the comparison between DEX 700 versus Sham in the proportion of patients with 15 or more letters improvement from baseline in BCVA at initial treatment day 90 was designated as the primary efficacy analysis.

According to the information provided by the applicant (and later confirmed in a GCP inspection), the amendment of the primary endpoint for study 008 was made while the database remained masked.

- **Results - Study 206207-009**

Participant flow



- **Recruitment and numbers analysed**

There had been 996 patients screened for the study, and 33% (328/996) failed to meet the entry criteria. A total of 668 patients were randomized and enrolled in the study. Approximately 95% of patients in each treatment group completed the initial 180 day treatment period.

The ITT population included all randomized patients: 226 in the DEX 700 group, 218 in the DEX 350 group, and 224 in the Sham group. Seven patients were randomized but not treated. The PP population included all randomized patients with no major protocol deviations (93%): 213 in the DEX 700 group, 201 in the DEX 350 group, and 209 in the Sham group. A total of 49 patients were excluded from the PP population: 14 patients in the DEX 700 group, 18 patients in the DEX 350 group, and 17 patients in the Sham group. The safety population included all randomized patients who received at least one dose of study medication: 225 in the DEX 700 group, 215 in the DEX 350 group, and 221 in the Sham group.

In the open label extension part of the study, patients in all three groups received a second DEX 700 implant and were followed up for a further 6 months (re-treated population). A number of patients who received only one treatment at baseline were followed up to 12 months (single treatment population).

- **Baseline data**

For the ITT population, overall, the mean (range) age was 63.6 years (31 to 96), 52.4% (350/668) were male, 67.2% (449/668) were Caucasian. The diagnosis was CRVO for 34.7% (232/668) and BRVO for 65.3% (436/668). There were no statistically significant differences among the treatment groups in the demographic and baseline characteristics in the ITT population, as summarised in the following table:

Table 3- Demography Study 206207-009

Characteristic	DEX 700 N = 226	DEX 350 N = 218	Sham N = 224	P-Value
Age (years)	63.7	64.0	63.1	0.776 [a]
mean (range)	(33 to 89)	(31 to 96)	(31 to 89)	
Sex				0.449 [b]
male	111 (49.1%)	116 (53.2%)	123 (54.9%)	
female	115 (50.9%)	102 (46.8%)	101 (45.1%)	
Race				0.995 [b, f]
Caucasian	152 (67.3%)	146 (67.0%)	151 (67.4%)	
Black	11 (4.9%)	11 (5.0%)	9 (4.0%)	
Asian [d]	31 (13.7%)	27 (12.4%)	34 (15.2%	
Japanese	0 (0.0%)	2 (0.9%)	1 (0.4%)	
Hispanic	20 (8.8%)	15 (6.9%)	12 (5.4%)	
Other [e]	12 (5.3%)	17 (7.8%)	17 (7.6%)	
Iris color				0.652 [b]
dark	132 (58.4%)	134 (61.5%)	140 (62.5%)	
light	94 (41.6%)	84 (38.5%)	84 (37.5%)	
Diagnosis in study eye				0.551 [b]
CRVO	75 (33.2%)	82 (37.6%)	75 (33.5%)	
BRVO	151 (66.8%)	136 (62.4%)	149 (66.5%)	
Duration of macular edema				0.569 [c]
< 90 days	42 (18.6%)	36 (16.5%)	41 (18.3%)	
90 to 179 days	108 (47.8%)	123 (56.4%)	120 (53.6%)	
180 to 269 days	51 (22.6%)	44 (20.2%)	44 (19.6%)	
≥ 270 days	25 (11.1%)	15 (6.9%)	19 (8.5%)	

Source: Tables 14.1-3.1, 14.1-4, and 14.1-7
a P-value based on 1-way ANOVA
b P-value based on Pearson's chi-square or Fisher's exact test
c P-value based on Cochran-Mantel-Haenszel method using modified ridit scores
d Asian race category excludes Japanese
e Description of "other" race in Listing 16.2.4-1
f P-value based on Pearson's chi-square or Fisher's exact test comparing Caucasians to non-Caucasians

Ophthalmic history, other than macular oedema in the study eye, was reported in the Eye disorders class by 99.9% of patients. The most common findings were retinal vein occlusion 99.1%, cataract 57.2%, retinal haemorrhage 17.5% , refraction disorder 12.0% , and vitreous detachment 10.5%.

Overall, treatment groups were well balanced with respect to other than ophthalmic baseline disorders, among which the most common were vascular disorders 65.4%, musculoskeletal/connective tissue disorders 35.6%, metabolism/nutrition disorders 33.8%, gastrointestinal disorders 25.1%, and infections/infestations 22.2%.

Prior medication: Overall, 8.5% (57/668) of patients reported prior procedures for the treatment of macular oedema in the study eye. All these patients had retinal laser coagulation, except one patient, who had intra-ocular injection.

Ocular concomitant medications in the study eye were reported for 46.5% (105/226) of patients in the DEX 700 group, 44.0% (96/218) in the DEX 350 group, and 22.3% (50/224) in the Sham group. The most frequently reported drug classes (more than 10% in any treatment group) were:

- ophthalmic beta blocking agents (25.7% [58/226] in the DEX 700 group, 21.6% [47/218] in the DEX 350 group, and 2.7% [6/224] in the Sham group),
- sympathomimetics in glaucoma therapy (12.8% [29/226] in the DEX 700 group, 12.8% [28/218] in the DEX 350 group, and 1.3% [3/224] group),
- ophthalmic prostaglandin analogues (9.7% [22/226] in the DEX 700 group, 11.5% [25/218] in the DEX 350 group, and 1.3% [3/224] in the Sham group), and

- other ophthalmologicals (9.7% [22/226] in the DEX 700 group, 11.0% [24/218] in the DEX 350 group, and 9.8% [22/224] in the Sham group).

The higher incidence of IOP-lowering medications is to be expected in the patients receiving intravitreal steroid injections. Information provided show that antiglaucoma medications were among the most prescribed concomitant medication.

- **Outcomes and estimation**

Primary endpoints

BCVA 15 or More Letters Improvement in ITT Population

The primary efficacy endpoint was the proportion of patients with a BCVA improvement of 15 or more letters from baseline at day 180 in the study eye for the ITT population, as summarised in the following table. The tables below also show the results following the open-label extension phase of the study for both the re-treated population and for the single treatment population.

Table 11–1 Patients with 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity in the Study Eye (ITT Population)

Visit	DEX 700 N = 226	DEX 350 N = 218	Sham N = 224	Difference / P-Value [a] DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Day 30	22.6%	20.6%	7.6%	15.0% < 0.001	13.1% < 0.001	1.9% 0.622
Day 60	29.6%	31.2%	12.1%	17.6% < 0.001	19.1% < 0.001	-1.5% 0.723
Day 90	21.2%	25.7%	13.8%	7.4% 0.039	11.8% 0.002	-4.4% 0.268
Day 180	23.5%	22.0%	17.0%	6.5% 0.087	5.1% 0.180	1.4% 0.719

Source: Table 14.2-1
Note: patients with missing baseline BCVA are considered non-responders; missing values are imputed by last observation carried forward (LOCF) at the follow-up visits.
a P-value based on Pearson's chi-square

Table 11–1 Patients with 15 or More Letters Improvement from First Baseline BCVA in the Study Eye (Re-Treated Population)

Visit	DEX 700/700 N = 179	DEX 350/700 N = 173	Sham/DEX 700 N = 168
IT Day 30	22.9%	18.5%	5.4%
IT Day 60	31.3%	31.2%	10.1%
IT Day 90	18.4%	23.1%	10.7%
IT Day 180	17.9%	17.3%	11.3%
OL Day 30	30.7%	33.5%	23.2%
OL Day 60	34.1%	31.8%	25.0%
OL Day 90	27.4%	31.8%	28.0%
OL Day 180	22.3%	23.7%	23.2%

Source: Table 14.2-2.1
Note: Baseline is relative to the first injection

Table 11–5 Patients with 15 or More Letters Improvement from Baseline BCVA in the Study Eye (Single Treatment Population)

Visit	DEX 700 N = 46	DEX 350 N = 42	Sham N = 53
IT Day 30	21.7%	31.0%	15.1%
IT Day 60	21.7%	33.3%	18.9%
IT Day 90	32.6%	38.1%	24.5%
IT Day 180	45.7%	42.9%	34.0%
OL Day 30	37.0%	40.5%	41.5%
OL Day 60	37.0%	40.5%	39.6%
OL Day 90	39.1%	47.6%	39.6%
OL Day 180	37.0%	50.0%	45.3%

Source: Table 14.2-2.2
Note: Baseline is relative to the first injection

The proportion of patients with 15 or more letters improvement from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90. At the primary time point initial treatment day 180, the difference (95% CI) between DEX 700 and Sham was 6.5% (-0.9% to 13.9%), p = 0.087. The difference (95% CI) between DEX 350 and Sham was 5.1% (-2.3% to 12.4%), p = 0.180. Neither comparison was statistically significant. There were no differences between the 2 doses of DEX.

Secondary endpoints

BRVO

The proportion of BRVO patients in the ITT population with a BCVA improvement of 15 or more letters from baseline in the study eye was similar to the overall ITT population. The proportion of patients with BCVA improvement of 15 or more letters from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at the early visits but not at initial treatment day 180. There were no differences between the 2 doses of DEX.

CRVO

The proportion of CRVO patients in the ITT population with a BCVA improvement of 15 or more letters from baseline in the study eye was similar to the overall ITT population for the DEX patients, but lower than the overall population for the Sham patients. The proportion of patients with BCVA improvement of 15 or more letters from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at the early visits, and with DEX 700 compared to Sham at initial treatment day 180. There were no differences between the 2 doses of DEX.

BCVA 15 or more letters improvement in patients with longer duration of macular oedema

The analysis was repeated excluding patients with a duration of macular oedema less than 90 days in order to assess the impact on the results of spontaneous improvement in BCVA. This subgroup was defined *a posteriori* and should therefore be read with caution. The proportion of patients with longer duration of macular oedema had similar BCVA improvement of 15 or more letters from baseline in the study eye as the ITT population. Excluding patients with acute macular oedema (<90days), the rate of

responders in the sham groups decreased leading to statistical, although not clinical, significant differences between DX700 and sham.

Time to 15 or more letters improvement in BCVA

Treatment response was defined *a posteriori* as 15 or more letters improvement from baseline BCVA in the study eye at any time during the initial treatment period. Time to response was analysed using a Kaplan-Meier survival analysis with the log-rank test for treatment differences. Overall, the cumulative response rate curves were significantly different for the DEX 700 and DEX 350 groups compared to the Sham group ($p < 0.001$). Cumulative response rates were consistently higher with DEX 700 and DEX 350 than with Sham from day 30 to the end of the initial treatment period. There was a separation of curves as early as day 30 which was consistent over time without any crossover at any visit. There were no differences between the 2 doses of DEX.

Categorical change from baseline BCVA

The categorical change from baseline showed statistically significant better visual acuity in the study eye with DEX 700 and DEX 350 compared to Sham at each follow-up visit. From initial treatment day 30 onward, the beneficial effects of DEX 700 and DEX 350 compared to Sham were shown, not only in terms of ≥ 15 letters improvement but also in the prevention of ≥ 15 letters worsening. There were no differences between the 2 doses of DEX.

BCVA 10 or more letters improvement in ITT population

The proportion of patients with a BCVA improvement of 10 or more letters from baseline in the study eye for the ITT population is summarised in the table below:

Table 11–3 Patients with 10 or More Letters Improvement from Baseline Best-Corrected Visual Acuity in the Study Eye (ITT Population)

Visit	DEX 700 N = 226	DEX 350 N = 218	Sham N = 224	Difference / P-Value [a] DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Day 30	45.6%	41.3%	16.5%	29.1% < 0.001	24.8% < 0.001	4.3% 0.362
Day 60	52.7%	53.7%	26.3%	26.3% < 0.001	27.3% < 0.001	-1.0% 0.830
Day 90	47.3%	45.9%	29.5%	17.9% < 0.001	16.4% < 0.001	1.5% 0.756
Day 180	40.3%	37.2%	29.9%	10.4% 0.021	7.2% 0.107	3.1% 0.501

Source: Table 14.2-5
Note: patients with missing baseline BCVA are considered non-responders; missing values are imputed by last observation carried forward (LOCF) at the follow-up visits.
a P-value based on Pearson's chi-square

Mean change from baseline BCVA

In the ITT population, the mean changes from baseline BCVA number of letters read correctly in the study. Changes from baseline peaked at day 60, and were significantly greater with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, 90, and 180 ($p \leq 0.016$). There were no differences between the 2 doses of DEX.

For BRVO patients, mean changes from baseline BCVA number of letters read correctly in the study eye were significantly greater with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, 90, and 180 ($p \leq 0.037$). There were no differences between the 2 doses of DEX.

For CRVO patients, mean changes from baseline BCVA number of letters read correctly in the study eye were significantly greater with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90 ($p \leq 0.044$), and with DEX 350 compared to Sham at day 180 ($p = 0.018$). There were no differences between the 2 doses of DEX.

Contrast sensitivity

At baseline, the mean number of letters read correctly in the study eye using contrast sensitivity was 27.3 in the DEX 700 group, 27.3 in the DEX 350 group, and 27.4 in the Sham group. There were no statistically significant differences between treatment groups at baseline or day 180. At day 180, the mean change from baseline number of letters read correctly in the study eye using contrast sensitivity was 1.2 in the DEX 700 group, 1.5 in the DEX 350 group, and 1.1 in the Sham group. There were no statistically significant between-group differences.

Retinal Thickness in ITT population and diagnostic subgroups

Retinal thickness was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p < 0.001$), though not at day 180. There were no differences between the 2 doses of DEX. For BRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p < 0.001$), though not at day 180. There were no differences between the 2 doses of DEX. For CRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p \leq 0.003$), though not at day 180. There were no differences between the 2 doses of DEX at day 90, however the mean thickness was significantly less with DEX 350 compared to DEX 700 at day 180.

Retinal volume measured by Optical Coherence Tomography

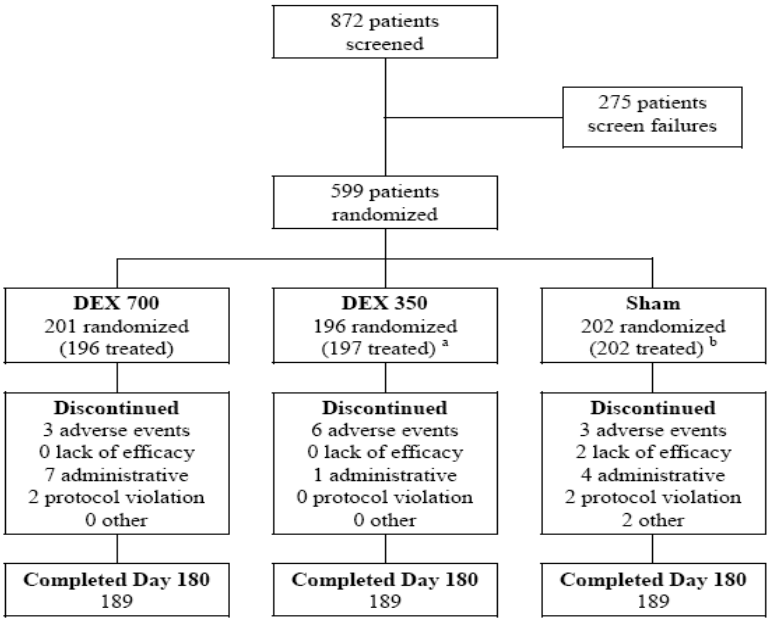
Retinal volume was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p \leq 0.005$), though not at day 180. There were no differences between the 2 doses of DEX.

Fluorescein Leakage

There were no statistically significant differences between the treatment groups in the distribution of change from baseline fluorescein leakage.

- **Results - Study 206207-008**

Participant flow



- **Recruitment and numbers analysed**

A total of 872 patients were screened. Of these 275 (32%) failed to meet the entry criteria patients failed to fulfil selection criteria. Fifty ninety nine patients were randomised and 3 out of them did not receive treatment.

The ITT population included all randomized patients: 201 in the DEX 700 group, 196 in the DEX 350 group, and 202 in the Sham group. The PP population included all randomized and treated patients with no major protocol deviations: 189 in the DEX 700 group, 181 in the DEX 350 group, and 185 in the Sham group. The safety population included all randomized patients who received at least one dose of study medication: 196 in the DEX 700 group, 197 in the DEX 350 group, and 202 in the Sham group. Forty-four patients (12 patients in the DEX 700 group, 15 patients in the DEX 350 group, and 17 patients in the Sham group) were excluded from the PP population and all by-visit analyses. These patients were excluded from the PP population due to one or more protocol violations at baseline.

In the open label extension part of the study, patients in all three groups received a second DEX 700 implant and were followed up for a further 6 months (re-treated population). A number of patients who received only one treatment at baseline were followed up to 12 months (single treatment population).

- **Baseline data**

For the ITT population, overall, the mean (range) age was 65.5 years (32 to 91), 54.6% (327/599) were male, 83.8% (502/599) were Caucasian. The diagnosis was CRVO for 34.2% (205/599) and BRVO for 65.8% (394/599). There were no statistically significant differences among the treatment groups in the demographic and baseline characteristics in the ITT population, as summarised in the following table:

Table 4 - Demography Study 206207-008

Table 10–1 Demographic and Baseline Characteristics (ITT Population)

Characteristic	DEX 700 N = 201	DEX 350 N = 196	Sham N = 202	P-Value
Age (years)	65.8	65.9	64.8	0.528 [a]
mean (range)	(36 to 90)	(37 to 88)	(32 to 91)	
Sex				0.505 [b]
male	106 (52.7%)	104 (53.1%)	117 (57.9%)	
female	95 (47.3%)	92 (46.9%)	85 (42.1%)	
Race				0.854 [b, f]
Caucasian	169 (84.1%)	166 (84.7%)	167 (82.7%)	
Black	4 (2.0%)	3 (1.5%)	11 (5.4%)	
Asian [d]	7 (3.5%)	9 (4.6%)	10 (5.0%)	
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Hispanic	17 (8.5%)	14 (7.1%)	13 (6.4%)	
Other [e]	4 (2.0%)	4 (2.0%)	1 (0.5%)	
Iris Color				0.215 [b]
dark	109 (54.2%)	110 (56.1%)	125 (62.5%)	
light	92 (45.8%)	86 (43.9%)	75 (37.5%)	
Diagnosis in study eye				0.355 [b]
CRVO	61 (30.3%)	72 (36.7%)	72 (35.6%)	
BRVO	140 (69.7%)	124 (63.3%)	130 (64.4%)	
Duration of macular edema				0.070 [c]
< 90 days	28 (13.9%)	40 (20.4%)	24 (11.9%)	
90 to 179 days	111 (55.2%)	95 (48.5%)	100 (49.5%)	
180 to 269 days	42 (20.9%)	44 (22.4%)	55 (27.2%)	
≥ 270 days	20 (10.0%)	17 (8.7%)	23 (11.4%)	

Source: Tables 14.1-3.1, 14.1-4, and 14.1-7

a P-value based on 1-way ANOVA
b P-value based on Pearson's chi-square or Fisher's exact test
c P-value based on Cochran-Mantel-Haenszel method using modified ridit scores
d Asian race category excludes Japanese
e Description of "other" race in Listing 16.2.4-1
f P-value based on Pearson's chi-square or Fisher's exact test comparing Caucasians to non-Caucasians

Ophthalmic history, other than macular oedema in the study eye, was reported by 99.2% of patients with eye disorders. The most common findings were retinal vein occlusion 98.5%, cataract 54.1%, retinal haemorrhage 12.7%, and cataract nuclear 10.5%.

In relation to the baseline disease characteristics, the proportion CRVO/BRCO parallels that seen in the target population. However, selection criteria reflect a population likely to improve. Only 11% of the studied population had macular oedema of more than 270 days (and no longer than 365 days). By contrary, up to 20% of patients had macular oedema of less than 90 days duration, for which a spontaneous improvement might be expected.

Prior medication: In BRVO patients, 5.6% (22/394) used medications prior to study entry for the treatment of macular oedema in the study eye. In CRVO patients, 8.8% (18/205) used medications prior to study entry for the treatment of macular oedema in the study eye. Overall, 12.5% of patients reported prior procedures for the treatment of macular oedema in the study eye. Most of these patients, 93.2%, had retinal laser coagulation, 5.4% had haemodilution, and 1 patient had intra-ocular injections. Overall, 18.2% of patient reported medications for other than the treatment of macular oedema prior to study entry. The most common prior medications (reported by greater than 2% of patients) were other ophthalmologicals 5.0%, other antiinfectives 3.3%, platelet aggregation inhibitors excluding heparin 2.7%, and beta blocking agents 2.7%. Antiglaucoma medication was reported for up to 4.5%, 7.6% and 4.5% in DEX 700, DEX 350 and Sham, respectively.

Ocular concomitant medications in the study eye were reported for 40.8% (82/201) of patients in the DEX 700 group, 39.8% (78/196) in the DEX 350 group, and 19.8% (40/202) in the Sham group. The most frequently reported drug classes (more than 10% in any treatment group) were:

- ophthalmic beta blocking agents
- sympathomimetics in glaucoma therapy
- ophthalmic prostaglandin analogues

Retinal laser coagulation and eye laser surgery were the most commonly performed procedures. Similar to the results seen in Study 009, the use of IOP-lowering medications was higher in the patients receiving intravitreal steroid injections.

- **Outcomes and estimation**

Primary endpoints

BCVA 15 or More Letters Improvement in ITT Population

The primary efficacy endpoint was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye for the ITT population on day 90, as summarised in the following table. The tables below also show the results following the open-label extension phase of the study for both the re-treated population and for the single treatment population.

Table 11–1 Patients with 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity in the Study Eye (ITT Population)

Visit	DEX 700 N = 201	DEX 350 N = 196	Sham N = 202	Difference / P-Value [a] DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Day 30	19.9%	14.8%	7.4%	12.5% < 0.001	7.4% 0.019	5.1% 0.180
Day 60	28.9%	25.5%	10.4%	18.5% < 0.001	15.1% < 0.001	3.3% 0.454
Day 90	22.4%	20.9%	12.4%	10.0% 0.008	8.5% 0.022	1.5% 0.722
Day 180	19.4%	16.3%	18.3%	1.1% 0.780	-2.0% 0.600	3.1% 0.424

Source: Table 14.2-1
Note: One patient with missing baseline BCVA was considered a non-responder; missing values were imputed by last observation carried forward (LOCF) at the follow-up visits.
a P-value based on Pearson's chi-square

Table 11–1 **Patients with 15 or More Letters Improvement from First Baseline BCVA in the Study Eye (Re-Treated Population)**

Visit	DEX 700/700 N = 162	DEX 350/700 N = 156	Sham/DEX 700 N = 159
IT Day 30	17.9%	13.5%	7.5%
IT Day 60	28.4%	25.0%	9.4%
IT Day 90	17.9%	19.9%	9.4%
IT Day 180	14.2%	12.2%	15.7%
OL Day 30	22.8%	30.1%	21.4%
OL Day 60	29.0%	32.1%	26.4%
OL Day 90	31.5%	33.3%	26.4%
OL Day 180	25.3%	22.4%	18.9%

Source: Table 14.2-2.1

Table 11–5 **Patients with 15 or More Letters Improvement from Baseline BCVA in the Study Eye (Single Treatment Population)**

Visit	DEX 700 N = 34	DEX 350 N = 41	Sham N = 43
IT Day 30	29.4%	19.5%	9.3%
IT Day 60	35.3%	26.8%	14.0%
IT Day 90	44.1%	26.8%	23.3%
IT Day 180	44.1%	31.7%	30.2%
OL Day 30	44.1%	31.7%	23.3%
OL Day 60	41.2%	31.7%	32.6%
OL Day 90	44.1%	36.6%	30.2%
OL Day 180	41.2%	41.5%	37.2%

Source: Table 14.2-2.2
Note: baseline is relative to the timepoint of injection

The proportion of patients with 15 or more letters improvement from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90. The comparison of DEX 700 versus Sham at day 90 was the primary endpoint, p = 0.008. There were no differences between the 2 doses of DEX.

Secondary endpoints

The results for BCVA 15 or more letters improvement in PP population were similar to the ITT population.

BRVO

The proportion of BRVO patients in the ITT population with a BCVA improvement of 15 or more letters from baseline in the study eye was similar to the overall ITT population. The proportion of patients with BCVA improvement of 15 or more letters from baseline was significantly higher with DEX 700 compared to Sham at days 30, 60, and 90 ($p \leq 0.021$) and with DEX 350 compared to Sham at day 60 ($p = 0.014$). The response rates in the DEX 700 group were consistently higher than that in the DEX 350 group, with a statistically significant difference at day 60 ($p = 0.038$). The results were not significant on day 180. Findings for BRVO patients in the PP population were similar to the ITT population.

CRVO

The proportion of CRVO patients in the ITT population with a BCVA improvement of 15 or more letters from baseline in the study eye was lower than the overall population for the DEX 700 group but generally higher than the overall ITT population for the DEX 350 group. The proportion of patients with BCVA improvement of 15 or more letters from baseline was significantly higher with DEX 350 compared to Sham at day 60 ($p = 0.002$) and day 90 ($p = 0.025$). There were no differences between the 2 doses of DEX. Findings for CRVO patients in the PP population were similar to the ITT population.

BCVA 15 or more letters improvement in patients with longer duration of macular oedema

The analysis was repeated excluding patients with duration of macular oedema less than 90 days in order to assess the impact on the results of spontaneous improvement in BCVA. The proportion of patients with longer duration of macular oedema had similar BCVA improvement of 15 or more letters from baseline in the study eye as the ITT population. The proportion of patients with BCVA improvement of 15 or more letters from baseline was significantly higher with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90. The proportion was not significant for any of the groups at day 180. There were no differences between the 2 doses of DEX. Overall, the results after excluding patients with shorter disease duration (<90 days), which represent less than 20% of patients, showed consistent results to those seen in the overall study population.

Time to 15 or more letters improvement in BCVA

The last amendment of the protocol establishes this as the primary endpoint for the FDA submission. Cumulative response rate curves were significantly different for the DEX 700 and DEX 350 groups compared to the Sham group ($p \leq 0.007$). The response rates were consistently higher with DEX 700 and DEX 350 than with Sham, starting at initial treatment day 30. Rates were somewhat lower with DEX 350 compared to DEX 700, although the difference between the 2 doses was not statistically significant.

Categorical change from baseline BCVA

The categorical change from baseline showed statistically significant better visual acuity in the study eye with DEX 700 and DEX 350 compared to Sham at days 30, 60 and 90.

BCVA 10 or more letters improvement in ITT population

The proportion of patients with a BCVA improvement of 10 or more letters from baseline in the study eye for the ITT population is summarised in the following table:

Table 11–3 Patients with 10 or More Letters Improvement from Baseline Best-Corrected Visual Acuity in the Study Eye (ITT Population)

Visit	DEX 700 N = 201	DEX 350 N = 196	Sham N = 202	Difference / P-Value [a] DEX 700 vs Sham	DEX 350 vs Sham	DEX 700 vs DEX 350
Day 30	41.3%	34.2%	18.3%	23.0% < 0.001	15.9% < 0.001	7.1% 0.144
Day 60	49.3%	45.4%	25.7%	23.5% < 0.001	19.7% < 0.001	3.8% 0.443
Day 90	39.3%	40.3%	27.2%	12.1% 0.010	13.1% 0.006	-1.0% 0.838
Day 180	32.3%	33.7%	29.7%	2.6% 0.567	4.0% 0.395	-1.3% 0.777

Source: Table 14.2-5
Note: patients with missing baseline BCVA are considered non-responders; missing values are imputed by last observation carried forward (LOCF) at the follow-up visits.
a P-value based on Pearson's chi-square

Mean change from baseline BCVA

In the ITT population, the mean changes from baseline BCVA number of letters read correctly in the study eye are summarised in the table below. Changes were significantly greater with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90 ($p \leq 0.003$), and peaked at day 60 with a difference of 6.4 mm Hg between DEX 700 and Sham, and 5.9 mm Hg between DEX 350 and Sham. Mean changes from baseline were consistently greater with DEX 700 than with DEX 350, however the difference was not statistically significant.

For BRVO patients, mean changes from baseline BCVA number of letters read correctly in the study eye were significantly greater with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, 90 ($p \leq 0.018$). Results were not significant on day 180. There were no differences between the 2 doses of DEX.

For CRVO patients, mean changes from baseline BCVA number of letters read correctly in the study eye were significantly greater with DEX 700 and DEX 350 compared to Sham at initial treatment days 30, 60, and 90 ($p \leq 0.046$), and with DEX 350 compared to Sham at days 30 and 60 ($p < 0.001$). Results were not significant on day 180. There were no differences between the 2 doses of DEX.

Contrast sensitivity

At baseline, the mean number of letters read correctly in the study eye using contrast sensitivity was 26.6 in the DEX 700 group, 27.0 in the DEX 350 group, and 27.0 in the Sham group. There were no statistically significant differences between treatment groups at baseline or day 180.

Retinal Thickness in ITT population and diagnostic subgroups

At day 90 in the ITT population, the mean decrease in retinal thickness was significantly greater with DEX 700 (-199.3 microns) and DEX 350 (-144.1 microns) compared to Sham (-78.2 microns), $p < 0.001$, and with DEX 700 compared to DEX 350 ($p = 0.002$). There were no between-group differences at day 180. For BRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham at day 90, though not at day 180. There were no differences between the 2 doses of DEX. For CRVO patients, mean central retinal thickness in the 1 mm subfield in the study eye measured by OCT was significantly less with DEX 700 and DEX 350 compared to Sham ($p \leq 0.020$), and with DEX 700 compared to DEX 350 ($p = 0.004$) at day 90. There were no between-group differences at day 180.

Retinal volume measured by Optical Coherence Tomography

Retinal volume was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p \leq 0.006$), though not at day 180. There were no differences between the 2 doses of DEX.

Fluorescein Leakage

At initial treatment day 180, change from baseline in fluorescein leakage at the macula was improved from baseline for 50.8% (91/179) of patients in the DEX 700 group, 46.4% (85/183) in the DEX 350 group, and 40.2% (74/184) in the Sham group. The difference between the DEX 700 group and the Sham group was statistically significant, p = 0.023.

- ***Ancillary analyses***

Pharmacokinetic blood samples were collected from a total of 33 patients in the two pivotal trials. This included patients who received DEX 350, DEX 700 or sham. Overall, systemic exposure of dexamethasone was minimal though dose dependent in patients who received DEX treatment.

- ***Analysis performed across trials (pooled analyses and meta-analysis)***

A pooled analysis of both pivotal studies was presented by the applicant. Results of this analysis were consistent with the results of individual studies.

Table 2.7.3.3–4 Proportion of Patients with 15 or More Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Studies 009 and 008, ITT Population)

	Study 206207-009			Study 206207-008			Pooled 008 and 009		
Visit	DEX 700 N = 226	DEX 350 N = 218	Sham N = 224	DEX 700 N = 201	DEX 350 N = 196	Sham N = 202	DEX 700 N = 427	DEX 350 N = 414	Sham N = 426
Day 30	22.6% [a]	20.6% [a]	7.6%	19.9% [a]	14.8% [e]	7.4%	21.3% [a]	17.9% [a]	7.5%
Day 60	29.6% [a]	31.2% [a]	12.1%	28.9% [a]	25.5% [a]	10.4%	29.3% [a]	28.5% [a]	11.3%
Day 90	21.2% [b]	25.7% [c]	13.8%	22.4% [d]	20.9% [f]	12.4%	21.8% [a]	23.4% [a]	13.1%
Day 180	23.5%	22.0%	17.0%	19.4%	16.3%	18.3%	21.5%	19.3%	17.6%

Source: Module 5.3.5.1 Report 206207-008, Table 14.2-1; Module 5.3.5.1 Report 206207-009, Table 14.2-1; Module 5.3.5.3 ISE Table 2-1

a Proportion significantly higher with DEX compared to Sham ($p < 0.001$)
b Proportion significantly higher with DEX compared to Sham ($p = 0.039$)
c Proportion significantly higher with DEX compared to Sham ($p = 0.002$)
d Proportion significantly higher with DEX compared to Sham ($p = 0.008$)
e Proportion significantly higher with DEX compared to Sham ($p = 0.019$)
f Proportion significantly higher with DEX compared to Sham ($p = 0.022$)

A subgroup analysis according to macular oedema duration was also presented. For patients with macular oedema of less than 90 days duration, spontaneous improvement was seen in up to 30% of patients after 6 months follow up, showing in general better rates of response the in the overall ITT population. However, differences over sham at D90 and D180 were neither statistically significant nor clinically relevant. In the subgroup of patients with >90 days duration, the overall benefit was lower to that seen in acute patients and differences over sham, although higher than those seen in acute patients, were not clinically relevant after 2 months.

Table 2.7.3.3–16 15 or More Letters Improvement in Best-Corrected Visual Acuity from Baseline in the Study Eye by Duration of Macular Edema (Studies 009 and 008, ITT Population)

	Duration < 90 Days			Duration ≥ 90 Days		
Visit	DEX 700 N = 70	DEX 350 N = 76	Sham N = 65	DEX 700 N = 357	DEX 350 N = 338	Sham N = 361
Day 30	24.3%	21.1%	15.4%	20.7% [c]	17.2% [c]	6.1%
Day 60	38.6% [a]	34.2% [b]	18.5%	27.5% [c]	27.2% [c]	10.0%
Day 90	25.7%	22.4%	20.0%	21.0% [d]	23.7% [c]	11.9%
Day 180	24.3%	19.7%	27.7%	21.0%	19.2%	15.8%

Source: Module 5.3.5.3 ISE Tables 3-12.1 and 3-12.2

a Proportion significantly higher with DEX compared to Sham (p = 0.010)
b Proportion significantly higher with DEX compared to Sham (p = 0.036)
c Proportion significantly higher with DEX compared to Sham (p < 0.001)
d Proportion significantly higher with DEX compared to Sham (p = 0.001)

- ***Clinical studies in special populations***

The applicant did not submit clinical studies to assess the efficacy of dexamethasone in special populations.

- ***Supportive studies***

As described earlier the applicant conducted and initially submitted the results from several studies (phase I-III) to evaluate the use of DEX PS DDS. The pivotal trials including the dose-ranging study have been discussed in detail in previous sections. The three studies listed below should therefore be seen as supportive.

- Study DC103-07, a phase 2 study to test the safety and performance of the DEX PS DDS applicator system compared to tableted DEX PS DDS in patients with persistent macular oedema. At baseline in study DC103-07, cataracts were reported for 78.9% of patients in the applicator group and 70% in the incision group. At day 180, cataracts were reported for 82.4% of patients in the applicator group and 80% in the incision group. There were no statistically significant between-group differences in the proportion of patients with cataracts at any visit.
- Studies 206207-010 and 206207-011 are 3-year, phase 3, multicentre, masked, randomized, sham-controlled trials to assess the safety and efficacy of 700 µg and 350 µg DEX PS DDS applicator system in the treatment of patients with diabetic macular oedema. These studies are currently ongoing, and when completed will provide long-term safety data on DEX PS DDS. The final clinical study report for the 2 studies will be available in Q4 2013. During the procedure the applicant submitted masked interim safety results. Although the DME safety data at present are still masked, some observations could be made. From the masked results there is no evidence so far, that the incidence of increased IOP increases with the second or subsequent implantations. The incidence of increased IOP seems to peak after the first implant and then taper off, in contrast to cataracts where the incidence appears to increase with the number of implants. As part of a follow-up measure that applicant was requested to provide the final study reports of the studies in order to provide assurance on the long-term safety (see section 2.7 of this report).

2.4.6. Discussion on clinical efficacy

As discussed earlier the applicant has conducted two pivotal phase III studies (008 and 009) to determine efficacy. The results were consistent in both studies and showed statistical significance on day 90, but not on day 180. Results of the open label extension were provided during the procedure.

The initial view of the CHMP was that the applicant had failed to robustly demonstrate efficacy in the two pivotal studies. Although study 008 was a successful study, the clinical relevance of the primary endpoint (90 days) was unclear to the CHMP. In response to this the applicant argued that both pivotal studies demonstrated substantial and clinically relevant efficacy and that day 90 is a clinically relevant time point. In the view of the applicant the intentions of the studies were to confirm the reduction of oedema as early and as much as possible and to reduce oedema for as long as possible to minimise the number of intravitreal injections. Therefore, although 15 letter improvement in visual acuity at 6 months was the development goal, it was not regarded by the applicant as the only definitive time point for a single dose of a product intended to treat macular oedema resulting from retinal vein occlusion. Rather 6 months was considered the maximum duration of effect estimated from the studies used to predict human ocular pharmacokinetics and the design limitations of an ocular implant of this type. The applicant further argued as the proportion of DEX 700 patients with 15 or more letters improvement from baseline BCVA was similar at day 180 (21.5%) to that seen at day 90 (21.8%), this would show that the treatment effect was maintained. Based on the submitted 12-month data the applicant also believed that the benefit of early treatment with DEX 700 was confirmed and although treatment with DEX 700 in the second 6 months resulted in an increased response in the Sham/DEX 700 group, the rates never reached the improvements shown in the DEX 700/700 treatment group. The applicant therefore concluded that early treatment with DEX 700 is important to achieving improved visual acuity. The CHMP acknowledged the applicant's view and agreed that it appears that patients treated with a second implant show a benefit in terms of improvement in visual acuity and prevention of visual acuity loss. However, as the applicant has not provided data on patients receiving more than 2 implants the CHMP requested that this was highlighted in the SPC and that, as part of a follow-up measure, the applicant should perform an observational study to provide additional information on patients requiring more than 2 implants (see section 2.7 of this report).

Although efficacy is shown at early time-points such as 60 and 90 days, the effect appeared to be somewhat less pronounced by day 180. The results at 12 months after re-implantation at 6 months showed a similar pattern. However, the CHMP had some concerns following assessment of the data from patients who were followed-up to 12 months but did not receive a second implant. Efficacy for these patients seemed to be sustained, with patients in the Sham group reaching the same levels (or even higher) of 15 or more letters improvement from baseline BCVA. The applicant was therefore asked to comment on these results. The applicant provided a plausible explanation for the continuing response in patients receiving only one implant even after the initial 6 months. These were patients with a good response after the first implant that did not fulfil the criteria for re-implantation (BCVA, 84 letters or retinal thickness by OCT >250 um and in the investigator's opinion the procedure would not put the patients at significant risk). The SPC therefore includes a clarification that patients who respond well should not be re-implanted until visual acuity starts to deteriorate. The impact of delaying treatment on visual loss was further discussed by the applicant. A statistically significant number of patients who initially received Sham followed by DEX 700 showed ≥15-letter worsening in BCVA compared to patients receiving two DEX 700 implants. The majority of patients benefited from treatment with DEX 700 in terms of improvement in visual acuity or prevention of visual loss; furthermore given that it is impossible to identify patients who may improve spontaneously deferring treatment may not be appropriate.

The CHMP initially also had concerns regarding the fact that the 12 month efficacy data do not seam to offer reassurance that patients benefit from a second implant. There was limited evidence that patients benefit from a second or further implants and although at early time-points of 60 and 90 days there was statistically significant improvement in the primary endpoint, there was limited evidence that patients benefit from this treatment in the long term. Furthermore, given that the second implant lead to an increase in IOP and cataracts it was not clear to the Committee that the risk/benefit of additional implants was considered positive. The applicant was therefore requested to discuss this further. In addition to the response that the applicant provided with regards to the CHMP question on the efficacy results from the pivotal studies, the applicant further explained that the majority of patients (80%) were eligible for re-treatment at day 180. These patients demonstrated similar response to the first implantation with greater changes on days 30, 60 and 90 as seen during the first period. As far as mean change from baseline in IOP was concerned, the pattern following the second injection was similar to that of the first. Increases in IOP peaked at day 60 and returned to baseline levels by day 180. There was no evidence of accumulation after the second implantation. Most importantly the majority of patients did not require treatment or were managed with topical IOP-lowering medications.

In addition to the CHMP queries on the clinical relevance, the CHMP also requested the applicant to try to more clearly identify a patient population that could clearly benefit from the treatment (i.e. according to the duration of macular oedema). From the re-analyses provided by the applicant in response to this CHMP request, it appeared to the CHMP that patients with a duration for macular oedema of more than 6 months at baseline, benefit more from treatment and results for this group were statistically significant at day 90 and day 180. This could be attributed to the fact that patients with macular oedema of less than 6 months are more likely to improve spontaneously. The CHMP therefore requested the applicant to explain whether efficacy is sustained for these patients in the open label extension. The applicant was also requested to provide data for patients with duration of macular oedema at baseline of more than 6 months at the end of the open label extension for both patients who were re-implanted and those who did not receive a second implant. In response the applicant provided analyses of BCVA stratified by duration of macular oedema at baseline (≤ 180 days and > 180 days) for the re-treated and single treatment populations. In the re-treated population, statistically significant treatment-group differences were observed at initial treatment days 30 and 60 in patients with duration ≤ 180 days or duration > 180 days. The statistically significant difference seen at day 90 in the patients with duration > 180 days relates to a lower Sham response rather than an improved effect in patients treated with DEX. In the single treatment population, statistically significant differences were (as for the re-treated population) driven by the Sham response rates, while the DEX response was similar among patients with duration ≤ 180 days or duration > 180 days. DEX response rates also appeared to be similar at all time points in the open-label extension for both patient subgroups, with a suggestion of a higher response in those patients with duration of macular oedema ≤ 180 days. Based on the data provided by the applicant the CHMP concluded that the patterns were similar for patients with long standing macular oedema and those with disease of shorter duration with regards to the mean change in BCVA from baseline and therefore it would not be possible to characterise a subset of patient that would be benefiting the most based on duration of existing macular oedema.

In a further attempt to identify a patient population that could clearly benefit from the treatment with DEX 700 the CHMP highlighted that despite not being authorised for the claimed indication, these patients are not left untreated and some other therapeutic alternatives are usually tested with some degree of success. The possible place in therapeutic of Ozurdex was therefore somewhat difficult for the CHMP to understand. The CHMP therefore requested the applicant to explore whether there is a subset of patients who could potentially benefit from Ozurdex in the light of the available treatments. The applicant argued that despite the burden of the disease, there are currently no licensed pharmacologic therapies and no agreed standard of care for macular oedema caused by BRVO and

CRVO. Treatment strategies used by ophthalmologists are based on clinical practices that have become established over time, but which have not been founded on level 1 evidence (Parodi, 2004). An evaluation of the 3 most commonly used therapeutic interventions, ie, laser photocoagulation, off-label use of VEGF inhibitors and corticosteroids, was included in the applicant's response. The most relevant historical comparator for DEX 700 is triamcinolone acetonide, which is also the therapy for which most published data are available. Based on the applicant's response, the CHMP concluded that comparable efficacy of DEX 700 to triamcinolone was shown from the comparison of the pivotal studies 008 and 009 to the published results of the SCORE study, but with a more favourable safety profile for DEX 700. Although this comparison is limited by the differences in the designs of the trials, it offers some insight on where DEX 700 can be placed in the therapeutic regimen, taking also into account the fact that there are currently no licensed treatments for the treatment of macular oedema secondary to BRVO or CRVO.

In a follow-up question to this the applicant was requested by the CHMP to further characterise those patients who could potentially benefit from repeated doses and translated into a clinical recommendation in the SPC. The applicant subsequently performed further analyses to help predict which patients would respond following re-treatment. These analyses demonstrated an additional prognostic characteristic of reduction in prior BCVA response by greater than 5 letters. This was subsequently proposed by the applicant to be included in the SPC.

Based on the applicant's responses to the concerns discussed above, the CHMP concluded that the data presented in patients treated with a second implant - even those initially randomised to Sham and subsequently treated with a DEX 700 implant at 6 months - show a significant benefit to patients in terms of improvement in visual acuity and prevention of visual acuity loss. Furthermore, increase in IOP was easily managed and there was no evidence of accumulation. Although, the applicant has defined in the proposed SPC the criteria for re-implantation, the CHMP recommended that the criteria for re-treatment should be based on current clinical practice, as in clinical practice retinal thickness by OCT assessment is not routinely used to guide treatment, and reflect the re-treatment criteria in the clinical studies. The applicant's proposal for re-treatment was not considered to be based on clinical trial requirements or on clinical practice recommendations. However, the proposal to include the criteria as established in the clinical trials was not entirely supported. Instead, the CHMP proposed that the criteria for retreatment should be when patients have responded to treatment and then experienced a loss in visual acuity and in the physician's opinion may benefit from retreatment, which reflect the re-treatment criteria utilised in the clinical studies. With regards to the minimum interval of treatments, the CHMP requested that this should be in line with the clinical studies, i.e. that there is only very limited experience of intervals less then 6 months. In conclusion the CHMP recommended that section 4.2 of the SPC, in relation to repeat doses, should read as follows:

> *"The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).*
>
> *Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk (see section 5.1).*
>
> *Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.*
>
> *There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.*
>
> *Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4)."*

2.4.7. Conclusions on the clinical efficacy

The provided data indicate that there is a maintained effect lasting up to 6 month but not thereafter with regards to improvement in visual acuity following treatment with Ozurdex in adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). These results were replicated following administration of a second implant. Patients with long standing macular oedema and those with disease of shorter duration have similar response patterns. As the criteria for re-implantation have been clearly defined in the SPC and the applicant has committed to provide additional efficacy data following administration of more then 2 implants, the CHMP considered the efficacy of Ozurdex sufficiently established.

2.4.8. Clinical safety

The focus of the safety evaluation in this submission is based on data from the two pivotal phase III trials (008 and 009) performed in the claimed indication. Supportive safety data from other Phase I and phase II studies and a phase III study in uveitis which terminated early due to slow enrolment, were also provided.

- ***Patient exposure***

Overall, safety data for DEX PS DDS were collected from nine clinical studies including 2114 patients. In the two main pivotal trials approximately 401 patients completed a 6-month initial treatment period under the dose intended for MA (DEX PS DDS 700). In addition, data from 477 patients (re-treated population) who received a second administration of DEX PS DDS 700 in the open-label extension, and completed 1-year of follow-up after the initial treatment and from 118 who received only one treatment at baseline (single treatment population) but were followed up to 12 months have also been provided.

Table 2.5.5–1 Exposure to DEX PS DDS

Study	Follow-up Duration	DEX 700	DEX 350	Control
DC103-04 [a]	1 year following last insertion	21 [b] (tablet)	0	0
DC103-05	up to 360 days	11 (tablet)	9 (tablet)	5 (placebo)
DC103-06	6 months	101 (tablet)	100 (tablet)	105 (observation)
DC103-07	6 months	19 [c] (extruded) 10 (tablet)	0	active control (tablet)
206207-008	12 months (single treatment)	34 (extruded)	41 (extruded)	43 (sham)
	12 months (re-treated with DEX 700)	162 DEX 700/700 (extruded)	156 DEX 350/700 (extruded)	159 Sham/DEX 700 (extruded)
206207-009	12 months (single treatment)	46 (extruded)	42 (extruded)	53 (sham)
	12 months (re-treated with DEX 700)	179 DEX 700/700 (extruded)	173 DEX 350/700 (extruded)	168 Sham/DEX 700 (extruded)
206207-015	26 weeks	2 (extruded)	2 (extruded)	1 (sham)
206207-014	8 weeks	77 (extruded)	76 (extruded)	76 (sham)
206207-016	6 months	123 (extruded with adjunctive Lucentis®)	0	120 (Lucentis® Alone)
TOTAL		785	599	730

Source: Module 2.7.4, Table 2.7.4.1-3
Masked data from ongoing studies 206207-010 and 206207-011 can not be included in the exposure counts.
a Report DC103-04 includes data from single-patient studies DC103-02 and DC103-03, as well as DC103-04.
b One patient was treated in both eyes, 1 patient had 2 insertions, and 1 patient had 3 insertions; 1 patient was lost to follow-up, had minimal data, and was not included in the database, tables or listings.
c Patient 2815 received a treatment assignment but did not undergo surgery.

To allow for a relatively straightforward assessment of the safety data, the presentation of common AEs, Ocular AEs and SAEs will primarily focus on the pivotal phase III trials, mainly showing data reported for the final intended dose (DEX 700).

- ***Adverse events***

The overall incidence of adverse events during the initial treatment period was 72.4% for the patients receiving DEX 700. For the retreated patients the incidence of adverse events was between 80.1% and 87.2% depending on the initial treatment. The detailed figures are provided in the tables below.

Table 2.5.5–2 Summary of Adverse Events (Studies 008 and 009, Safety Population, 6-Month Pooled Data)

	DEX 700 N = 421	DEX 350 N = 412	Sham N = 423
All adverse events	305 (72.4%)	296 (71.8%)	241 (57.0%)
Treatment-related adverse events	199 (47.3%)	192 (46.6%)	74 (17.5%)
Non-ocular adverse events	126 (29.9%)	119 (28.9%)	131 (31.0%)
Ocular adverse events in study eye	265 (62.9%)	255 (61.9%)	181 (42.8%)
Adverse Events > 5% incidence in any treatment group			
Intraocular pressure increased	106 (25.2%)	102 (24.8%)	5 (1.2%)
Conjunctival haemorrhage	85 (20.2%)	72 (17.5%)	63 (14.9%)
Eye pain	31 (7.4%)	18 (4.4%)	17 (4.0%)
Conjunctival hyperaemia	28 (6.7%)	27 (6.6%)	20 (4.7%)
Maculopathy	19 (4.5%)	22 (5.3%)	23 (5.4%)
Serious adverse events	21 (5.0%)	27 (6.6%)	25 (5.9%)
Discontinuations for adverse events	7 (1.7%)	8 (1.9%)	8 (1.9%)

Source: Module 5.3.5.3 ISS (6 month), Table 2-1, 2-2, 2-4, 2-19, 2-22

Table 2.5.5–3 Summary of Adverse Events (Studies 009 and 008, Re-Treated and Single Treament Populations, 12-Month Pooled Data)

	Re-Treated Population			Single Treatment Population		
	DEX 700/700 N = 341	DEX 350/700 N = 329	Sham/ DEX 700 N = 327	DEX 700 N = 80	DEX 350 N = 83	Sham N = 96
All adverse events	291 (85.3%)	287 (87.2%)	262 (80.1%)	65 (81.3%)	63 (75.9%)	55 (57.3%)
Treatment-related adverse events	216 (63.3%)	205 (62.3%)	163 (49.8%)	42 (52.5%)	40 (48.2%)	10 (10.4%)
Ocular adverse events in study eye	266 (77.7%)	262 (79.6%)	235 (71.9%)	57 (71.3%)	51 (61.4%)	46 (47.9%)
Adverse Events > 5% incidence in any treatment group						
Intraocular pressure increased	111 (32.6%)	119 (36.2%)	92 (28.1%)	28 (35.0%)	22 (26.5%)	2 (2.1%)
Conjunctival haemorrhage	85 (24.9%)	74 (22.5%)	73 (22.3%)	11 (13.8%)	11 (13.3%)	11 (11.5%)
Cataract subcapsular	44 (12.9%)	20 (6.1%)	13 (4.0%)	2 (2.5%)	4 (4.8%)	1 (1.0%)
Cataract	40 (11.7%)	28 (8.5%)	11 (3.4%)	1 (1.3%)	3 (3.6%)	3 (3.1%)
Eye pain	33 (9.7%)	24 (7.3%)	28 (8.6%)	6 (7.5%)	6 (7.2%)	2 (2.1%)
Conjunctival hyperaemia	29 (8.5%)	30 (9.1%)	27 (8.3%)	8 (10.0%)	5 (6.0%)	2 (2.1%)
Retinal haemorrhage	26 (7.6%)	17 (5.2%)	19 (5.8%)	5 (6.3%)	0 (0.0%)	2 (2.1%)
Macular oedema	25 (7.3%)	21 (6.4%)	26 (8.0%)	2 (2.5%)	1 (1.2%)	1 (1.0%)
Maculopathy	20 (5.9%)	22 (6.7%)	20 (6.1%)	4 (5.0%)	3 (3.6%)	5 (5.2%)
Vitreous detachment	19 (5.6%)	21 (6.4%)	13 (4.0%)	0 (0.0%)	5 (6.0%)	3 (3.1%)
Ocular hypertension	18 (5.3%)	16 (4.9%)	18 (5.5%)	5 (6.3%)	7 (8.4%)	0 (0.0%)
Retinal exudates	14 (4.1%)	8 (2.4%)	20 (6.1%)	0 (0.0%)	1 (1.2%)	2 (2.1%)
Conjunctival oedema	11 (3.2%)	17 (5.2%)	15 (4.6%)	1 (1.3%)	2 (2.4%)	0 (0.0%)
Visual acuity reduced	10 (2.9%)	12 (3.6%)	17 (5.2%)	3 (3.8%)	0 (0.0%)	2 (2.1%)
Retinal neovascularisation	5 (1.5%)	5 (1.5%)	8 (2.4%)	1 (1.3%)	4 (4.8%)	7 (7.3%)
Retinal vein occlusion	4 (1.2%)	10 (3.0%)	6 (1.8%)	5 (6.3%)	2 (2.4%)	0 (0.0%)
Iris neovascularisation	2 (0.6%)	3 (0.9%)	2 (0.6%)	1 (1.3%)	2 (2.4%)	5 (5.2%)
Hypertension	19 (5.6%)	17 (5.2%)	20 (6.1%)	5 (6.3%)	3 (3.6%)	4 (4.2%)
Serious adverse events	32 (9.4%)	27 (8.2%)	35 (10.7%)	8 (10.0%)	9 (10.8%)	10 (10.4%)
Discontinuations for adverse events	4 (1.2%)	3 (0.9%)	3 (0.9%)	7 (8.8%)	8 (9.6%)	9 (9.4%)

Source: Module 5.3.5.3, ISS (12 month) Tables 1-1, 2-1.3, 2-1.4, 2-2.3, 2-2.4, 2-3.3, 2-3.4, 2-11.3, 2-11.4; Section 2.7.4, Table 2.7.4.2-28

Non-ocular AEs

The most common non-ocular events reported were influenza 9 (2.1%) DEX 700 vs 2 (0.5%) Sham,

headache 14 (3.3%) DEX 700 vs 7 (1.7%) Sham and hypertension 17 (4.0%) DEX 700 vs 15 (3.5%) Sham. Thus, so far, for systemic adverse reactions, no specific pattern indicating safety risks with the active treatment was revealed.

Ocular AEs

Initial treatment

The overall incidence of ocular adverse events in the study eye during the initial treatment was; 62.9% for DEX 700, 61.9% for DEX 350 and 42.8% for Sham treatment respectively.

The most frequently reported events in patients who received DEX 700 were increased IOP (25.2 %) and conjunctival haemorrhage (20.2 %). Ocular adverse events related to the insertion procedure included conjunctival haemorrhage, conjunctival hyperaemia, eye pain, vitreous haemorrhage and conjunctival oedema, which are reported generally occurring soon after the injection procedure.

Specific recommendations have been included in section 4.4 of the SPC regarding monitoring for elevation in intraocular pressure and for endophtalmitis after the intravitreal injection procedure. These include monitoring of perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection.

Open-label extension

During the open label extension, the adverse event profile was similar among the 3 treatment groups, each of whom had received DEX 700 as their second injection. The incidences of cataracts and subcapsular cataracts however were higher in the second 6 months following re-treatment. The incidence of intraocular pressure increased was comparable between patients receiving either 1 or 2 doses of DEX. The incidence of intraocular pressure increased was 32.6% in the DEX 700/700 group and 36.2% in the DEX 350/700 group compared to 28.1% in the Sham/DEX 700 group.

The incidence of AEs did not differ in a meaningful way considering subgroups based on age (mid-age 45 to 65 years and > 65 years), sex, race (Caucasians, non-Caucasians), iris colour and baseline diagnosis (macular oedema due to CRVO or due to BRVO). The incidence of increased intraocular pressure was however higher in younger patients <45 years. Although patients under 45 represented only a small number of patients included in the studies (5%) not enabling a firm conclusion to be made, CHMP recommended that this information should be included in the special warnings of section 4.4 of the SPC.

- ***Serious adverse event and deaths***

Deaths

There was 1 death during the initial treatment period in study 009 and 3 deaths during the initial treatment period in study 008. Two deaths were due to myocardial infarction, one due to cardiac arrest and one accidental drowning. There was also 1 death in study 009 and 1 death in study 008 in the re-treated population. These are in addition to the deaths reported for the 6-month safety population. There were no additional deaths during the 6-month extension for the 12-month single treatment population. None of the deaths were considered to be related to study treatment. 6 patients died during study DC103-06. None of these deaths were considered to be related to study treatment. Deaths were due to drowning, brain damage, cerebrovascular accidents, metastatic prostate cancer, respiratory arrest, acute myeloid leukaemia.

Serious adverse events in the phase III studies

The overall incidence of serious adverse events in the initial treatment period for the pooled phase 3 studies was 5.0% (21/421) in the DEX 700 group, 6.6% (27/412) in the DEX 350 group, and 5.9% (25/423) in the Sham group. One additional Sham patient developed a recurrence of melanoma in the right axilla which met the criteria for a serious event but was reported as non serious. The rates of ocular serious events and non-ocular serious events were similar among the 3 treatment groups. None of the serious adverse events was related to treatment with the following exceptions: ocular hypertension in the study eye (1 DEX 700) and intraocular pressure increased in the study eye (1 DEX 700 and 3 DEX 350).

The overall cumulative incidence of serious adverse events during the 12-month treatment period for the pooled phase 3 studies (re-treated population) was 9.4% in the DEX 700/700 group, 8.2% in the DEX 350/700 group, and 10.7% in the Sham/DEX 700 group. The serious adverse event profile was similar between the 3 treatment groups. Four of the serious events in the re-treated population were considered by the investigator to be related to the study treatments. Three were intraocular pressure increased (one in each group) and one was retinal detachment (in DEX 700/700).

The cumulative incidence of serious adverse events during the 12-month treatment period for the pooled phase 3 studies (single treated population) was 10.0% in the DEX 700 group, 10.8% in the DEX 350 group, and 10.4% in the Sham group. Five of the serious events in the single treatment population were considered by the investigator to be related to the study treatments. Ocular hypertension and IOP in DEX 700 group, two cases of IOP in the DEX 350 group and one corneal disorder in the Sham group.

- ***Laboratory findings***

According to protocol, standard clinical laboratory data were not collected in the clinical safety and efficacy studies.

- ***Safety in special populations***

The analyses of adverse event rates did not identify any patient characteristics that would indicate a need to individualise therapy or patient management because of safety considerations. The same pattern was seen in each demographic subgroup of higher incidences with DEX than Sham for selected events (e.g. increased intraocular pressure), and no difference between the 700 and 350 µg doses. There were no demographic patterns among the serious adverse events or discontinuations due to adverse events.

Use in pregnancy and lactation

Safety for use in pregnancy and lactation has not been established. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application. There was 1 live birth without complications associated with the initial treatment period of the phase 3 study 009. There were no pregnancies associated with the initial treatment period of the phase 3 study 008.

Overdose

Overdose has not been reported in clinical trials. The applicant explains that overdose is unlikely as the DEX PS DDS applicator system is administered by a physician.

- ***Safety related to drug-drug interactions and other interactions***

No interaction studies have been performed, however due to the low systemic levels of dexamethasone, drug interactions are not expected. In the analyses of the initial treatment period for the pooled phase 3 studies, there was no evidence of drug-drug interactions. However, specific

analyses to identify such interactions were not conducted. As expected, many of the patients in these studies were using multiple concomitant medications, such as proton pump inhibitors, systemic antihypertensives, anti-inflammatory and antirheumatic agents, lipid modifying agents, and analgesics.

- ***Discontinuation due to adverse events***

Notable, less than 2% of patients in each treatment group, withdrew from the initial treatment period of the phase III studies due to adverse events. None of the events were considered to be related to the study treatment with the exception of 2 patients receiving DEX 350 who reported intraocular pressure increased in the study eye.

Adverse events leading to discontinuation in the re-treated population for the pooled phase 3 studies were reported for 1.2% (4/341) in the DEX 700/700 group, 0.9% (3/329) in the DEX 350/700 group, and 0.9% (3/327) in the Sham/DEX 700 group. Adverse events led to discontinuation in the single treatment population for 8.8% (7/80) of patients in the DEX 700 group, 9.6% (8/83) in the DEX 350 group, and 9.4% (9/96) in the Sham group. In the single treatment group, all discontinuations due to adverse events occurred in the initial 6-month treatment period, with the exception of one Patient in the Sham group.

- ***Post marketing experience***

There are no post-marketing exposure data for DEX PS DDS 700 µg as the product has not been licensed for any indication.

2.5. Discussion on clinical safety

In both pivotal studies during the first 6 months of treatment, the majority of patients (72%) in the active treatment groups (both doses DEX PS DDS 700 and DEX PS DDS 350) experienced at least one AE. Overall the incidence of adverse events was significantly higher in the DEX groups compared to Sham. Ocular adverse events were more commonly reported with DEX 700 and DEX 350 than with Sham. The most frequently reported adverse events were Increased Intraocular Pressure (IOP): DEX 106 (25.2%) vs. Sham 5 (1.2%), Conjunctival haemorrhage: DEX 85 (20.2%) vs. Sham 63 (14.9%), Eye pain: DEX 31 (7.4%) vs. Sham 16 (3.8%), Conjunctival hyperaemia: DEX 28 (6.7%) vs. Sham 20 (4.7%) , Ocular Hypertension: DEX 17 (4%) vs. Sham 3 (0.7%) and Cataract: DEX 15 (3.6%) vs. Sham 6 (1.4%). Most complications were reported as self-limited.

The overall incidence of serious adverse events in the initial treatment period for the pooled phase III studies was 5.0% (21/421) in the DEX 700 group, 6.6% (27/412) in the DEX 350 group, and 5.9% (25/423) in the Sham group. Discontinuations in the study eye were mainly due to increased intraocular pressure.

The percentage of subjects who experienced any adverse event in the study eye generally increased over time after the second DEX 700 device implantation (i.e. All AEs Initial treatment Period 79% vs. Open Label Extension 85%). As far as mean change from baseline in IOP was concerned, the pattern following the second injection was similar to that of the first. Increases in IOP peaked at day 60 and returned to baseline levels by day 180. There was no evidence of accumulation after the second implantation. Most importantly the majority of patients did not require treatment or were managed with topical IOP-lowering medications.

The safety profile of DEX PS DDS in patients with macular oedema due to CRVO and BRVO did not show any unexpected signal related with the administration technique or the drug. With a few notable exceptions, the occurrence of non-serious ocular AEs following intravitreal DEX administration does not raise any major concern. One such exception is the appearance of IOP increases reported in nearly

25% of actively treated participants in the pivotal programme. It is emphasised that only a few of these patients were in need of acute medical and surgical intervention and warnings are appropriately included in section 4.4 of the SPC.

2.6. Conclusions on the clinical safety

As expected for an intravitreal corticosteroid implant, an increased incidence of ocular adverse events such as cataracts and increased IOP was observed, these were however manageable and only a few patients were in need of acute interventions.

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

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

2.7.2 Risk management plan

The MAA submitted a risk management plan, which included a risk minimisation plan. The updated version of the Risk Management Plan has taken into account the comments and recommendations and was considered to be acceptable by the CHMP.

Table 5 - Summary of the risk management plan

Safety concern	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
Important Identified risks		
Increased intraocular pressure (IOP), Glaucoma and Ocular Hypertension	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011 • Conduct of an observational study to gain experience with repeat administration. This study will recruit patients requiring a 2nd or subsequent implant due to deteriorating visual acuity with the aim of collecting long term outcome and safety data in such patients. The study design will ensure that sufficient patients requiring more than 2 implants are recruited to provide additional useful information on this patient group.	Included in section 4.4 of the SPC : • As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. Of the patients experiencing an increase of IOP of ≥ 10 mm Hg from baseline, the greatest proportion showed this IOP increase at around 60 days following an injection. Patients of less than 45 years of age are more likely to experience increases in IOP. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post injection as needed. Included as "very common" adverse reaction in Section 4.8; Undesirable effects. Educational material to instruct prescribers on the recommended injection technique and important risks associated with OZURDEX. Educational material to instruct patients on important risks including increased intraocular pressure and ocular hypertension associated with OZURDEX.
Cataracts including traumatic cataracts related to injection techniques	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: Long-term safety data studies 206207-010 and 206207-011	Included in section 4.4 of the SPC: • Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections. In clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second injection (see section 4.8) with only 1

		patient out of 368 requiring cataract surgery during the first treatment and 3 patients out of 302 during the second treatment. Included as "common" adverse reaction" in Section 4.8; Undesirable effects. Educational material to instruct prescribers on the recommended injection technique and important risks associated with OZURDEX.
Vitreous Detachment/haemorrhage	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Included as "common" adverse reaction" in section 4.8 of the SPC Educational material to instruct prescribers on the recommended injection technique and important risks associated with OZURDEX.
Important Potential Risks		
Endophthalmitis	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Included in section 4.4 of the SPC: • Any intravitreous injection can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. • Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay. Educational material to instruct prescribers on the recommended injection technique and important risks associated with OZURDEX.
Retinitis secondary to reactivation of latent viral or other ophthalmic infections	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety	Section 4.3- Contraindications; OZURDEX is contraindicated in: Active or suspected ocular or periocular infection including most viral diseases of the cornea and

	reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Included in section 4.4 of the SPC: Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex and not be used in active ocular herpes simplex.
Retinal tear/detachment	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Included as "uncommon" adverse reaction" in section 4.8 of the SPC
Significant vitreous leak or hypotony	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.2: Posology and method of administration of the SPC has clear instruction on the proper injection procedure. • Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same

		direction as used to enter the vitreous. Educational material to instruct prescribers on the recommended injection technique.
Systemic corticosteroid effects	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Bilateral administration could potentially lead to increased systemic absorption of the steroid. Section 4.4 addresses this as follows: The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.
Mechanical failure of device and implant misplacement	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.2: Posology and method of administration of the SPC has clear instruction on the proper injection procedure. • Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualization is possible in the large majority of cases. In cases in which the implant cannot be visualized, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view. Educational material to instruct prescribers on the recommended injection technique
Missing Information		
Paediatric Use	Routine pharmacovigilance	Section 4.2 Posology and method of administration: There is no relevant use of OZURDEX in the paediatric population in macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion

		(CRVO).
Pregnancy and lactation	Routine pharmacovigilance	Section 4.6 Pregnancy and lactation: Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Systemic levels of dexamethasone in humans have been shown to be low. OZURDEX is not recommended during pregnancy unless clearly necessary. Dexamethasone is excreted in breast milk. However, no effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.
Long-term safety, repeat dosing data	Routine pharmacovigilance Additional activities: • Long-term safety data studies 206207-010 and 206207-011 • Conduct of an observational study to gain experience with repeat administration. This study will recruit patients requiring a 2nd or subsequent implant due to deteriorating visual acuity with the aim of collecting long term outcome and safety data in such patients. The study design will ensure that sufficient patients requiring more than 2 implants are recruited to provide additional useful information on this patient group.	
Concurrent use of anticoagulants	Routine pharmacovigilance Additional activities:	Section 4.4: Anti-coagulant therapy was used in 1.7% of patients receiving OZURDEX;

	• Long-term safety data studies 206207-010 and 206207-011	there were no reports of hemorrhagic adverse events in these patients. Anti platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%). OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.
Patients with significant retinal ischaemia	Routine pharmacovigilance Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.4: OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia. Therefore OZURDEX is not recommended.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch, all physicians who are expected to prescribe/use Ozurdex are provided with a physician information pack containing the following:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Aseptic techniques to minimise the risk of infection
- Use of antibiotics
- Techniques for the intravitreal injection
- Patient monitoring after IVT injection

- Key signs and symptoms of IVT injection related adverse events including increased intraocular pressure, glaucoma, ocular hypertension, cataract, traumatic cataract related to injection technique, vitreous detachment, vitreous haemorrhage, endophthalmitis, mechanical failure of device and implant misplacement
- Management of IVT injection related adverse events

The patient information pack should be provided in both the form of a patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for OZURDEX treatment
- What are the steps following treatment with OZURDEX
- Key signs and symptoms of serious adverse events including increased intraocular pressure and ocular hypertension
- When to seek urgent attention from their health care provider

- **User consultation**

The applicant has submitted results from user testing of the package leaflet, which was performed in English. Overall, the user test is found acceptable. The results demonstrated a sufficient percentage of identification and comprehension of product related information. Therefore, the package leaflet was considered to be in line with the current readability requirements.

2.7.3. Benefit-risk balance

The proposed product is a dexamethasone intravitreal implant intended for the treatment of macular oedema due to branch or central retinal vein occlusion.

- **Benefits**

Limited pharmacokinetic information is available and this was derived from pharmacokinetic evaluations conducted in a small number of patients in the pivotal phase III studies. These indicated that systemic exposure is low.

The applicant has conducted a number of clinical studies in various indications. Two were relevant to this application.

The studies (008 and 009) which were identical in design, were six-month randomised, sham-controlled with a 6-month open label extension, assessing the safety and efficacy of 700 microgram and 350 microgram implant in patients with macular oedema due to Branch or Central Retinal Vein Occlusion. The primary endpoint was defined as the proportion of patients with a best corrected visual acuity (BCVA) improvement of 15 or more letters from baseline in the study eye at 180 days. In study 008, this was, subsequently, modified to 90 days. The results were consistent in both studies and showed statistical significance on day 90, but not on day 180. The results from the open label extension from patients receiving a second implant at 6 months, showed a similar pattern.

Beneficial effects

A statistically significant improvement in visual acuity was demonstrated in patients receiving the 700 microgram implant. This was replicated following a second implantation. Furthermore, a statistically significant number of patients who initially received Sham followed by DEX 700 showed ≥15-letter worsening in BCVA compared to patients receiving two DEX 700 implants. The majority of patients benefited from treatment with DEX 700 in terms of improvement in visual acuity or prevention of visual loss.

Uncertainty in the knowledge about the beneficial effects.

There is a lack of experience with repeat administration (more than 2 implantations).

- **Risks**

The most commonly observed adverse events were increased intraocular pressure, cataracts and adverse events related to the procedure of intravitreal injection such as conjunctival haemorrhage, conjunctival oedema and hyperaemia, eye pain and vitreous haemorrhage.

The adverse event pattern was similar following re-implantation. The majority of patients presenting with increased IOP did not require surgical intervention and were treated conservatively.

Unfavourable effects

The most commonly observed adverse events are increased IOP and cataracts. These are well recognised complications following administration of intravitreal corticosteroids and adequate warnings in the SPC are included.

Uncertainty in the knowledge about the unfavourable effects

As with efficacy, there is lack of experience with repeat administration. An observational study as a follow up measure has been requested in patients requiring a second or subsequent implant due to deteriorating visual acuity with the aim of collecting long term outcome and safety data in such patients.

- **Benefit-risk balance**

Importance of favourable and unfavourable effects

Improvement in visual acuity and prevention of visual loss are extremely important clinical outcomes to patients with macular oedema due to BRVO and CRVO. The clinical studies submitted in support of this application have demonstrated a significant effect on these outcomes. Although, as expected for an intravitreal corticosteroid implant, an increased incidence of ocular adverse events such as cataracts and increased IOP was observed, these were manageable.

Benefit-risk balance

An overall clinically relevant and statistically significant efficacy was demonstrated. Although there was an increase in ocular adverse events in the implanted eyes compared to the sham group, these in most cases were easily managed.

- **Discussion on the benefit-risk balance**

The provided data indicate that there is a maintained effect up to 6 month, but not thereafter, with regards to visual acuity and prevention of visual loss in treatment with Ozurdex in adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). These efficacy results were replicated following a second implant. Furthermore,

increase in IOP was easily managed and there was no evidence of accumulation. The implant is administered through a needle with minimal trauma to the eye and slowly releases dexamethasone into the vitreous with effects lasting up to 6 months, preventing the need for frequent intravitreal injections which can increase the risk for complications.

- **Risk management plan**

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required:

The MAH shall ensure that, at launch, all physicians who are expected to prescribe/use Ozurdex are provided with a physician information pack containing the following:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Aseptic techniques to minimise the risk of infection
- Use of antibiotics
- Techniques for the intravitreal injection
- Patient monitoring after IVT injection
- Key signs and symptoms of IVT injection related adverse events including increased intraocular pressure, glaucoma, ocular hypertension, cataract, traumatic cataract related to injection technique, vitreous detachment, vitreous haemorrhage, endophthalmitis, mechanical failure of device and implant misplacement
- Management of IVT injection related adverse events

The patient information pack should be provided in both the form of a patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for OZURDEX treatment
- What are the steps following treatment with OZURDEX
- Key signs and symptoms of serious adverse events including increased intraocular pressure and ocular hypertension
- When to seek urgent attention from their health care provider

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

2.7.4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Ozurdex in the treatment of of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) was favourable and therefore recommended the granting of the marketing authorisation.