Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dexamethasone

Proprietary Product Name: Ozurdex

Sponsor: Allergan Australia Pty Ltd

October 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Dose Form, New Route of Administration, Extension of Indications
Decision:	Withdrawn
Date of Decision:	12 July 2011
Active ingredient(s):	Dexamethasone
Product Name(s):	Ozurdex
Sponsor's Name and Address:	Allergan Australia Pty Ltd Level 4, 810 Pacific Highway Gordon NSW 2072
Dose form(s):	Intraocular implant
Strength(s):	700 µg
Container(s):	Dose delivery system
Pack size(s):	1 implant
Route(s) of administration:	Intraocular
Dosage:	The recommended dose is one Ozurdex implant to be administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended. 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. Patients who experience and retain improved vision should not be retreated. Patients who experience deterioration in vision, which is not slowed by Ozurdex, should not be retreated.

Product Background

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, sequelae of cataract surgery, macular epiretinal membranes, and inherited or acquired retinal degeneration.[1] 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.[1]

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).[1] Retinal vein occlusive disease is thought to occur as a consequence of thrombus formation at the

[1] EMA. CHMP Assessment Report Ozurdex (EPAR). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001140/WC500095503.pdf

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.[1]

No drug is currently approved in Australia for this indication although there is some use of triamcinolone (Triesence, Alcon) via the Special Access Scheme and there are published studies on the use of the Lucentis brand of ranibizumab in this indication.

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.[1] 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.[1]

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.[1]

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.[1]

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.[1]

This AusPAR describes the evaluation of an application by Allergan Australia Pty Ltd (the sponsor) for a new dose form and route of administration of dexamethasone (Ozurdex) and an extension of indications for:

the treatment of adult patients with macular oedema due to either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO).

This was later amended.

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.

Regulatory Status

Dexamethasone has been registered nor many years for a number of different indications but not in the proposed dose from or route of administration.

A similar application has been submitted the US 23 December 2008, the UK on 24 February 2009, Canada on 08 April 2009, New Zealand on 23 March 2009 and Switzerland

on 30 June 2009. Approval was granted in all five regions on 17 June 2009, 27 July 2010, 10 February 2011, 17 December 2010 and 10 January 2011 respectively. In Canada, approval was given for CRVO only.

II. Quality Findings

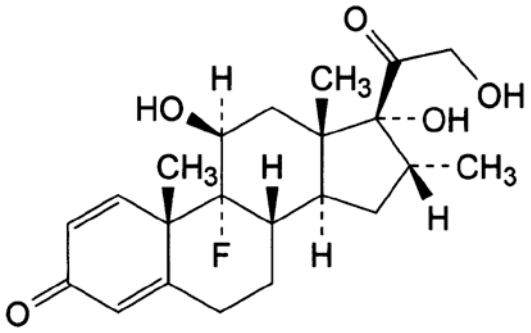
Drug Substance (active ingredient)

The sponsor sought to register Ozurdex dexamethasone ocular implants for use in the treatment of macular oedema. At the time of application, the trade name Posurdex was proposed and this was later amended to Ozurdex.

Ozurdex is formulated with dexamethasone, a synthetic steroid:

dexamethasone

$C_{22}H_{29}FO_5$



Dexamethasone itself is currently registered in a number of products (frequently in combination with other drugs, not shown here):

- *Maxidex* 0.1% eye drops suspension [1 mg/mL] (Alcon Laboratories)
- *Dexmethsone* 4 mg dexamethasone tablet (Aspen Pharmacare)
- *Dexmethsone* 0.5 mg dexamethasone tablet (Aspen Pharmacare)
- *Sofradex* Ear Drops dexamethasone 0.5 mg/mL (Sanofi-Aventis)
- *Otodex* Ear Drops dexamethasone 0.5 mg/mL (Sanofi-Aventis)
- *Cresophene* Buccal Solution dexamethasone 1 mg/g (Specialites Septodont)
- *Endomethasone* Buccal Paste dexamethasone 0.1 mg/g (Specialites Septodont)
- *Septomixine Forte* Root Canal (Buccal) Paste 0.5 mg/g (Specialites Septodont)

There also dexamethasone derivatives:

- *Pulpomixine* dexamethasone acetate (Specialites Septodont)
- *Tobispray Metered Aerosol* dexamethasone isonicotinate (Boehringer Ingelheim)
- *DBL Dexamethasone Sodium Phosphate Injections* dexamethasone sodium phosphate (Hospira)

There are pharmacopoeial monographs for steroid eye preparations (including Dexamethasone Suspension Eye Drops BP, Dexamethasone Sodium Phosphate Solution Eye Drops BP, Dexamethasone Ophthalmic Suspension USP, Dexamethasone Sodium Phosphate Ophthalmic Ointment USP and Dexamethasone Sodium Phosphate Ophthalmic Solution USP).[2]

The dexamethasone drug substance used in Ozurdex is the subject of BP and USP monographs. Micronised drug is used. Dexamethasone is practically insoluble in water (0.06 mg/mL). Control of the drug substance was considered acceptable.

[2] BP: British Pharmacopoeia, USP: United States Pharmacopoeia

Drug Product

Ozurdex delivers a biodegradable, extended release intravitreal implant. Two Ozurdex strengths were used in clinical trials: 350 µg and 700 µg but it was only proposed to register the 700 µg implant in Australia.

The dexamethasone is dispersed in a poly(D,L-lactide-co-glycolide) polymer matrix and formed into an implant. The polymer matrix is a mixture of two different poly(D,L-lactide-co-glycolide) polymers. The implant is comprised of dexamethasone, poly (D,L-lactide-co-glycolide) 50:50 PLGA ester and poly (D,L-lactide-co-glycolide) 50:50 PLGA acid.

The polymers slowly degrade *in vivo* by hydrolysis to lactic acid and glycolic acid. This erosion is an element in the controlled release of dexamethasone from the implant. Related polymers are used to make absorbable sutures (such as *Dexon* sutures used for ophthalmic surgery).

The implant is supplied pre-loaded in a single use, injector 'pen':

Pressing the button directly ejects the implant into the patient's eye (it is not spring loaded). The implant is loaded close to the needle tip to minimise introduction of air into the eye. The 22 gauge needle projects 6 mm beyond the sleeve. Device aspects were reviewed and are considered acceptable. There were no significant changes to the device in clinical trials.

The finished product is sterilised by gamma irradiation. Manufacture causes minor degradation of dexamethasone to known impurities which have been toxicologically qualified.[3]

Trials up to and including Phase IIa used 350 and 700 µg compressed tablets with a different polymer composition. The 700 µg tablets were and were surgically inserted. There were manufacturing difficulties with the tablets which led to development of the implant. Phase III trials used the proposed implant formulation. Unlike some related products, recovered implants cannot be usefully assayed to assess *in vivo* drug release. An *in vitro* drug release test was developed which is chiefly a quality control test of batch uniformity. This *in vitro* test was used in product development, with comparison to drug release into the vitreous humour of rabbit eye.

Quality control, stability and device aspects of the finished product were considered acceptable.

Related Dosage Forms

Another intravitreal implant registered in Australia is *Vitrasert* ganciclovir 4.5 mg slow release implant, used to treat cytomegalovirus retinitis. It is intended to release drug over 6 to 8 months. The implant is formulated with ethylene/vinyl acetate copolymer; it is later removed as it is not biodegradable.

Biopharmaceutics

No bioavailability studies were provided. The dose (0.7 mg) is relatively low and the product is locally acting. Plasma concentrations in patients were almost all below the lower limit of quantification (0.05 ng/mL). Systemic exposure is low.

[3] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Quality Summary and Conclusions

The application was not considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) given related dosage forms. Registration was recommended with respect to chemistry and quality control aspects.

III. Nonclinical Findings

Introduction

The data submitted in support of the application contained no major deficiencies. All toxicity studies were Good Laboratory Practice (GLP) compliant. Safety pharmacology, genotoxicity, carcinogenicity and reproductive toxicity studies were not submitted, generally on the basis of the long clinical history with dexamethasone and negligible systemic exposure with the ocular implant. The implant used in the single dose toxicity studies was manufactured using a different process to that for the clinical product, although a comparison of the pharmacokinetic profiles of the two dose forms was conducted.

Pharmacology

Primary pharmacodynamics

Mechanism of action

The potent antiinflammatory activity of dexamethasone is well established. The sponsor did not perform studies to examine the mechanism of action of dexamethasone in macula oedema due to retinal vein occlusion but did provide some published papers of relevance. Inhibition of vascular endothelial growth factor (VEGF) expression by dexamethasone and other corticosteroids is reported in the literature (Nauck *et al.*, 1998).[4] VEGF has been implicated as a mediator in the disease (Adamis *et al.*, 1996; Pai *et al.*, 2007) with ocular levels of the cytokine correlated with severity (Noma *et al.*, 2008).[5,6,7] Corticosteroids also inhibit prostaglandin release/ synthesis, which has been implicated in the pathogenesis of cystoid macular oedema (Flach, 1998).[8]

Efficacy

Macular oedema involves breakdown of the inner blood retinal barrier (BRB) at the level of the capillary endothelium, resulting in swelling and thickening due to vascular leakage and fluid accumulation. The sponsor submitted an *in vivo* study investigating the effect of dexamethasone implants on VEGF induced ocular changes in rabbits. This model mimics many of the pathologies associated with retinal vein occlusive disease, including the breakdown of the blood retinal and blood aqueous barriers and accumulation of retinal fluid

[4] Nauck M., Karakiulakis G., Perruchoud A.P., Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. Eur J Pharmacol 1998; 341: 309–315.

[5] Adamis AP, Shima DT, Tolentino MJ et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol 1996; 114: 66–71.

[6] Pai SA, Shetty R., Vijayan PB et al. Clinical, anatomic, and electrophysiologic evaluation following intravitreal bevacizumab for macular edema in retinal vein occlusion. Am J Ophthalmol 2007; 143: 601–606.

[7] Noma H, Funatsu H, Yamasaki M et al. Aqueous humour levels of cytokines are correlated to vitreous levels and severity of macular oedema in branch retinal vein occlusion. Eye (Lond) 2008; 22: 42–48.

[8] Flach AJ. The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc 1998; 96: 557–634.

(Edelman *et al.*, 2005).[9] Implantation with dexamethasone implants (350 or 700 µg/eye) produced a significant, dose related reduction in retinal fluorescein leakage at 2 and 6 weeks postdose (by 32–74%). This was accompanied by a dose related reduction in retinal vasodilation, measured by fundus imaging (by 11–56%). The greatest reductions were observed after two weeks for both parameters and values were similar to controls after 10 weeks. The doses of implanted dexamethasone used in this study are approximately 3 and 5 times higher than the proposed clinical dose when adjusted for species differences in the volume of vitreous humour (refer to *Relative exposure* below); thus, efficacy at the anticipated clinical exposure level was not established in the study.

Secondary pharmacodynamics and safety pharmacology

Dexamethasone was shown to not bind to melanin in an *in vitro* study. No safety pharmacology studies were submitted for the dexamethasone implant, due to the long history of clinical use of dexamethasone. This was considered acceptable.

Pharmacokinetics

Dexamethasone release from implants

Dexamethasone release from the implants appeared to be highly variable in rabbits and monkeys. In 6 month studies, standard deviations for percent release from the 700 µg implant were up to 37% in rabbits and 16% in monkeys. The majority (≥98%) of dexamethasone was generally released from implants in rabbit eyes in approximately four weeks and complete release occurred within 91 days in monkeys. Implants were generally not visible in rabbit or monkey eyes 3 months post-implantation. Fragmentation of the implant did not appear to alter the overall rate of dexamethasone release in rabbits.

Differences in the release profile were observed between the tableted (used in single dose toxicity studies) and extruded (clinical product) forms of the implant in comparative studies in rabbits. Release from the extruded implant was slower in the first two weeks following implantation, with ~2–3 times less dexamethasone released than from the tablet form. The amount of dexamethasone released by three weeks post-implantation was similar for both dose forms (~75–80%). The relative distribution of dexamethasone to the aqueous and vitreous humour and to plasma was also comparable.

Absorption and distribution

The pharmacokinetics of dexamethasone (extruded form of the implant) were investigated following a single implantation to healthy rabbit and cynomolgus monkey eyes (six months observation), into vitrectomised rabbits (31 days observation) and following repeated administration (2 doses) in toxicity studies in rabbits and monkeys (6 months observation). Pharmacokinetic data were also obtained following intravitreal administration of a solution of radioactive dexamethasone in both species. Validated methods were used for the detection and quantification of dexamethasone in plasma and ocular tissues. Distribution to non-ocular tissues was not investigated in the set of studies submitted.

Ocular exposure

Exposure (based on the area under the plasma concentration time curve [AUC]) to dexamethasone following a single ocular implantation in rabbits (350 or 700 µg/eye) was approximately dose proportional. Distribution throughout the eye appeared to be extensive; dexamethasone was detected in all analysed parts of treated eyes (aqueous and

[9] Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. Exp Eye Res 2005; 80: 249–258.

vitreous humours, retina, ciliary body and iris) in rabbits and monkeys. Dexamethasone concentration time profiles were biphasic in most matrices, with peak dexamethasone concentrations observed approximately 7 and 40 days post-implantation. Consistent with the slow release properties of the implant, clearance in rabbits and monkeys was slow, based on respective half-lives of 10–13 and 11–18 days.

In rabbits, highest exposure was observed in the retina and the vitreous humour and exposure was highest in the ciliary body, retina and iris in monkeys. Exposure in the aqueous humour in both species was an order of magnitude lower than other ocular tissues. Exposure (AUC-based) to dexamethasone in most parts of the eye was reduced (by 27–56%) in vitrectomised eyes of rabbits compared with non-vitrectomised eyes, although the qualitative release and distribution profiles appeared to be similar. The overall pattern of dexamethasone distribution to various parts of the eye appeared to be similar to that of free ^{14}C-dexamethasone when administered intravitreally.

Systemic exposure

Exposure (AUC-based) in plasma following implantation was dose proportional or slightly greater than dose proportional in rabbits and moderately greater than dose proportional in monkeys. Plasma exposure was ≤0.04% of exposure in the retina in both species and 0.04–0.18% of exposure in the vitreous humour. Dexamethasone was detectable in plasma for up to 28 days in rabbits at the highest dose (1400 µg) and for nine weeks at 700 µg in monkeys. There was no evidence for accumulation with repeated dosing (administration 3 months apart). Dexamethasone was detected in the untreated eyes (aqueous and vitreous humours) of treated rabbits and monkeys in pharmacokinetic studies, indicative of ocular distribution following absorption into the systemic circulation.

Metabolism

The ocular metabolism of dexamethasone was investigated in an *in vitro* study with human ocular tissue and in *ex vivo* studies following intravitreal administration of free ^{14}C-dexamethasone to rabbits and monkeys. No dexamethasone metabolites (only the unchanged drug) were detected in human corneal, iris-ciliary body, choroid, retinal, vitreous humour and scleral tissue following incubation for 18 hours (h), or in the aqueous and vitreous humour, retina, ciliary body, iris, choroid, cornea, lens and sclera from rabbits and monkeys for up to 24 h postdose, apart from low levels of oxygenated ^{14}C-dexamethasone in one monkey aqueous humour sample. No data regarding the systemic metabolism of dexamethasone were submitted. This was considered acceptable, as the pathways of metabolism of corticosteroids are well understood.

The sponsor submitted published data indicating that the polymer excipients from the implant are degraded via backbone hydrolysis to lactic acid and glycolic acid and are incorporated into endogenous metabolic pathways for elimination.

Excretion

No conventional excretion studies were submitted, which was considered acceptable for a product with low systemic exposure. The pathway of systemic elimination of dexamethasone is well understood. The sponsor postulated that elimination from the vitreous occurred via diffusion into the retina/choroids/sclera membrane, based on the pattern of dexamethasone exposure in ocular tissue.

Pharmacokinetic drug interactions

No drug interaction studies were submitted; this was considered acceptable.

Relative exposure

Ocular exposure

Ocular dexamethasone concentrations were not determined for human exposure in clinical trials, for obvious ethical reasons. Relative ocular exposure in the toxicity studies is therefore estimated based on comparisons of the dose administered per volume of vitreous humour (Table 1). The No Observable Adverse Effect Level (NOAEL) established in the study in monkeys is highlighted in bold. An NOAEL was not obtained in rabbits, due to ocular toxicity at all doses tested.

Table 1: Relative ocular exposure to dexamethasone in toxicity studies

Study no.		Species	Dose		Relative exposure[b]
			(µg/eye)	(µg/mL vitreous)[a]	
X7I062G, X81310G, P0701002	(single dose)	**Rabbit** (NZW)	700	467	2.7
			1400	933	5.3
			2100	1400	8.0
TX05030	(12 months; 2 doses)	**Rabbit** (NZW)	700	467	2.7
			1400	933	5.3
TX05029	(12 months; 2 doses)	**Monkey** (Cynomolgus)	350	175	1.0
			700	**350**	**2.0**
NA		**Human**	700	175	NA

[a]Calculated based on vitreous humour volumes of 1.5 mL in rabbits, 2 mL in cynomolgus monkeys and 4 mL in humans (Short, 2008). [b]Animal:human dose per vitreous humour volume.
NA = not applicable; The NOAEL is highlighted in bold.

Systemic exposure

Pharmacokinetic parameters were not calculated for systemic exposure to dexamethasone in clinical studies with macular oedema patients with the dexamethasone implant, as plasma dexamethasone concentrations were below the limit of quantification (0.05 ng/mL) in most patients, or at low levels (0.05–0.094 ng/mL) in 5/13 patients on one or two time points post-implantation. Systemic exposure comparisons are therefore made based on doses adjusted for body surface area, as shown in Table 2.

Table 2: Relative systemic exposure to dexamethasone in toxicity studies

Study no.		Species	Dose			Relative exposure[c]
			(µg/eye)	(µg/kg)[a]	(µg/m²)[b]	
X7I062G, X81310G,	(single dose; both eyes)	**Rabbit** (NZW)	700	467	5604	12
			1400	933	11196	24
			2100	1400	16800	36
P0701002	(single dose)	**Rabbit** (NZW)	700	233	2796	6
			1400	467	5604	12
			2100	700	8400	18
TX05030	(12 months; 2 doses)	**Rabbit** (NZW)	700	233	2796	6
			1400	467	5604	12
TX05029	(12 months; 2 doses)	**Monkey** (Cynomolgus)	350	117	1404	3
			700	**233**	**2796**	**6**
NA		**Human**	700	14	462	NA

[a]Calculated based on rabbit and monkey body weights of 3 kg, and human adult body weights of 50 kg.
[b]Calculated using µg/kg to µg/m² conversion factors of 12 for rabbits and monkeys and 33 for humans.
[c]Animal:human dose per m² body surface area. NA = not applicable; The NOAEL is highlighted in bold.

Toxicology

Single dose toxicity studies (with observation periods of 6–13 weeks) were conducted in rabbits and repeat dose toxicity studies (two implantations, 3 months apart) of 12 months duration were conducted in rabbits and cynomolgus monkeys. The single dose studies employed a tableted form of the implant and surgical implantation (sclerotomy), while the repeat dose studies used the clinical (extruded) form of the implant, administered using the DEX PS DDS applicator system. The studies were GLP compliant and generally adequate, although analysis of potential systemic toxicity was limited in some of the studies in rabbits. Animals in control groups received sham treatment and/or placebo implants.

Ocular toxicity

Gross and microscopic examinations revealed effects on multiple structures of the eye, with findings present at high incidence in rabbits and monkeys at all doses of dexamethasone (after one or two implantations) and also in eyes treated with placebo implant(s); findings were generally more pronounced in rabbits, consistent with their higher local exposure compared with monkeys.

In rabbits, treatment with dexamethasone was associated with the development of small opacities in the central area of the posterior cortex of the lens. This was observed at both doses in the 12 month study (in 1/8 and 2/8 animals; estimated relative exposure ≥2.7) from 5 months of treatment onwards; there was evidence of reversibility at the high dose level. The prolonged use of glucocorticoids is identified as a significant risk factor for the development of cataracts in the literature. The development of inflammatory cysts appeared to be related to dexamethasone treatment in the single dose studies in rabbits but this was not observed in the repeat dose study (relative exposure, ≤5.3). There were no dexamethasone related ocular findings in monkeys (relative exposure ≤2.0) and no clear effect on intraocular pressure in either species.

Most ocular findings in the two laboratory animal species appeared to be related to the implantation procedure or the implant itself, rather than dexamethasone treatment. Findings in rabbits included posterior capsular cataracts, focal inflammation, retinal disruption (including detachment and haemorrhage), vitreous opacity, haemorrhage and haziness and pannus in single dose studies and mixed cell infiltration of the eyelid in the 12 month study. Conjunctival congestion, swelling and discharge and fibroplasia/fibrosis of the implant site were observed in both species. Ocular findings were fewer and less severe in the 12 month studies compared with the single dose studies, attributable to the use of the DEX PS DDS applicator system for the implantation rather than sclerotomy. Most of the minor findings in the studies, particularly those associated with inflammation, appeared to resolve within several weeks of implantation; fibrosis at the site of implant insertion was not reversed within nine months of implantation.

The degree of ocular toxicity in one single dose study in rabbits was markedly greater than other single dose studies with the same treatment regimen. This was attributable to postoperative infection; steps were subsequently taken by the sponsor to ensure the sterility of the surgical suite.

Systemic toxicity

Systemic toxicity was investigated in both species, although the analysis was limited in most studies in rabbits (apart from one single dose study with a 13 week observation period). Dexamethasone was well tolerated in monkeys, with no clear systemic treatment related effects at estimated relative exposure levels of 3–6 (based on body surface area adjusted doses). Evidence of systemic toxicity was observed at all doses in all single dose studies in rabbits (relative exposure, 6–36). The findings were generally consistent with corticosteroid treatment and included reduced body weight gain, lymphoid depletion (reduced white blood cell [WBC] counts and lymphoid atrophy of the thymus, spleen and lymph nodes) and liver toxicity (fatty change predominantly in females, elevated liver enzymes and cloudy swelling and hydropic degeneration). Most systemic findings appeared to be reversible upon cessation of exposure to dexamethasone. In the 12 month rabbit study, there was suppression of body weight gain at the high dose level (relative exposure, 12); non-ocular tissues were not subjected to microscopic examination in this study.

Reproductive toxicity, genotoxicity and carcinogenicity

No reproductive toxicity, genotoxicity or carcinogenicity studies were submitted. This was justified by the sponsor based on the long clinical use of dexamethasone and the low expected systemic exposure with the implant and was considered acceptable.

Pregnancy classification

The sponsor proposed a Pregnancy Category A for dexamethasone implants. This categorisation is consistent with the Pregnancy Category for corticosteroids intended for systemic administration, although another dexamethasone containing product (Maxidex) intended for ocular administration has a Pregnancy Category B3. In consideration of the accompanying statement proposed by the sponsor, a Pregnancy Category B3 was considered more appropriate for Ozurdex.

Use in children

Ozurdex is not proposed for use in children.

Photosafety

No study investigating the photosafety of dexamethasone was submitted. The sponsor stated that such studies were not conducted as dexamethasone absorbs outside the UVA,

UVB or visible light spectrum and due to the long history of clinical use of topical ocular dexamethasone preparations. This was considered acceptable.

Nonclinical Summary and Conclusions

Dexamethasone implants at doses estimated to yield exposure approximately 3–5 times the clinical level inhibited VEGF induced blood retinal barrier and blood aqueous barrier breakdown in rabbit eyes for 6 weeks post-implantation. Efficacy at the clinical exposure level was not investigated in the model.

The time course for dexamethasone release from implants in rabbit and monkey eyes was highly variable, although the majority (≥98%) was generally released within 4 weeks in rabbits and 3 months in monkeys.

Ocular exposure to dexamethasone was approximately dose proportional and distribution throughout the eye was extensive, with highest exposure generally in the retina. There was no evidence for metabolism of free dexamethasone in rabbit, monkey or human ocular tissue; clearance of the drug from the eye following implantation appeared to be slow, based on half-lives of 10–13 (rabbits) and 11–18 days (monkeys).

Systemic exposure to dexamethasone following ocular implantation in rabbits and monkeys occurred for a similar duration as ocular exposure; plasma levels of dexamethasone were very much smaller than levels in the eye, with the plasma AUC ≤0.04% of retinalexposure in both species.

Single dose toxicity studies with observation periods of up to 13 weeks were conducted in rabbits and repeat dose toxicity studies of 12 months duration (two implantations, 3 months apart) were conducted in rabbits and monkeys. The single dose studies involved surgical (sclerotomy) implantation of a form of the implant different from that to be used in patients, and which displayed a faster *in vivo* release profile. The repeat dose studies, though, used the clinical form of the implant and the specialised injector system for implantation.

Dexamethasone related ocular toxicity in rabbits included inflammatory cysts in single dose studies and the development of small opacities in the central area of the posterior cortex of the lens in the 12 month study (estimated relative exposure, ≥2.7 [based on dose adjusted for vitreous humour volume]). No dexamethasone related ocular toxicity was observed in monkeys (relative exposure, ≤2.0). Other ocular findings related to the implantation procedure or the physical presence of the implant itself. These included posterior capsular cataracts, focal inflammation, retinal disruption (including detachment and haemorrhage), vitreous opacity, haemorrhage and haziness, pannus in the single dose studies in rabbits and mixed cell infiltration of the eyelid in the repeat dose rabbit study; conjunctival congestion, swelling and discharge and fibroplasia/fibrosis of the implant site were observed in both species. There were no clear effects on intraocular pressure in either species.

Systemic toxicity was evident in rabbits at estimated relative exposure levels ≥6 (based on doses adjusted for body surface area). Findings were generally consistent with corticosteroid administration (reduced body weight gain, lymphoid depletion and liver findings, namely fatty change predominantly in females, elevated liver enzymes and cloudy swelling and hydropic degeneration) and reversible upon cessation of dexamethasone exposure. There was no evidence of systemic toxicity in monkeys at doses estimated to yield 3–6 times the clinical exposure.

No safety pharmacology, reproductive toxicity, genotoxicity or carcinogenicity studies were submitted, which was considered acceptable for a drug with a long history of clinical use, and given the low expected systemic exposure.

There were no nonclinical objections to the registration of Ozurdex implants, provided that the efficacy and ocular safety of the product are satisfactorily addressed by clinical data.

IV. Clinical Findings

Introduction

The application included reports of two similar pivotal studies (206207-008 and 206207-009). Only the 6 month controlled phase was covered by each report, although each study proceeded to a further 6 months of open label treatment. The report of one other major study (DC103-06) was also included in the submission but this related to a product other than the subject of the present application.

The product consists of a drug form with associated applicator device.

Applicator Device

The term "DEX PS DDS" (Dexamethasone Posterior Segment Drug Delivery System) used in the submission covers several dosage forms of dexamethasone (tableted and extruded) at either the 350 µg or 700 µg strength, intended for intravitreal insertion. The subject of the present application is a 700 µg DEX PS DDS dose form, with associated applicator designed to implant the dose into the vitreous. As the protocol for study 206207-008 states: "Two forms of the DEX PS DDS have been used in clinical studies. The first was a tableted form which was implanted through a small pars plana incision. The tableted form was used in Phase I and II studies of the DEX PS DDS. An extruded form was developed which is manufactured as fine filaments, capable of delivery through a 22 gauge needle. For convenience and ease of delivery, the extruded DEX PS DDS is preloaded into an applicator to be used for intravitreal placement. The extruded DEX PS DDS and applicator together are referred to as the DEX PS DDS Applicator System. The DEX PS DDS Applicator System was used in a Phase IIb study."

The evaluator noted, however, that the Phase IIb study referred to in the above paragraph was not included in the submission. The evaluator also recommended that the sponsor submit a declaration stipulating precisely which of the studies covered by the submission used the product (drug form with associated applicator device) which is the subject of the present application.

Pharmacokinetics

Study CPK-08-042

This was the pharmacokinetic component of the 6 month open label extension of study 206207-008. Pharmacokinetic (PK) data were collected from 16 patients including 6 who had received the Sham treatment. Data from 10 patients (6 who had received 700 µg implant and 4 who had received the 350 µg implant) were included in the pharmacokinetic analysis.

Study CPK-08-028

This was the pharmacokinetic component of the 6 month open label extension of study 206207-009. PK data were collected from 17 patients including 6 who had received the Sham treatment. Data from 11 patients (7 who had received the 700 µg implant and 4 who had received the 350 µg implant) were included in the PK analysis.

Comment on the pharmacokinetic studies

Plasma dexamethasone concentrations were generally below the limit of quantification in each study and no PK data were reported. No detailed human data on the drug release properties of the product or on the time course of distribution in ocular tissues were

submitted. It may be impossible to obtain such data, in which case additional reliance must be placed on (a) animal data and (b) clinical efficacy and safety data. Thus, if it is not possible to show on pharmacokinetic and pharmacodynamic grounds that use of the product is less likely than (say) use of other modes of corticosteroid ocular treatment (for example, drops or standard intraocular injection) to lead to toxic effects (either local or systemic), then direct clinical comparison of this product with other corticosteroid treatments is required. Also, if reliable pharmacokinetic data are not available, then it is not possible to put an argument that one formulation is sufficiently like another to enable trials of the one to be relevant in assessing the efficacy and safety of the other – any variation will result in the need to re-examine a product's efficacy and safety in clinical trials.

The clinical evaluator noted that the sponsor's *Nonclinical Overview* did not contain information sufficient to alleviate his concern at the lack of human PK data. The animal studies discussed there used a variety of Dex PS DDS products: a "tableted" version; and extruded versions - the last presumably being the same as the product which is the subject of the present application. A 31 day rabbit study, a 6 month rabbit study and a 6 month monkey study used the "extruded" version. The vitreous humour pharmacokinetics (in particular, the early release characteristics) were found to be different for tableted and extruded forms. Release rates were generally lower in monkey eyes than in rabbit eyes.

Pharmacodynamics

No pharmacodynamic data were presented.

Efficacy

Study DC103-06

This was a Phase II, multicentre, randomised, dose ranging study of Ozurdex in the treatment of persistent macular oedema. The dexamethasone products used in the study were different from that which is the subject of the present application.

Inclusion criteria included the following (all to be met):

- Age at least 12 years
- Macular oedema, with:
    - Retinal thickening at the centre of the fovea, and
    - Visual acuity (VA) ≤ 20/40 attributable to persistent macular oedema (PME), and
    - Angiographic evidence of leakage in the perifoveal capillary net.
- PME, defined as clinically observable macular oedema (ME) associated with diabetic retinopathy, uveitis, retinal vein occlusion, or Irving-Gass syndrome, persisting ≥ 90 days after laser treatment or medical management by a physician.

Exclusion criteria included:

- VA < 20/200 in the study eye.
- History of pars plana vitrectomy in the study eye.
- Known steroid responder.
- Use of systemic steroids, immunosuppressants, immunomodulators, alkylating agents, or depot periocular steroids (in the study eye) within 30 days of enrolment. Use of systemic steroids for non-ocular disease with a dose of ≤ 15 mg prednisone orally once

a day or equivalent was allowed, as long as the level of steroid was stable and the dose was not anticipated to change during the first 90 days of the study.

- Ocular hypertension > 22 mmHg or required more than one medication to maintain intraocular pressure (IOP) < 22 mmHg, had prior filtration surgery or glaucoma implant surgery in the study eye, and/or had a cup/disc ratio of > 0.8 in the study eye.
- Media opacity in the study eye.
- Any active ocular infection (that is, bacterial, viral, parasitic or fungal) in either eye. History of herpetic infection in either eye.
- Monocular, or worse than 5/200 in fellow eye.
- Hypertension or diabetes.
- Active retinal or choroidal neovascularisation in the study eye.

Treatments and assessments

Patients were randomised to either dose of Dex PS DDS or observation only. Those randomised to active treatment received it on Day 0 and were blinded as to the dose level. Assessors and readers of outcome measurements were masked as to treatment group.

Patients were monitored for 180 days, with detailed ocular reviews at Days 7, 30, 60 and 90 and a final safety review at Day 180.

The primary efficacy variable was best corrected visual acuity (BCVA) and the primary efficacy endpoint was the 2 line BCVA improvement rate at Day 90, defined as the proportion of patients who had ≥ 2 lines improvement from baseline using the Early Treatment of Diabetic Retinopathy Study (ETDRS) method.

Until Day 90, if any patient had a VA loss from baseline ≥ 3 lines (15 letters) using the EDTRS method, treatment could be given *ad lib*. This was an endpoint and the patient was followed thereafter for safety only.

For all patients, IOP < 25 mmHg was not to be treated. IOP ≥ 25-29 mmHg was to be treated with β-blockers, topical carbonic anhydrase inhibitors, α-agonists and prostaglandin analogs. Prostaglandin analogs were to be used as the last line of therapy given the potential to exacerbate intraocular inflammation and macular oedema. If the IOP was ≥ 30 mmHg, treatment was at the investigator's discretion. After Day 90, concomitant medication use was at the investigator's discretion. No steroids, immunosuppressants, immunomodulators or alkylating agents were to be utilized on Days 0 - 90 unless medically necessary. The use of topical nonsteroidal antiinflammatory drugs (NSAIDs) had to be discontinued by the time of enrolment and was not to be initiated on Days 0 - 90. When there was an underlying bilateral inflammatory condition in the fellow eye, topical steroids, periocular or intravitreal steroid injections could be used. Systemic steroids were permitted for non-ocular diseases to the extent stipulated in the exclusion criteria.

Outcomes

The primary efficacy outcome, that is, for ≥ 2-line BCVA improvement rate for the “intent to treat” (ITT) population, using the last observation carried forward (LOCF) methodology was 26.1% (24/92) for Dex PS DDS 350 µg, 36.7% (36/98) (p-value, 700 µg vs Observation, 0.005) for Dex PS DDS 700 µg and 19.0% (19/100) on observation.

Mean BCVA changes from baseline (LOCF data) also showed dose related improvement, as shown in Table 3.

Table 3: Mean BCVA change from baseline

Group	Mean BCVA change from baseline (logMAR units)			
	Day 30	Day 60	Day 90	Day 180
Dex PS DDS 350µg	-0.04	-0.08	-0.06	-0.07
Dex PS DDS 700µg	-0.05	-0.11	-0.11	-0.12
Observation	-0.02	-0.01	-0.02	0.00

logMAR unit: log of minimal angle of resolution

Efficacy results in the subgroup of 165 patients with diabetic retinopathy as aetiology of PME at baseline followed those of the ITT population.

Terminations

Reasons for premature termination are shown in Table 4

Table 4: Reasons for termination

	Treatment group		
	Dex PS DDS 350µg	Dex PS DDS 700µg	Observation
Patients randomised	105	105	105
Patients who received assigned treatment	100	101	105
Patients who completed Day 90 visit	99	100	93
Patients terminating before Day 90	1	1	12
AE	0	1	1
Death	1	0	0
Non-compliance	0	0	1
Personal reason	0	0	1
Withdrew consent	0	0	6
Lost to follow-up	0	0	3
Patients who completed Day 180 visit	98	97	91
Patients terminating Days 90-179	1	3	2
AE	0	0	0
Death	0	2	0
Non-compliance	0	0	0
Personal reason	0	1	0
Withdrew consent	1	0	1
Lost to follow-up	0	0	0
Other	0	0	1

Comment

The study was carefully conducted. A dose response relationship was demonstrated. The proportion of patients responding was not great but to a considerable extent the admission criteria covered cases that could be regarded as refractory.

As this study used dexamethasone products which were different from that which is the subject of the present application, it is of limited direct relevance to the present application, although it was no doubt valuable as part of the product development program.

Study 206207-008

This was a pivotal Phase III, multicentre, randomised, parallel study of Ozurdex in the treatment of macular oedema due to BRVO or CRVO. The study comprised two components: a 6 month randomised, sham controlled period, followed by a 6 month open label extension. The report included in the submission was an interim report, covering the first component only.

Inclusion criteria included the following (all to be met):

- Age at least 18.
- Macular oedema in the study eye, with all of the following characteristics:
    - due to BRVO or CRVO
    - a duration of 3-9 months prior to qualification/baseline visit for CRVO patients and a duration of 3-12 months prior to qualification/baseline visit for BRVO patients
    - VA decrease attributable to the oedema
    - in the investigator's opinion, unlikely to be adversely affected if not treated for 6 months.
- BCVA score between 34 letters (approximately 20/200 Snellen equivalent) and 68 letters (approximately 20/50 Snellen equivalent) in the study eye measured by the ETDRS method at qualification/baseline.
- Retinal thickness ≥ 300 μm by optical coherence tomography (OCT) in the central subfield of the study eye at qualification/baseline as determined by the investigator.

Exclusion criteria included:

- Uncontrolled systemic disease.
- Any ocular condition that in the opinion of the investigator would prevent a 15 letter improvement in VA (for example, severe macular ischaemia).
- Presence of an epiretinal membrane in the study eye which, in the opinion of the investigator, is the primary cause of the macular oedema, or is severe enough to prevent improvement in VA despite reduction in macular oedema.
- History of clinically significant IOP elevation in response to steroid treatment in either eye
- History of glaucoma or optic nerve head change consistent with glaucoma damage, and/or glaucomatous visual field loss in the study eye
- Ocular hypertension in the study eye requiring more than one medication to maintain IOP < 22 mmHg at qualification/baseline
- Aphakia or presence of anterior chamber intraocular lens in the study eye[10]
- Active retinal neovascularisation in the study eye at qualification/baseline
- Diabetic retinopathy in either eye
- Active or history of choroidal neovascularisation in the study eye
- Presence of rubeosis iridis in the study eye at qualification/baseline
- Any active ocular infection in either eye at qualification/baseline
- History of herpetic infection in the study eye or adnexa
- Presence of active or inactive toxoplasmosis in either eye at qualification/baseline
- Presence of visible scleral thinning or ectasia in the study eye at qualification/baseline

[10] Aphakia is the absence of the lens of the eye.

- Media opacity in the study eye at qualification/baseline that precludes clinical and photographic evaluation
- Intraocular surgery, and/or laser of any type in the study eye within 90 days prior to qualification/baseline
- History of central serous chorioretinopathy in either eye
- History of pars plana vitrectomy in the study eye
- Anticipated need for ocular surgery in the study eye during the 12 month study period
- Use of haemodilution for the treatment of retinal vein occlusion within 3 months prior to the qualification/baseline visit
- History of use of intravitreal steroids or any intravitreal injectable drug in the study eye
- Periocular depot of steroids to the study eye within 6 months prior to qualification/baseline
- Use of systemic steroids within 1 month prior to qualification/baseline visit or anticipated use at any time during the study
- Use of carbonic anhydrate inhibitors within 1 month prior to qualification/baseline visit or anticipated use at any time during the study
- For patients who participate in the therapeutic drug monitoring only: current use (or use within 1 month prior to qualification/baseline) or anticipated use during the first 90 study days of dexamethasone in any form/route of administration
- Use of immunosuppressants, immunomodulators, antimetabolites, and/or alkylating agents use within 6 months prior to qualification/baseline or anticipated use at any time during the study
- Use of topical ophthalmic steroids or topical NSAIDs within 1 month prior to qualification/baseline or anticipated use within the 12 month study period in the study eye
- Use of warfarin/heparin within 1 month prior to qualification/baseline or anticipated use within the 12 month study period
- BCVA score < 34 letters (approximately 20/200 Snellen equivalent) in the non-study eye using the ETDRS method at qualification/baseline

Treatments and assessments

Patients were randomised to either dose of Dex PS DDS or to Sham treatment. The numbers of patients actually treated were: 196 in the Dex 700 µg group, 197 in the Dex 350 µg group and 202 in the Sham group.

The randomised treatment period was for 180 days, with treatment on Day 0 and visits (which included detailed ocular review) on Days 1, 7, 30, 60, 90 and 180. At Day 180, all enrolled patients were eligible to participate in a Dex PS DDS 700 µg open label extension of 180 days, unless:

- BCVA ≥ 84 letters (approximately 20/20) and retinal thickness by OCT ≤ 250 µm in the central subfield, or
- in the investigator's opinion the procedure may put the patient at significant risk.

The primary efficacy variable and its proposed method of analysis were stipulated as follows:

"The primary efficacy variable will be the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. The primary efficacy analyses include the comparisons between the 700 µg DEX PS DDS Applicator System ... and Sham DEX PS DDS Applicator System ... groups and between the 350 DEX PS DDS

Applicator System ... and Sham groups on the primary efficacy variable at initial treatment Day 180. The ITT population will be used for the analysis."

Secondary efficacy variables were:

- Contrast sensitivity, measured in the study eye.
- Optical coherence tomography, measured in the study eye.
- Fundus photography evaluation of the study eye.
- Fluorescein angiography of both eyes.

Therapy considered necessary for the patient's welfare could be given at the discretion of the investigator. This included treatment of elevated IOP and cataract surgery. Topical steroids or NSAIDs were allowed up to 6 weeks following cataract surgeries. Topical steroids and periocular or intravitreal steroid injections could be used for an inflammatory condition in the non-study eye. If systemic NSAIDs were regularly used prior to enrolment, these medications could be continued during the study.

Intravitreal steroids (other than study medication) in the study eye, systemic steroids, dexamethasone were prohibited during the first 90 days of study in any form/route for patients who participated in the therapeutic drug monitoring, as were periocular steroids to the study eye, laser/surgical treatment for macular oedema in the study eye, immunosuppressants, immunomodulators, antimetabolites and alkylating agents, topical ophthalmic steroids or NSAIDs in the study eye (except post cataract surgery), warfarin, heparin, enoxaparin or similar anticoagulants, and additional non-study procedure or surgery on the study eye were prohibited. The decision to administer a prohibited medication/treatment was done with the safety of the patient as the primary consideration.

Comment

It was not clear from the Protocol whether use of the "prohibited" medications or treatments listed in the above paragraph necessarily required termination of further efficacy monitoring for the patient concerned.

Outcomes

The primary efficacy outcome, that is, the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye were 16.3% for Dex PS DDS 350 µg, 19.4% for Dex PS DDS 700 µg and 18.3% for Sham treatment.

The null hypothesis stipulated in the Protocol (no difference in proportion of patients with BCVA improvement of ≥ 15 letters compared to baseline, between the 700 µg and Sham groups) was not rejected at the p=0.05 level. However, on the basis of other measures, efficacy was demonstrated.

Categorical changes from baseline BCVA for the ITT population, using LOCF, are shown in Table 5.

Table 5: BCVA changes from baseline, Study 206207-008

Categorical Change from Baseline BCVA	Dex 700 N = 201	Dex 350 N = 196	Sham N = 202
Day 30			
≥ 15 letters improvement	40 (19.9%) [a]	29 (14.8%) [a]	15 (7.4%)
≥ 5 and < 15 letters improvement	84 (41.8%)	100 (51.0%)	66 (32.7%)
No Change (between -5 to +5 letters)	65 (32.3%)	53 (27.0%)	93 (46.0%)
≥ 5 and < 15 letters worsening	10 (5.0%)	9 (4.6%)	20 (9.9%)
≥ 15 letters worsening	2 (1.0%)	5 (2.6%)	8 (4.0%)
Day 60			
≥ 15 letters improvement	58 (28.9%) [a]	50 (25.5%) [a]	21 (10.4%)
≥ 5 and < 15 letters improvement	83 (41.3%)	81 (41.3%)	69 (34.2%)
No Change (between -5 to +5 letters)	50 (24.9%)	54 (27.6%)	76 (37.6%)
≥ 5 and < 15 letters worsening	9 (4.5%)	9 (4.6%)	28 (13.9%)
≥ 15 letters worsening	1 (0.5%)	2 (1.0%)	8 (4.0%)
Day 90			
≥ 15 letters improvement	45 (22.4%) [a]	41 (20.9%) [a]	25 (12.4%)
≥ 5 and < 15 letters improvement	80 (39.8%)	83 (42.3%)	69 (34.2%)
No Change (between -5 to +5 letters)	55 (27.4%)	46 (23.5%)	70 (34.7%)
≥ 5 and < 15 letters worsening	14 (7.0%)	18 (9.2%)	27 (13.4%)
≥ 15 letters worsening	7 (3.5%)	8 (4.1%)	11 (5.4%)
Day 180			
≥ 15 letters improvement	39 (19.4%)	32 (16.3%)	37 (18.3%)
≥ 5 and < 15 letters improvement	70 (34.8%)	74 (37.8%)	56 (27.7%)
No Change (between -5 to +5 letters)	59 (29.4%)	50 (25.5%)	61 (30.2%)
≥ 5 and < 15 letters worsening	22 (10.9%)	21 (10.7%)	30 (14.9%)
≥ 15 letters worsening	11 (5.5%)	19 (9.7%)	18 (8.9%)

[a] Distribution of BCVA changes with Dex significantly different from Sham ($p < 0.001$, based on Wilcoxon rank-sum test).

The mean decrease in retinal thickness by OCT was significantly greater with Dex 700 and Dex 350 compared to Sham at Day 90, as was retinal volume. There were no significant treatment group differences in the number of letters read correctly with the study eye using contrast sensitivity. A two Grade or greater improvement in central retinal thickening in the study eye using fundus photography was noted for a significantly higher proportion of patients in the Dex 700 group (9.9%) compared to Sham (4.2%) at Day 90. A significantly higher proportion of patients in the Dex 700 group (50.8%) showed improvement from baseline in fluorescein leakage at Day 180 compared to Sham (40.2%).

Terminations

Reasons for premature termination are shown in Table 6.

Table 6: Reasons for premature termination, Study 206207-008

	Treatment group		
	Dex PS DDS 700µg	**Dex PS DDS 350µg**	**Sham**
Patients randomised	201	196	202
Patients who completed Day 180 visit	189	189	189
Patients terminating before Day 180	12	7	13
AE	3	6	3
Ocular	2	2	2
Non-ocular	1	4	1
Lack of efficacy	0	0	2
Administrative reason	7	1	4
Lost to follow-up	2	0	1
Personal reasons	5	1	3
Protocol violation	2	0	2
Other	0	0	2

Study 206207-009

The protocol for this study was the same as that for study 206207-008.

Treatments and assessments

The numbers of patients actually treated were: 225 in the Dex 700 g group, 215 in the Dex 350 g group, and 221 in the Sham group.

Outcomes

The primary efficacy outcome, that is, the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye were 22.0% for Dex PS DDS 350 µg, 23.5% for Dex PS DDS 700 µg and 17.0% for Sham treatment.

The null hypothesis stipulated in the Protocol (no difference in proportion of patients with BCVA improvement of ≥ 15 letters compared to baseline, between the 700 µg and Sham groups) was not rejected at the p=0.05 level. However, on the basis of other measures, efficacy was demonstrated.

Categorical changes from baseline BCVA for the ITT population, using LOCF, are shown in Table 7.

Table 7: BCVA changes from baseline, Study 206207-009

Categorical Change from Baseline BCVA	Dex 700 N = 226	Dex 350 N = 218	Sham N = 224
Day 30			
≥ 15 letters improvement	51 (22.6%) [a]	45 (20.6%) [a]	17 (7.6%)
≥ 5 and < 15 letters improvement	110 (48.7%)	104 (47.7%)	73 (32.6%)
No Change (between -5 to +5 letters)	51 (22.6%)	57 (26.1%)	101 (45.1%)
≥ 5 and < 15 letters worsening	11 (4.9%)	11 (5.0%)	27 (12.1%)
≥ 15 letters worsening	3 (1.3%)	1 (0.5%)	6 (2.7%)
Day 60			
≥ 15 letters improvement	67 (29.6%) [a]	68 (31.2%) [a]	27 (12.1%)
≥ 5 and < 15 letters improvement	107 (47.3%)	98 (45.0%)	78 (34.8%)
No Change (between -5 to +5 letters)	43 (19.0%)	42 (19.3%)	81 (36.2%)
≥ 5 and < 15 letters worsening	4 (1.8%)	6 (2.8%)	25 (11.2%)
≥ 15 letters worsening	5 (2.2%)	4 (1.8%)	13 (5.8%)
Day 90			
≥ 15 letters improvement	48 (21.2%) [a]	56 (25.7%) [a]	31 (13.8%)
≥ 5 and < 15 letters improvement	102 (45.1%)	85 (39.0%)	83 (37.1%)
No Change (between -5 to +5 letters)	58 (25.7%)	58 (26.6%)	67 (29.9%)
≥ 5 and < 15 letters worsening	10 (4.4%)	14 (6.4%)	25 (11.2%)
≥ 15 letters worsening	8 (3.5%)	5 (2.3%)	18 (8.0%)
Day 180			
≥ 15 letters improvement	53 (23.5%)	47 (21.6%)	38 (17.0%)
≥ 5 and < 15 letters improvement	79 (35.0%)	74 (33.9%)	64 (28.6%)
No Change (between -5 to +5 letters)	61 (27.0%)	63 (28.9%)	64 (28.6%)
≥ 5 and < 15 letters worsening	18 (8.0%)	23 (10.6%)	31 (13.8%)
≥ 15 letters worsening	15 (6.6%)	11 (5.0%)	27 (12.1%)

[a] Distribution of BCVA changes with Dex significantly different from Sham ($p < 0.001$, based on Wilcoxon rank-sum test).

The mean decrease in retinal thickness by OCT was significantly greater with Dex 700 and Dex 350 compared to Sham at Day 90, as was retinal volume. There were no significant treatment group differences in the number of letters read correctly with the study eye using contrast sensitivity, or in fluorescein leakage at Day 180 compared to Sham. No consistent differences between groups were observed in central retinal thickening in the study eye using fundus photography.

Terminations

Reasons for premature termination are shown in Table 8.

Table 8: Reasons for premature termination, Study 206207-009

	Treatment group		
	Dex PS DDS 700µg	**Dex PS DDS 350µg**	**Sham**
Patients randomised and receiving any treatment	225	215	221
Patients who completed Day 180 visit	214	206	209
Patients terminating before Day 180	11	9	12
AE	4	2	5
Ocular	2	2	4
Non-ocular	2	0	1
Lack of efficacy	0	3	2
Administrative reason	2	2	3
Lost to follow-up	0	0	2
Personal reasons	2	2	1
Protocol violation	2	0	0
Other	3	2	2

Efficacy summary

The two pivotal Phase III studies (206207-008 and 206207-009) were carefully done. The pooled efficacy results for these studies are shown in Table 9.

Table 9: Proportion of patients with a BCVA improvement of 15 or more letters from baseline – pooled studies

Proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye			
	Dex 700 N=427	**Dex 350 N=414**	**Sham N=426**
Day 30	21.3%	17.9%	7.5%
Day 60	29.3%	28.5%	11.3%
Day 90	21.8%	23.4%	13.1%
Day 180	21.5%	19.3%	17.6%

The difference between the Dex 700 µg and Sham groups at 180 days (the stipulated primary efficacy endpoint) was not statistically significant. However, the difference between active and Sham treatment groups was statistically significant ($p < 0.05$) at the other 3 time points.

A degree of efficacy was demonstrated, based on a variety of measures other than the primary efficacy variable. However, the level of response was only moderate (admittedly, in a population which could be described as refractory cases), and by 90 days post treatment, it had started to diminish.

Safety

Study DC103-06

Six deaths were reported, all classified as "not related" to the study treatment. Other serious adverse events (AEs) were reported for 14.0% (14/100) of patients in the Dex PS DDS 350 µg group, 23.8% (24/101) of patients in the Dex PS DDS 700µg group and 10.5% (11/105) of patients in the Observation group. These were all classified as "not related" to study treatment, except one (vitreous haemorrhage, Dex PS DDS 700 µg group) which was considered "possibly related".

The numbers of patients with AEs reported by > 5% in any treatment group are shown in Table 10.

Table 10: AEs reported by > 5% patients in any group, Study DC103-06

System Organ Class Preferred Term	Dex PS DDS 350 µg N = 100	Dex PS DDS 700 µg N = 101	Observation N = 105
Blood And Lymphatic System Disorders			
anaemia	6 (6.0%)	9 (8.9%)	2 (1.9%)
Eye Disorders (either eye)			
visual acuity reduced	19 (19.0%)	21 (20.8%)	14 (13.3%)
anterior chamber cell	27 (27.0%)	23 (22.8%)	3 (2.9%)
anterior chamber flare	24 (24.0%)	20 (19.8%)	6 (5.7%)
vitreous haemorrhage	22 (22.0%)	24 (23.8%)	3 (2.9%)
eye pain	20 (20.0%)	15 (14.9%)	5 (4.8%)
vitreous disorder	19 (19.0%)	16 (15.8%)	4 (3.8%)
retinal haemorrhage	8 (8.0%)	9 (8.9%)	14 (13.3%)
eye irritation	11 (11.0%)	17 (16.8%)	2 (1.9%)
abnormal sensation in eye	10 (10.0%)	13 (12.9%)	4 (3.8%)
vitreous floaters	10 (10.0%)	14 (13.9%)	3 (2.9%)
maculopathy	13 (13.0%)	6 (5.9%)	6 (5.7%)
conjunctival haemorrhage	13 (13.0%)	10 (9.9%)	0 (0.0%)
macular oedema	10 (10.0%)	4 (4.0%)	9 (8.6%)
cataract cortical	6 (6.0%)	8 (7.9%)	6 (5.7%)
eye pruritus	9 (9.0%)	8 (7.9%)	3 (2.9%)
diabetic retinopathy	3 (3.0%)	7 (6.9%)	8 (7.6%)
eye redness	5 (5.0%)	10 (9.9%)	1 (1.0%)
cataract nuclear	3 (3.0%)	7 (6.9%)	3 (2.9%)
vitreous opacities	3 (3.0%)	8 (7.9%)	2 (1.9%)
vision blurred	2 (2.0%)	7 (6.9%)	3 (2.9%)
visual disturbance	3 (3.0%)	6 (5.9%)	1 (1.0%)
Injury, Poisoning And Procedural Complications			
post procedural pain	9 (9.0%)	5 (5.0%)	0
Investigations			
IOP increased	17 (17.0%)	13 (12.9%)	0
Nervous System Disorders			
headache	5 (5.0%)	6 (5.9%)	2 (1.9%)
Vascular Disorders			
hypertension	22 (22.0%)	40 (39.6%)	27 (25.7%)

AEs reported during the study are shown in Table 11, classified by system organ class (SOC) and preferred term. Note that for each class, only selected preferred terms are

included, but all patients reporting AEs are included in the number for SOC. Patients may have more than one AE within a class.

Table 11: AEs by SOC, Study DC103-06

	Dex PS DDS 350µg		Dex PS DDS 700µg		Observation	
	n	%	n	%	n	%
Patients who received treatment	100		101		105	
Patients with one or more clinical adverse experiences	97	97.0	99	98.0	84	80.0
Patients with no clinical adverse experiences	3	3.0	2	2.0	21	20.0
Blood And Lymphatic System Disorders	6	6.0	9	8.9	2	1.9
Anaemia	6	6.0	9	8.9	2	1.9
Cardiac Disorders	5	5.0	7	6.9	2	1.9
Cardiac Failure Congestive	1	1.0	4	4.0	0	0
Angina	1	1.0	3	3.0	0	0
Ear And Labyrinth Disorders	2	2.0	2	2.0	2	1.9
Endocrine Disorders	0	0	0	0	1	1.0
Eye Disorders	88	88.0	88	87.1	58	55.2
Gastrointestinal Disorders	8	8.0	11	10.9	7	6.7
General Disorders And Administration	10	10.0	10	9.9	3	2.9
Hepatobiliary Disorders	1	1.0	0	0	1	1.0
Immune System Disorders	2	2.0	1	1.0	2	1.9
Infections And Infestations	17	17.0	20	19.8	15	14.3
Injury, Poisoning And Procedural	16	16.0	8	7.9	4	3.8
Post-procedural Pain	9	9.0	5	5.0	0	0
Investigations	19	19.0	22	21.8	3	2.9
IOP Increased	17	17.0	13	12.9	0	0
Metabolism and Nutrition Disorders	2	2.0	6	5.9	4	3.8
Musculoskeletal and Connective Tissue	10	10.0	7	6.9	3	2.9
Arthralgia	4	4.0	1	1.0	0	0
Back Pain	0	0	1	1.0	3	2.9
Neoplasms	5	5.0	3	3.0	1	1.0
Nervous System Disorders	15	15.0	14	13.9	5	4.8
Headache	5	5.0	6	5.9	2	1.9
Dizziness	3	3.0	3	3.0	1	1.0
Psychiatric Disorders	2	2.0	4	4.0	6	5.7
Renal and Urinary Disorders	2	2.0	3	3.0	2	1.9
Reproductive System And Breast	2	2.0	0	0	2	1.9
Respiratory, Thoracic and Mediastinal	4	4.0	6	5.9	3	2.9
Skin and Subcutaneous Tissue Disorders	2	2.0	6	5.9	2	1.9
Surgical And Medical Procedures	0	0	1	1.0	0	0
Vascular Disorders	23	23.0	43	42.6	27	25.7
Hypertension	22	22.0	40	39.6	27	25.7

IOP tended to be higher in treated patients. However, increases in IOP either did not require treatment or were successfully managed with topical medication.

Based on slit lamp examination, the majority (> 70%) of patients in each group had no anterior chamber cells or flare and no anterior vitreous cells at baseline or during follow up.

At baseline, cataracts were reported for 66/100 patients in the Dex PS DDS 350 µg group, 63/100 in the Dex PS DDS 700 µg group and 67/103 in the Observation group. At Day 180, the corresponding proportions were 62/95, 60/93 and 57/87, respectively.

Study 206207-008

Three deaths were reported, all classified as "not related" to study treatment. Other serious AEs were reported for 5.1% (10/196) of patients in the Dex 700 group, 11.2% (22/197) of patients in the Dex 350 group, and 6.4% (13/202) of patients in the Sham group.

The numbers of patients with AEs reported by > 2% in any treatment group are shown in Table 12.

Table 12: AEs reported by > 2% patients in any group, Study 206207-008

System Organ Class Preferred Term	Dex PS DDS 700 µg N = 196	Dex PS DDS 350 µg N = 197	Sham N = 202
Investigations			
IOP increased	46 (23.5%)	46 (23.4%)	6 (3.0%)
Eye Disorders (either eye)			
conjunctival haemorrhage	39 (19.9%)	35 (17.8%)	26 (12.9%)
eye pain	13 (6.6%)	8 (4.1%)	7 (3.5%)
maculopathy	11 (5.6%)	7 (3.6%)	17 (8.4%)
conjunctival hyperaemia	10 (5.1%)	11 (5.6%)	7 (3.5%)
retinal haemorrhage	8 (4.1%)	3 (1.5%)	5 (2.5%)
ocular hypertension	7 (3.6%)	9 (4.6%)	2 (1.0%)
foreign body sensation	6 (3.1%)	3 (1.5%)	3 (1.5%)
vitreous floaters	6 (3.1%)	2 (1.0%)	4 (2.0%)
cataract cortical	5 (2.6%)	1 (0.5%)	2 (1.0%)
cataract	4 (2.0%)	6 (3.0%)	2 (1.0%)
vitreous detachment	4 (2.0%)	6 (3.0%)	1 (0.5%)
vitreous haemorrhage	4 (2.0%)	5 (2.5%)	3 (1.5%)
conjunctival oedema	3 (1.5%)	9 (4.6%)	2 (1.0%)
VA reduced	3 (1.5%)	2 (1.0%)	5 (2.5%)
Vascular Disorders			
hypertension	5 (2.6%)	4 (2.0%)	4 (2.0%)
Nervous System Disorders			
headache	7 (3.6%)	1 (0.5%)	4 (2.0%)
Infections and Infestations			
influenza	5 (2.6%)	2 (1.0%)	2 (1.0%)

AEs reported during the study are shown in Table 13, classified by SOC and preferred term. Note that for each class, only selected preferred terms are included, but all patients reporting AEs are included in the number for SOC. Patients may have more than one AE within a class.

Table 13: AEs by SOC, Study 206207-008

	Dex PS DDS 700µg		Dex PS DDS 350µg		Sham	
	n	%	n	%	n	%
Patients randomised	196		197		202	
Patients with one or more clinical adverse experiences	140	71.4	141	71.6	103	51.0
Patients with no clinical adverse experiences	56	28.6	56	28.4	99	49.0
Blood And Lymphatic System Disorders	1	0.5	2	1.0	0	0
Cardiac Disorders	4	2.0	8	4.1	4	2.0
Myocardial infarction	1	0.5	4		0	0
Congenital, Familial and Genetic	0	0	0	0	1	0.5
Ear And Labyrinth Disorders	1	0.5	0	0	0	0
Eye Disorders	88	44.9	96	48.7	79	39.1
Gastrointestinal Disorders	9	4.6	5	2.5	10	5.0
General Disorders And Administration Site Conditions	3	1.5	4	2.0	1	0.5
Immune System Disorders	4	2.0	3	1.5	1	0.5
Infections And Infestations	17	8.7	27	13.7	15	7.4
Injury, Poisoning And Procedural Complications	7	3.6	10	5.1	11	5.4
Procedural Pain	0	0	1	0.5	0	0
Investigations	48	24.5	47	23.9	9	4.5
IOP Increased	46	23.5	46	23.4	6	3.0
Metabolism and Nutrition Disorders	6	3.1	2	1.0	7	3.5
Musculoskeletal and Connective Tissue Disorders	7	3.6	9	4.6	11	5.4
Neoplasms	1	0.5	1	0.5	4	2.0
Nervous System Disorders	12	6.1	9	4.6	13	6.4
Headache	7	3.6	1	0.5	4	2.0
Psychiatric Disorders	2	1.0	2	1.0	2	1.0
Renal and Urinary Disorders	2	1.0	2	1.0	0	0
Reproductive System And Breast	1	0.5	3	1.5	1	0.5
Respiratory, Thoracic and Mediastinal Disorders	4	2.0	3	1.5	6	3.0
Skin and Subcutaneous Tissue Disorders	4	2.0	3	1.5	4	2.0
Vascular Disorders	7	3.6	6	3.0	5	2.5
Hypertension	5	2.6	4	2.0	4	2.0

Findings on biomicroscopy and ophthalmoscopy were similar among the 3 treatment groups. Conjunctival haemorrhage was more common with Dex 700 (66.3%) and Dex 350 (68.0%) than with Sham (44.6%). At Day 180, the incidence of new or progressed posterior subcapsular opacities was 10.0%, 7.8% and 2.7% in the Dex 700, Dex 350 and Sham groups, respectively.

Study 206207-009

One death was reported, classified as "not related" to study treatment. Other serious AEs were reported for 4.9% (11/225) of patients in the Dex 700 group, 2.3% (5/215) of patients in the Dex 350 group, and 5.4% (12/221) of patients in the Sham group.

Numbers of patients with AEs reported by > 2% in any treatment group are shown in Table 14.

Table 14: AEs reported by > 2% patients in any group, Study 206207-009

System Organ Class Preferred Term	Dex PS DDS 700 µg N = 225	Dex PS DDS 350 µg N = 215	Sham N = 221
Investigations			
IOP increased	60 (26.7%)	56 (26.0%)	5 (2.3%)
Eye Disorders (either eye)			
conjunctival haemorrhage	46 (20.4%)	37 (17.2%)	37 (16.7%)
conjunctival hyperaemia	18 (8.0%)	16 (7.4%)	13 (5.9%)
eye pain	18 (8.0%)	10 (4.7%)	10 (4.5%)
retinal haemorrhage	11 (4.9%)	8 (3.7%)	6 (2.7%)
cataract	11 (4.9%)	5 (2.3%)	5 (2.3%)
ocular hypertension	10 (4.4%)	7 (3.3%)	2 (0.9%)
vitreous detachment	9 (4.0%)	10 (4.7%)	9 (4.1%)
maculopathy	8 (3.6%)	15 (7.0%)	6 (2.7%)
vitreous floaters	7 (3.1%)	3 (1.4%)	4 (1.8%)
vitreous haemorrhage	6 (2.7%)	8 (3.7%)	9 (4.1%)
conjunctival oedema	6 (2.7%)	8 (3.7%)	5 (2.3%)
retinal exudates	6 (2.7%)	2 (0.9%)	12 (5.4%)
vision blurred	6 (2.7%)	2 (0.9%)	4 (1.8%)
macular oedema	6 (2.7%)	1 (0.5%)	6 (2.7%)
foreign body sensation	5 (2.2%)	4 (1.9%)	8 (3.6%)
lacrimation increased	5 (2.2%)	2 (0.9%)	3 (1.4%)
retinal vein occlusion	5 (2.2%)	2 (0.9%)	1 (0.5%)
photopsia	4 (1.8%)	7 (3.3%)	2 (0.9%)
visual acuity reduced	4 (1.8%)	5 (2.3%)	4 (1.8%)
eye irritation	4 (1.8%)	4 (1.9%)	5 (2.3%)
cataract nuclear	4 (1.8%)	2 (0.9%)	5 (2.3%)
optic disc vascular	3 (1.3%)	5 (2.3%)	3 (1.4%)
cataract subcapsular	3 (1.3%)	3 (1.4%)	5 (2.3%)
cataract cortical	2 (0.9%)	3 (1.4%)	7 (3.2%)
macular degeneration	0 (0.0%)	5 (2.3%)	1 (0.5%)
retinal neovascularization	0 (0.0%)	3 (1.4%)	8 (3.6%)
Vascular Disorders			
hypertension	12 (5.3%)	9 (4.2%)	11 (5.0%)
Nervous System Disorders			
headache	7 (3.1%)	9 (4.2%)	3 (1.4%)
Infections and Infestations			
nasopharyngitis	6 (2.7%)	6 (2.8%)	6 (2.7%)
URTI	2 (0.9%)	4 (1.9%)	7 (3.2%)

AEs reported during the study are shown in Table 15, classified by SOC and preferred term. Note that for each class, only selected preferred terms are included, but all patients reporting AEs are included in the number for SOC. Patients may have more than one AE within a class.

Table 15: AEs by SOC, Study 206207-009

	Dex PS DDS 700µg		Dex PS DDS 350µg		Sham	
	n	%	n	%	n	%
Patients randomised and treated	225		215		221	
Patients with one or more clinical adverse experiences	165	73.3	155	72.1	139	62.9
Patients with no clinical adverse experiences	60	26.7	60	27.9	82	37.1
Cardiac Disorders	5	2.2	4	1.9	5	2.3
Myocardial infarction	1	0.4	1	0.5	0	0
Congenital, Familial and Genetic	0	0	1	0.5	0	0
Ear And Labyrinth Disorders	1	0.4	1	0.5	2	0.9
Endocrine Disorders	2	0.9	1	0.5	0	0
Eye Disorders	127	56.4	109	50.7	108	48.9
Gastrointestinal Disorders	8	3.6	6	2.8	7	3.2
General Disorders And Administration Site Conditions	7	3.1	3	1.4	9	4.1
Hepatic Disorders	1	0.4	0	0	1	0.5
Immune System Disorders	2	0.9	2	0.9	3	1.4
Infections And Infestations	22	9.8	20	9.3	28	12.7
Injury, Poisoning And Procedural Complications	11	4.9	7	3.3	10	4.5
Investigations	63	28.0	57	26.5	10	4.5
IOP Increased	60	26.7	56	26.0	5	2.3
Metabolism and Nutrition Disorders	2	0.9	5	2.3	8	3.6
Musculoskeletal and Connective Tissue Disorders	11	4.9	8	3.7	13	5.9
Neoplasms	6	2.7	4	1.9	2	0.9
Nervous System Disorders	13	5.8	14	6.5	7	3.2
Headache	7	3.1	9	4.2	3	1.4
Psychiatric Disorders	5	2.2	3	1.4	5	2.3
Renal and Urinary Disorders	2	0.9	1	0.5	1	0.5
Reproductive System And Breast	1	0.4	3	1.4	1	0.5
Respiratory, Thoracic and Mediastinal Disorders	7	3.1	7	3.3	5	2.3
Skin and Subcutaneous Tissue Disorders	3	1.3	1	0.5	4	1.8
Vascular Disorders	13	5.8	11	5.1	11	5.0
Hypertension	12	5.3	9	4.2	11	5.0

Findings on biomicroscopy and ophthalmoscopy were similar among the 3 treatment groups. Conjunctival haemorrhage was more common with Dex 700 (57.3%) and Dex 350 (60.0%) than with Sham (38.0%). At Day 180, the incidence of new or progressed posterior subcapsular opacities was 12.7%, 6.1% and 4.9% in the Dex 700, Dex 350 and Sham groups, respectively.

Uncontrolled studies

Studies DC103-02, DC103-03 and DC103-04

A consolidated *Abbreviated Clinical Study Report* was presented for these 3 studies, all of which related to compassionate and emergency use of DEX PS DDS in patients with posterior segment disease who had failed all standard therapies. Studies DC103-02, DC103-03 and DC103-04 had enrolled 1 (both eyes), 1 and 20 patients, respectively. One patient had 1 repeat treatment and 1 patient had 2 repeat treatments. Patients each received treatment with a DEX PS DDS 700 µg product but further details of the products used were not reported.

There were 13 male and 9 female patients, mean age 43.5 (range 5-81) years. Duration of follow up was < 6 months for 1/22 eyes, 6-12 months for 9/22, and > 12 months for 12/22.

AEs were reported in all patients. Those classified as at least "possibly" related to study drug are shown in Table 16.

Table 16: Related adverse events from uncontrolled studies

AE	No. of eyes in which AE reported N=22
Cataract subcapsular	2
Cataract nuclear	2
Retinal oedema	1
IOP increased	6

Comment

The evaluator found it puzzling that the 5 reported cases of "post procedural pain" were classified "not related".

Other studies

Study DC103-05

This was planned as a Phase I/II randomised, multicentre, double blind, placebo controlled, dose ranging study in the treatment of ocular inflammation following pars plana vitrectomy. Planned enrolment was 128, but because of slow enrolment, the study was terminated after 25 had been enrolled. The formulations of DEX PS DDS 700 g and DEX PS DDS 350 g used in the study appear to be "tableted" versions, unlike the one which is the subject of the present application.

Duration of follow up was < 6 months for 1/22 eyes, 6-12 months for 9/22, and > 12 months for 12/22. Of the 25 patients enrolled, 9 received Dex 350 µg, 11 Dex 350 µg and 5 placebo. Twenty patients completed the 360 day follow up period.

The number of patients with ocular AEs reported for > 1 patient in any treatment group is shown in Table 17.

Table 17: Patients with ocular AEs reported by > 2 patients in any group, Study DC103-05

System Organ Class Preferred Term	Dex PS DDS 350 µg N = 9	Dex PS DDS 700 µg N = 11	Placebo N = 5
Eye Disorders (study eye)			
conjunctival hyperaemia	9 (100%)	11 (100%)	5 (100%)
ciliary hyperaemia	9 (100%)	9 (81.8%)	5 (100%)
anterior chamber flare	7 (77.8%)	8 (72.7%)	4 (80.0%)
vitreous opacities	3 (33.3%)	4 (36.4%)	3 (60.0%)
retinal haemorrhage	3 (33.3%)	3 (27.3%)	3 (60.0%)
vitreous disorder	1 (11.1%)	5 (45.5%)	3 (60.0%)
vitreous haemorrhage	1 (11.1%)	4 (36.4%)	3 (60.0%)
anterior chamber cell	3 (33.3%)	0	2 (40.0%)
cataract subcapsular	2 (22.2%)	1 (9.1%)	2 (40.0%)
macular oedema	2 (22.2%)	3 (27.3%)	0
cataract nuclear	1 (11.1%)	1 (9.1%)	2 (40.0%)
cataract cortical	2 (22.2%)	0	1 (20.0%)
eye pain	0	2 (18.2%)	1 (20.0%)
retinal tear	0	3 (27.3%)	0
Investigations			
IOP increased	2 (22.2%)	4 (36.4%)	0

Study DC103-07

This was a Phase II, randomised, controlled safety study whose object was to evaluate the safety and performance of the DDS applicator for the intravitreal insertion of an extruded form of the Dex 700 µg product, compared with a tableted form inserted with forceps *via* a pars plana incision.

Inclusion criteria included:

- Age ≥ 18.
- VA ≤ 20/40 attributable to ME in study eye.

Exclusion criteria included:

- VA < 20/200 in study eye.
- Ocular hypertension > 22 mmHg.
- Current or anticipated use of corticosteroid or NSAID in study eye (other than the study drug).

Patients were to be followed for 180 days, then every 3 months if they had residual Dex PS DDS drug visible at the Day 180 visit. Of the 19 treated with the applicator, 2 terminated early and 1 was lost to follow up. All 10 controls completed 180 days.

Outcome

Vitreous leakage due to insertion was significantly less in the applicator group (3/19) than in the incision group (10/10).

Adverse events were reported for (14/19) of patients in the applicator group and (9/10) of patients in the incision group. Ocular adverse events in the study eye were reported for 68.4% (13/19) of patients in the applicator group and 90.0% (9/10) of patients in the incision group. The most frequently reported ocular events in the applicator study eyes

were visual disturbance (5 patients), retinal haemorrhage and IOP increased (3 patients each), and eye pain, visual acuity reduced, vitreous floaters, eye irritation and vision blurred (2 patients each). The most frequently reported ocular events in the incision study eyes were eye pain and IOP increased (3 patients each) and visual acuity reduced, abnormal sensation in eye, eye pruritus and vitreous haemorrhage (2 patients each).

Study 206207-015

This was planned as a 6 week, multicentre, patient and assessor masked, randomised trial with 20 week masked extension, whose objective was to assess the safety and efficacy of 700 µg and 350 µg strengths of Dex PS DDS applicator system compared with Sham treatment, in patients with anterior uveitis. Planned enrolment was 189 patients.

The drug products used in the study were from lot numbers also used in studies 206207-008 and 206207-009.

Due to slow enrolment, the study was terminated after enrolment of 5 patients (1M, 4F), age range 25-58 years: 2 in the DDS 700 group, 2 in the DDS 350 group and 1 in the Sham group. All completed the 26 week study period.

In view of the small numbers, little is worth reporting. At some visits, increased IOP in the study eye was observed in some patients, but this responded well to topical medical therapy.

Overall exposure

The overall l exposure to extruded versions of Dex PS DDS in studies with reports included in the submission are shown in Table 18.

Table 18: Overall exposure in studies

Study	Follow-up duration[1]	Dex 700	Dex 350
DC103-07	26 weeks	19	0
206207-008	26 weeks	196	197
206207-009	26 weeks	225	215
206207-015	26 weeks	2	2

[1]Not taking account of early terminations.

Safety summary

Systemic toxicity

The two pharmacokinetic studies show that use of the product is associated with low plasma levels of dexamethasone. No evidence of extraocular toxicity emerged from the controlled studies.

Ocular toxicity

Ocular adverse events related to DEX PS DDS included the known effects of prolonged use of ophthalmic steroids: increased intraocular pressure , ocular hypertension and cataracts. Other ocular adverse events considered related to the dexamethasone were vitreous detachment and visual disturbance. Ocular adverse events related to the applicator/insertion included conjunctival haemorrhage, conjunctival hyperaemia, eye pain, vitreous haemorrhage and conjunctival oedema and generally occurred soon after the injection procedure and were transient. In addition, less common events possibly related to the procedure were vitreous opacities (including vitreous floaters), anterior chamber cell, photopsia, retinal tear and anterior chamber flare.

Conjunctival haemorrhage and conjunctival oedema

Findings on biomicroscopy and ophthalmoscopy generally corroborated the AE reports. For conjunctival haemorrhage and conjunctival oedema, the incidences were significantly higher with Dex compared to Sham. These were expected after an intravitreal injection and were generally transient. The incidence of retinal tears was low in all treatment groups. Eight patients (2 Dex 700, 4 Dex 350 and 2 Sham) had retinal tears in the study eye reported post-baseline during the initial treatment period. None of the tears was considered serious or progressed to retinal detachments. Retinal detachment was rare (1 Dex 700 and 1 Sham).

Cataracts

Over 50% of patients entered the Phase III studies with a history of cataracts. During the initial treatment period, cataract adverse events in the study eye were reported as summarised in Table 19.

Table 19: Reports of cataract in the Phase III studies

Preferred Term	Dex 700 N = 421	Dex 350 N = 412	Sham N = 423
cataract	15 (3.6%)	7 (1.7%)	6 (1.4%)
cataract subcapsular	7 (1.7%)	4 (1.0%)	3 (0.7%)
cataract nuclear	6 (1.4%)	2 (0.5%)	5 (1.2%)
cataract cortical	5 (1.2%)	4 (1.0%)	8 (1.9%)

For over 30% of patients, the cataracts were bilateral (that is, reported in both the study eye and non-study eye). Two patients (1 Dex 700 and 1 Dex 350) had surgery for cataracts in the study eye during the initial treatment period. Four patients (2 Dex 350 and 2 Sham) had surgery for cataracts in the non-study eye.

Endophthalmitis

No cases of this possible complication were reported.

Adequacy of follow up

The length of follow up reported in the data submitted was minimal. In the opinion of the evaluator, data covering at least 2 years should be required, to obtain a better indication of the rates of cataract formation in relation to treatment, the effects on VA of DEX PS DDS after any cataracts have been treated and some assurance that late endophthalmitis will not be an unacceptably common complication.

Initial Clinical Summary and Conclusions

Dosage was not been adequately justified. The two pivotal studies (206207-008 and 206207-009) suggest that with the product proposed for registration there is a dose related increase in response between 350 and 700 µg, without a dose related increase in toxicity. This raises the question of whether a higher dose could be safely used, with further increase in efficacy – particularly as the 700 µg dexamethasone dosage used in the implant appears to be comparable in potency to standard intraocular corticosteroid injections reported in the literature (see for example Ciardella et al. 2004; Ip et al. 2004).[11,12]

[11] Ciardella AP et al. Intravitreal triamcinolone for the treatment of refractory diabetic macular oedema with hard exudates: an optical coherence tomography study. Br J Ophthalmol 2004; 88: 1131–1136.

Another reason for assessing the efficacy of intravitreal depot against other modes of administration is the known ocular toxicity. With some modes of administration, exposure to corticosteroid can be ceased more rapidly if it appears that the benefit of any response is outweighed by toxic effects and this needs to be taken into account in assessing a depot type product.

The evaluator therefore recommended rejection of the application, on the ground that the product has not yet been adequately studied. In particular, further information is required on:

- Justification of dosage; and
- Comparison with other modes of ocular corticosteroid treatments, in terms of safety and efficacy.

The evaluator also believed that safety data covering at least 2 years post-treatment will be necessary.

Supplementary Clinical Evaluation

Following the receipt of the clinical evaluation report, the sponsor submitted supplementary data which comprised 12 month *Clinical Study Reports* (CSRs) for the two pivotal studies (206207-008 and 206207-009), to supplement the 6 month CSRs submitted previously.

Efficacy - Study 206207-008

This pivotal Phase III, multicentre, randomised, parallel study of Ozurdex in the treatment of macular oedema due to BRVO or CRVO comprised 2 components: a 6 month randomised, sham controlled period, followed by a 6 month open label extension. The first 6 month period was discussed earlier in this AusPAR and the 6 month extension is discussed here. The disposition of patients is shown in Figure 1.

The "first baseline" is initial treatment (IT) Day 0. The "second baseline" is IT Day 180 = open label (OL) Day 0.

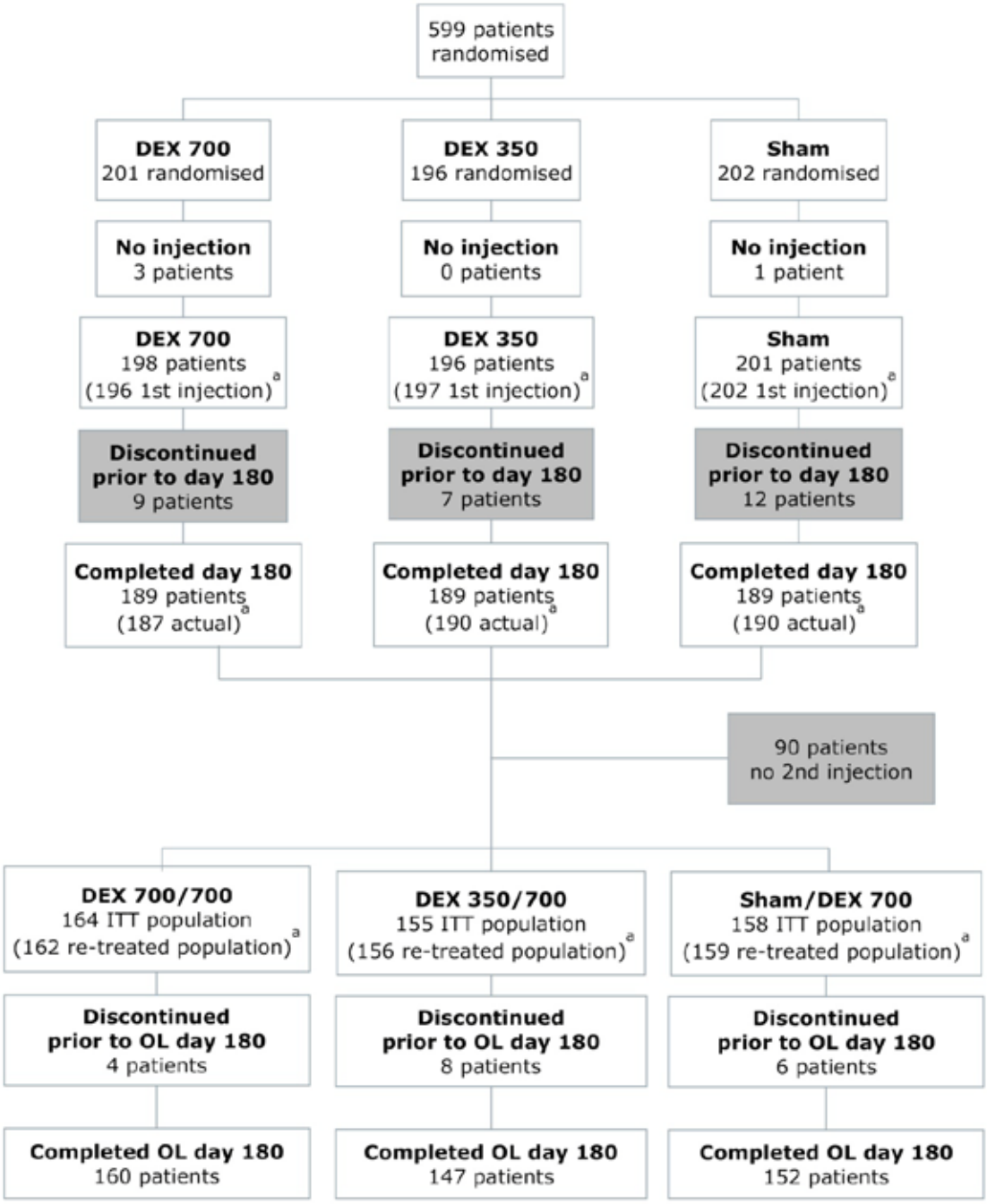
At the end of the randomised treatment period (IT Day 180 days), all enrolled patients were eligible to participate in a Dex PS DDS 700 μg open label extension of 180 days, unless:

- BCVA ≥ 84 letters (approximately 20/20) and retinal thickness by OCT ≤ 250 μm in the central subfield, or
- in the investigator's opinion the procedure may put the patient at significant risk.

Those who received treatment at the beginning of the open label extension (the "Re-treated Population") were reviewed on OL Day 1 (that is, the day after re-treatment), and OL Days 7, 30, 60, 90 and 180. Those who were not treated in the open label extension (the "Single Treatment Population") were reviewed at the same intervals, except that they were not reviewed on OL Days 1 or 7. Assessments were similar to those which were performed in the IT period. Restrictions relating to concomitant treatments were also similar.

[12] Ip MS et al. Intravitreal triamcinolone for the treatment of macular oedema associated with central retinal vein occlusion. Arch Ophthalmol 2004; 122: 1131-1136.

Figure 1: Disposition of patients, ITT population. Study 206207-008



Shaded boxes comprise the single treatment population.

[a] 2 patients randomised to Dex 700 were actually assigned to other treatment: 1 actually received Dex 350 and 1 received Sham as the initial treatment.

Outcomes

All efficacy measurements in the OL period are regarded as secondary. As the CSR states: "The focus is on descriptive statistics only, and no between group statistical comparisons have been made ...".

Results for the proportion of patients with a BCVA improvement of 15 or more letters from IT baseline in the study eye and BCVA categorical change from first baseline (IT Day 0) in the study eye are shown in Table 20. A ≥ 15 letters worsening in BCVA from the

second baseline was lowest in the Dex 700/700 group at each visit, occurring in 3.7% of patients in the Dex 700/700 group compared with 7.7% in the Dex 350/700 and 8.8% in the Sham/Dex 700 groups at OL Day 180.

Table 20: BCVA categorical change from first baseline in the study eye, Re-treated population, LOCF, Study 206207-008

Categorical change from baseline BCVA	Dex 700/700 N = 162	Dex 350/700 N = 156	Sham/Dex 700 N = 159
IT Day 30			
≥ 15 letters improvement	17.9%	13.5%	7.5%
≥ 15 letters worsening	0.6%	3.2%	2.5%
IT Day 60			
≥ 15 letters improvement	28.4%	25.0%	9.4%
≥ 15 letters worsening	0.0%	0.6%	3.1%
IT Day 90			
≥ 15 letters improvement	17.9%	19.9%	9.4%
≥ 15 letters worsening	3.1%	3.2%	4.4%
IT Day 180			
≥ 15 letters improvement	14.2%	12.2%	15.7%
≥ 15 letters worsening	4.9%	9.6%	8.8%
OL Day 30			
≥ 15 letters improvement	22.8%	30.1%	21.4%
≥ 15 letters worsening	3.7%	3.8%	5.0%
OL Day 60			
≥ 15 letters improvement	29.0%	32.1%	26.4%
≥ 15 letters worsening	3.1%	4.5%	5.0%
OL Day 90			
≥ 15 letters improvement	31.5%	33.3%	26.4%
≥ 15 letters worsening	3.1%	6.4%	6.9%
OL Day 180			
≥ 15 letters improvement	25.3%	22.4%	18.9%
≥ 15 letters worsening	5.6%	12.2%	11.3%

In the re-treated population, the BCVA mean change from first baseline in the study eye is shown in Table 21 while the mean change from the second baseline after the second injection was similar across the three treatment groups (Table 22).

Table 21: BCVA mean change from first baseline in the study eye, Re-treated population, LOCF, Study 206207-008

Visit	Dex 700/700 N=162	Dex 350/700 N=156	Sham/Dex 700 N=159
Baseline	54.5	53.6	54.6
IT Day 30	7.4	7.0	2.5
IT Day 60	9.3	8.8	2.8
IT Day 90	6.7	6.1	2.4
IT Day 180	3.5	3.1	1.5
OL Day 30	7.7	8.3	5.9
OL Day 60	8.7	10.0	7.3
OL Day 90	8.4	7.4	6.8
OL Day 180	5.7	3.8	3.3

Table 22: BCVA mean change from second baseline in the study eye, Re-treated population, LOCF, Study 206207-008

Visit	Dex 700/700 N=162	Dex 350/700 N=156	Sham/Dex 700 N=159
2nd Baseline	58.0	56.4	56.2
OL Day 30	4.1	5.4	4.5
OL Day 60	5.1	7.1	5.9
OL Day 90	4.8	4.5	5.3
OL Day 180	2.1	0.9	1.7

In the re-treated population, the mean change in retinal thickness from first baseline in the study eye is shown in Table 23. The mean change from the second baseline after the second injection showed reductions greater at OL Day 90 than at OL Day 180.

Table 23: Mean change in retinal thickness (microns) from first baseline in the study eye, Re-treated population, LOCF, Study 206207-008

Visit	Dex 700/700 N=162	Dex 350/700 N=156	Sham/Dex 700 N=159
Baseline	559.3	551.7	555.1
IT Day 90	-205.3	-142.7	-71.6
IT Day 180	-99.1	-66.6	-98.9
OL Day 90	-258.5	-239.9	-271.3
OL Day 180	-160.3	-140.1	-161.2

In the single treatment population, the BCVA proportion of patients with improvement of 15 or more letters from IT baseline in the study eye is shown in Table 24, the BCVA mean change from first baseline in the study eye is shown in Table 25 and the mean change in retinal thickness from first baseline in the study eye is shown in Table 26.

Table 24: BCVA proportion of patients with improvement of 15 or more letters from IT baseline in the study eye, Single treatment population, LOCF, Study 206207-008

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%

Table 25: BCVA mean change from first baseline in the study eye, Single treatment population, LOCF, Study 206207-008

Visit	Dex 700 N=34	Dex 350 N=41	Sham N=43
Baseline	54.4	54.6	53.3
IT Day 30	8.7	7.6	3.0
IT Day 60	11.3	9.9	4.4
IT Day 90	9.8	8.4	4.6
IT Day 180	9.6	10.0	7.9
OL Day 30	8.8	9.5	8.4
OL Day 60	8.6	10.0	8.5
OL Day 90	9.3	9.8	8.4
OL Day 180	9.0	6.8	7.4

Table 26: Mean change in retinal thickness (microns) from first baseline in the study eye, Single treatment population, LOCF, Study 206207-008

Visit	Dex 700 N=34	Dex 350 N=41	Sham N=43
Baseline	505.0	508.1	456.7
IT Day 90	-179.2	-156.9	-106.8
IT Day 180	-137.2	-174.5	-143.7
OL Day 90	-136.0	-175.9	-143.7
OL Day 180	-126.5	-170.9	-145.2

Efficacy - Study 206207-009

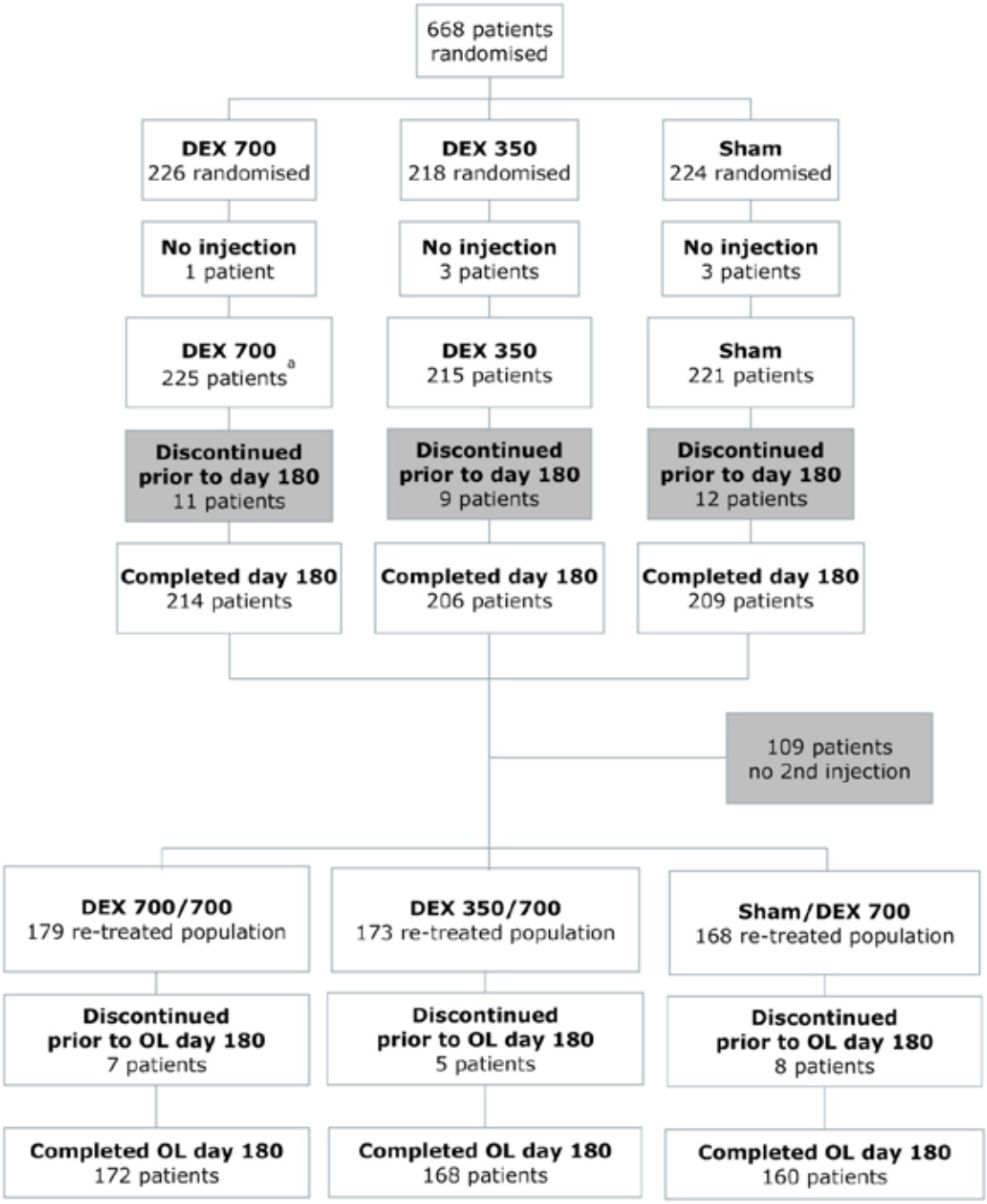
As for Study 206207-008, the first 6 month period was discussed earlier in this AusPAR and the 6 month extension is discussed here. The disposition of patients is shown in Figure 2.

Outcomes

As for Study 206207-008, all efficacy measurements in the OL period are regarded as secondary. As the CSR states: "Among-group comparisons were mainly descriptive and no between-group statistical comparisons have been made ...".

Results for proportion of patients with a BCVA improvement of 15 or more letters from IT baseline in the study eye as well as the BCVA categorical change from first baseline (IT Day 0) in the study eye in the re-treated population are shown in Table 27. The change from the second baseline showed no clear difference among treatment groups.

Figure 2: Disposition of patients, ITT population. Study 206207-009



Shaded boxes comprise the single treatment population.

[a] 1 patient underwent the injection procedure but injection of the study medication failed.

Table 27: BCVA categorical change from first baseline in the study eye, Re-treated population, LOCF, Study 206207-009

Categorical change from baseline BCVA	Dex 700/700 N = 179	Dex 350/700 N = 173	Sham/Dex 700 N = 168
IT Day 30			
≥ 15 letters improvement	22.9%	18.5%	5.4%
≥ 15 letters worsening	1.1%	0.0%	3.0%
IT Day 60			
≥ 15 letters improvement	31.3%	31.2%	10.1%
≥ 15 letters worsening	1.7%	1.7%	5.4%
IT Day 90			
≥ 15 letters improvement	18.4%	23.1%	10.7%
≥ 15 letters worsening	2.8%	2.3%	8.3%
IT Day 180			
≥ 15 letters improvement	17.9%	17.3%	11.3%
≥ 15 letters worsening	6.7%	5.2%	13.1%
OL Day 30			
≥ 15 letters improvement	30.7%	33.5%	23.2%
≥ 15 letters worsening	2.8%	1.2%	7.1%
OL Day 60			
≥ 15 letters improvement	34.1%	31.8%	25.0%
≥ 15 letters worsening	3.9%	2.9%	6.5%
OL Day 90			
≥ 15 letters improvement	27.4%	31.8%	28.0%
≥ 15 letters worsening	5.0%	5.8%	6.5%
OL Day 180			
≥ 15 letters improvement	22.3%	23.7%	23.8%
≥ 15 letters worsening	7.8%	11.0%	10.7%

In the re-treated population, the BCVA mean change from first baseline in the study eye is shown in Table 28 while the mean change from the second baseline after the second injection is shown in Table 29.

Table 28: BCVA mean change from first baseline in the study eye, Re-treated population, LOCF, Study 206207-009

Visit	Dex 700/700 N=179	Dex 350/700 N=173	Sham/Dex 700 N=168
Baseline	53.4	54.0	55.1
IT Day 30	8.8	8.1	2.2
IT Day 60	10.6	10.1	2.6
IT Day 90	7.4	7.6	2.6
IT Day 180	4.6	5.0	0.5
OL Day 30	9.6	9.9	5.8
OL Day 60	10.5	9.6	6.6
OL Day 90	8.0	8.5	6.1
OL Day 180	4.4	5.5	3.7

Table 29: BCVA mean change from second baseline in the study eye, Re-treated population, LOCF, Study 206207-009

Visit	Dex 700/700 N=179	Dex 350/700 N=173	Sham/Dex 700 N=168
Second Baseline	58.1	59.0	55.7
OL Day 30	5.0	4.8	5.2
OL Day 60	5.8	4.5	6.0
OL Day 90	3.3	3.4	5.5
OL Day 180	-0.2	0.4	3.1

In the re-treated population, the mean change in retinal thickness from first baseline in the study eye is shown in Table 30. The mean change from the second baseline after the second injection showed further reductions, greater at OL Day 90 than at OL Day 180 (Table 30).

Table 30: Mean change in retinal thickness (microns) from first baseline in the study eye, Re-treated population, LOCF, Study 206207-009

Visit	Dex 700/700 N=179	Dex 350/700 N=173	Sham/Dex 700 N=168
Baseline	579.1	576.7	548.9
IT Day 90	-208.3	-201.9	-70.0
IT Day 180	-95.6	-135.1	-104.2
OL Day 90	-267.8	-283.1	-262.2
OL Day 180	-170.4	-182.6	-179.2

In the single treatment population, the BCVA proportion of patients with improvement of 15 or more letters from IT baseline in the study eye is shown in Table 31, the BCVA mean change from first baseline in the study eye is shown in Table 32 and the mean change in retinal thickness from first baseline in the study eye is shown in Table 33.

Table 31: BCVA proportion of patients with improvement of 15 or more letters from IT baseline in the study eye, Single treatment population, LOCF, Study 206207-009

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%	45.2%	34.0%
OL Day 30	37.0%	42.9%	41.5%
OL Day 60	37.0%	42.9%	39.6%
OL Day 90	39.1%	50.0%	39.6%
OL Day 180	37.0%	50.0%	45.3%

Table 32: BCVA mean change from first baseline in the study eye, Single treatment population, LOCF, Study 206207-009

Visit	Dex 700 N=46	Dex 350 N=42	Sham N=53
Baseline	56.7	54.8	54.7
IT Day 30	8.5	9.7	4.7
IT Day 60	8.7	11.6	5.2
IT Day 90	7.9	12.7	6.3
IT Day 180	9.6	11.9	8.5
OL Day 30	9.3	12.0	9.3
OL Day 60	9.6	12.0	8.6
OL Day 90	9.5	12.6	10.2
OL Day 180	8.2	11.3	11.1

Table 33: Mean change in retinal thickness (microns) from first baseline in the study eye, Single treatment population, LOCF, Study 206207-009

Visit	Dex 700 N=46	Dex 350 N=42	Sham N=53
Baseline	549.0	532.5	526.2
IT Day 90	-227.7	-218.1	-160.0
IT Day 180	-252.8	-213.8	-209.3
OL Day 90	-245.1	-220.8	-222.3
OL Day 180	-260.6	-225.1	-215.4

Efficacy summary

The extension period efficacy data are of only preliminary status, being not subject to statistical testing. It appears that in patients selected as described above, if a second injection is given, a response in VA may again be expected – perhaps with increased persistence.

Safety - Study 206207-008

Serious Adverse Events

One death (myocardial infarction in a patient in the Dex 350/700 group) was reported in the OL period, classified as "not related" to study treatment. Serious ocular AEs classified as related to study treatment were reported as follows:

Re-treated population - Sham/Dex 700 group: 1 (IOP increased).

Single treatment population - Sham group: 1 (high grade squamous dysplasia in limbal area of cornea).

Discontinuations

The evaluator was unable to ascertain details of the 14 patients who did not receive the second injection because of "safety concerns".

Adverse Events

Table 34: AEs by SOC, OL period, Re-treated population, Study 206207-008

	Dex 700/700 N=162		Dex 350/700 N=156		Sham/Dex 700 N=159	
	n	%	n	%	n	%
Patients with one or more clinical adverse experiences	128	79.0	111	71.2	111	69.8
Blood And Lymphatic System Disorders	2	1.2	3	1.9	1	0.6
Cardiac Disorders	6	3.7	6	3.8	6	3.8
Congenital, Familial and Genetic	1	0.6	0	0.0	1	0.6
Ear And Labyrinth Disorders	1	0.6	0	0.0	0	0.0
Eye Disorders[1]						
Conjunctival haemorrhage	29	17.9	25	16.0	22	13.8
Macular oedema	9	5.6	11	7.1	14	8.8
Retinal haemorrhage	9	5.6	1	0.6	4	2.5
Maculopathy	8	4.9	7	4.5	4	2.5
Vitreous detachment	6	3.7	8	5.1	3	1.9
Eye Pain	6	3.7	5	3.2	9	5.7
Vitreous floaters	5	3.1	6	3.8	4	2.5
Ocular hypertension	5	3.1	3	1.9	8	5.0
Retinal neovascularisation	5	3.1	3	1.9	4	2.5
Retinal degeneration	5	3.1	2	1.3	3	1.9
VA reduced	4	2.5	3	1.9	7	4.4
Foreign body sensation in eyes	4	2.5	1	0.6	3	1.9
Conjunctival hyperaemia	3	1.9	4	2.6	3	1.9
Conjunctivitis	3	1.9	4	2.6	1	0.6
Optic disc vascular disorder	3	1.9	3	1.9	4	2.5
Retinal exudates	3	1.9	2	1.3	5	3.1
Lacrimation increased	3	1.9	1	0.6	0	0.0
Vitreous haemorrhage	1	0.6	4	2.6	6	3.8
Gastrointestinal Disorders	3	1.9	7	4.5	7	4.4
General Disorders And Administration Site Conditions	0	0.0	1	0.6	0	0.0
Hepatobiliary Disorders	1	0.6	2	1.3	1	0.6
Immune System Disorders	0	0.0	2	1.3	2	1.3
Infections And Infestations	13	8.0	17	10.9	13	8.2
Injury, Poisoning And Procedural Complications	7	4.3	8	5.1	7	4.4
Investigations	44	27.2	42	26.9	43	27.0
IOP Increased	43	26.5	40	25.6	40	25.2
Metabolism and Nutrition Disorders	4	2.5	1	0.6	7	4.4
Musculoskeletal and Connective Tissue Disorders	11	6.8	5	3.2	6	3.8
Back Pain	4	2.5	1	0.6	0	0.0
Neoplasms	2	1.2	0	0.0	2	1.3
Nervous System Disorders	8	4.9	10	6.4	9	5.7
Headache	3	1.9	1	0.6	3	1.9
Psychiatric Disorders	4	2.5	3	1.9	0	0.0
Renal and Urinary Disorders	2	1.2	2	1.3	0	0.0
Reproductive System And Breast	2	1.2	0	0.0	1	0.6
Respiratory, Thoracic and Mediastinal Disorders	2	1.2	2	1.3	0	0.0
Skin and Subcutaneous Tissue Disorders	3	1.9	0	0.0	2	1.3
Vascular Disorders	8	4.9	5	3.2	6	3.8
Hypertension	6	3.7	4	2.6	4	2.5

[1]Data relating to cataracts, and to the SOC *Eye Disorders*, are not shown but are presented in Table 35.

AEs reported in the re-treated population during the OL period of the study are shown in Table 34, classified by SOC and preferred term. Note that for each class, only selected preferred terms are included, but all patients reporting AEs are included in the number for SOC. Patients may have more than one AE within a class.

Cataract AEs are shown in Table 35.

Table 35: Cataracts in the study eye, Baseline status and AEs, Re-treated population, Study 206207-008

Preferred Term	DEX 700/700	DEX 350/700 N = 156	Sham/DEX 700 N =159
Baseline			
cataract	90 (55.6%)	95 (60.9%)	83 (52.2%)
cataract subcapsular	18 (11.1%)	17 (10.9%)	19 (11.9%)
cataract nuclear	6 (3.7%)	7 (4.5%)	10 (6.3%)
cataract cortical	0 (0.0%)	2 (1.3%)	0 (0.0%)
any cataract	108 (66.7%)	116 (74.4%)	104 (65.4%)
Initial Treatment Only			
cataract	4 (2.5%)	4 (2.6%)	0 (0.0%)
cataract subcapsular	5 (3.1%)	1 (0.6%)	1 (0.6%)
cataract nuclear	2 (1.2%)	1 (0.6%)	0 (0.0%)
cataract cortical	4 (2.5%)	1 (0.6%)	2 (1.3%)
any cataract	12 (7.4%)	5 (3.2%)	3 (1.9%)
IT and OL Extension			
cataract	11 (6.8%)	11 (7.1%)	1 (0.6%)
cataract subcapsular	20 (12.3%)	11 (7.1%)	2 (1.3%)
cataract nuclear	5 (3.1%)	3 (1.9%)	0 (0.0%)
cataract cortical	5 (3.1%)	3 (1.9%)	3 (1.9%)
any cataract	33 (20.4%)	23 (14.7%)	5 (3.1%)

The data for the open label extension only are not provided in this table because during evaluation, in response to a query, the sponsor replied:

As cataract formations do not resolve spontaneously, patients who experienced cataract AEs during the IT stage of the study were commonly reported again in the OL stage, unless the patient underwent cataract surgery. The "Open-Label Extension Only" section of the table therefore may contain AEs that are also reported under the "Initial Treatment Only" section.

The "IT and OL Extension" section of Table 35 summarizes cataract AEs that were reported over the entire duration of the study, regardless of stage. In this section of the table, each patient is counted only once, and therefore is not a summation of the IT and OL stages of the study.

AEs reported in the single treatment population were not separately presented in the submission for the IT and OL periods. For this population, AEs reported during the whole study are shown in Table 36, classified as described in the preceding paragraph and subject to the same caveat.

Table 36: AEs by SOC, IT+OL periods, Single treatment population, Study 206207-008

	Dex 700 N=34		Dex 350 N=41		Sham N=43	
	n	%	n	%	n	%
Patients with one or more clinical adverse experiences	26	76.5	29	70.7	25	58.1
Cardiac Disorders	1	2.9	3	7.3	1	2.3
Endocrine	0	0.0	0	0.0	1	2.3
Eye Disorders	19	55.9	20	48.8	20	46.5
Conjunctival hyperaemia	4	11.8	3	7.3	1	2.3
Conjunctival haemorrhage	3	8.8	5	12.2	7	16.3
Conjunctivitis	3	8.8	1	2.4	2	4.7
Retinal haemorrhage	3	8.8	0	0.0	1	2.3
Eye Pain	2	5.9	3	7.3	1	2.3
Maculopathy	2	5.9	0	0.0	2	4.7
VA reduced	2	5.9	0	0.0	2	4.7
Optic disc vascular disorder	2	5.9	0	0.0	0	0.0
Vitreous floaters	2	5.9	0	0.0	0	0.0
Vitreous opacities	2	5.9	0	0.0	0	0.0
Vitritis	2	5.9	0	0.0	0	0.0
Gastrointestinal Disorders	0	0.0	2	4.9	0	0.0
General Disorders And Administration Site Conditions	2	5.9	2	4.9	0	0.0
Immune System Disorders	1	2.9	0	0.0	1	2.3
Infections And Infestations	4	11.8	6	14.6	6	14.0
Injury, Poisoning And Procedural Complications	0	0.0	1	2.4	4	9.3
Investigations	12	35.3	13	31.7	2	4.7
IOP Increased	12	35.3	12	29.3	0	0.0
Metabolism and Nutrition Disorders	1	2.9	1	2.4	2	4.7
Musculoskeletal and Connective Tissue Disorders	1	2.9	1	2.4	1	2.3
Neoplasms	0	0.0	1	2.4	0	0.0
Nervous System Disorders	3	8.8	2	4.9	1	2.3
Headache	2	5.9	0	0.0	0	0.0
Psychiatric Disorders	0	0.0	0	0.0	2	4.7
Renal and Urinary Disorders	1	2.9	1	2.4	0	0.0
Reproductive System And Breast	0	0.0	1	2.4	0	0.0
Respiratory, Thoracic and Mediastinal Disorders	1	2.9	3	7.3	2	4.7
Skin and Subcutaneous Tissue Disorders	1	2.9	0	0.0	0	0.0
Vascular Disorders	2	5.9	1	2.4	1	2.3

AEs reported for the single treatment population in the OL period and classified as treatment related were as follows:

Dex 700 group: 1 vitreous haemorrhage; 2 IOP increased; 1 glaucoma; 1 worsening cataract.

Dex 350 group: 1 vitreous detachment; 1 IOP increased; 2 ocular hypertension; 1 eyelid ptosis; 1 ocular hypertension and cataract; 1 cataract.

Sham group: 1 corneal disorder (the case of squamous dysplasia mentioned above).

Biomicroscopy and ophthalmoscopy findings for the combined IT+OL periods are summarised as follows:

Re-treated population

A total of 151/162 patients in the Dex 700/700 group, 148/156 in the Dex 350/700 group, and 150/159 in the Sham/Dex 700 group had biomicroscopy / ophthalmoscopy findings with ≥ 1 grade deterioration from IT baseline in the study eye. The most common (≥ 25% in any group) were conjunctival haemorrhage, conjunctival hyperaemia and retinal haemorrhage. There were no notable differences between groups.

Single treatment population

A total of 32/34 patients in the Dex 700 group, 35/41 in the Dex 350 group, and 35/43 in the Sham group had biomicroscopy/ophthalmoscopy findings with ≥ 1 grade deterioration from IT baseline in the study eye. The most common (≥ 10% in any group) were conjunctival haemorrhage, retinal haemorrhage and conjunctival hyperaemia, for which there were no notable differences between groups. Frequencies of other findings were too small to draw any conclusions.

Summary of safety results from the whole study (IT + OL periods)

1. In the re-treated population, during the IT period, the AE profile was similar among treatment groups, apart from IOP increase and cataracts.
2. In the re-treated population, during the OL extension, the non-cataract AE profile was similar between the 3 re-treated groups. IOP increase was reported at comparable rates following the first and second injections of Dex. However, at the end of the study, the prevalence of cataract AEs was higher in patients who had received 2 doses of Dex than in those who had initially received Sham.
3. The most frequently reported AEs (incidence > 10% in any treatment group) in the re-treated population over the 12 month period were intraocular pressure increase, conjunctival haemorrhage and subcapsular cataracts.
4. IOP ≥ 25 mmHg or ≥ 35 mmHg and IOP increases ≥ 10 mmHg peaked at Day 60 and declined to near baseline levels by 6 months following the first or second injection of Dex. The majority of elevations were managed with standard IOP lowering medications; 4 re-treated patients and 2 single treatment patients required surgery. Approximately 70% of re-treated patients entered the study with a history of cataracts. Cataract AEs of any kind in the study eye over the 1 year follow up were reported for 20.4% of patients in the Dex 700/700 group and 14.7% in the Dex 350/700 group compared to 3.1% in the Sham/Dex 700 group. Surgery was required for 5 re-treated patients in the study eye and 4 in the non-study eye. In the single treatment population, surgery was required for 1 patient in the study eye and 1 in the non-study eye.
5. Based on retroillumination photography, there were no differences in the incidence of cortical opacities in the study eye among the 3 treatment groups in the re-treated population. For posterior subcapsular opacities, the prevalence at 1 year was similar with Dex 700/700 (11.4%) and Dex 350/700 (13.4%), though notably higher compared to Sham/Dex 700 (3.2%).
6. In general, findings on biomicroscopy and ophthalmoscopy were similar among the 3 treatment groups in the re-treated population. The incidence of retinal tears and retinal detachment was low.

7. In the re-treated population, the proportion of patients experiencing ≥ 3 line vision loss from baseline was consistently lower with Dex 700/700 compared to Sham/Dex 700 throughout the IT and OL extension visits.

Safety - Study 206207-009

Serious Adverse Events

One death (aspiration pneumonia in a patient in the Sham/Dex 700 group) was reported in the OL period, classified as "not related" to study treatment. Serious ocular AEs classified as related to study treatment were reported as follows:

Re-treated population: Dex 700/700 group: 2 (1 retinal detachment, 1 IOP increased).

Single treatment population: Dex 700 group: 1 (ocular hypertension).

Discontinuations

From the data provided, the evaluator was unable to ascertain details of the 22 patients who did not receive the second injection because of "safety concerns".

Adverse Events

AEs reported in the re-treated population during the OL period of the study are shown in Table 37, classified by SOC and preferred term. Note that for each class, only selected preferred terms are included, but all patients reporting AEs are included in the number for SOC. Patients may have more than one AE within a class.

Table 37: AEs by SOC, OL period, Re-treated population, Study 206207-009

	Dex 700/700 N=179		Dex 350/700 N=173		Sham/Dex 700 N=168	
	n	%	n	%	n	%
Patients with one or more clinical adverse experiences	147	82.1	147	85.0	133	79.2
Blood And Lymphatic System Disorders	3	1.7	2	1.2	1	0.6
Cardiac Disorders	4	2.2	2	1.2	7	4.2
Congenital, Familial and Genetic	2	1.1	0	0.0	0	0.0
Ear And Labyrinth Disorders	1	0.6	2	1.2	0	0.0
Endocrine Disorders	2	1.1	1	0.6	0	0.0
Eye Disorders[1]						
Conjunctival haemorrhage	37	20.7	29	16.8	36	21.4
Macular oedema	14	7.8	9	5.2	9	5.4
Retinal haemorrhage	14	7.8	11	6.4	13	7.7
Maculopathy	12	6.7	14	8.1	14	8.3
Vitreous detachment	13	7.3	13	7.5	9	5.4
Eye Pain	16	8.9	11	6.4	7	4.2
Vitreous floaters	4	2.2	6	3.5	7	4.2
Ocular hypertension	8	4.5	7	4.0	10	6.0
VA reduced	4	2.2	7	4.0	8	4.8
Conjunctival hyperaemia	12	6.7	10	5.8	12	7.1
Optic disc vascular disorder	5	2.8	6	3.5	7	4.2
Retinal exudates	6	3.4	5	2.9	14	8.3
Vitreous haemorrhage	7	3.9	5	2.9	8	4.8
Dry eye	7	3.9	4	2.3	5	3.0
Retinal pigment epitheliopathy	5	2.8	3	1.7	5	3.0
Gastrointestinal Disorders	1	0.6	1	0.6	0	0.0
General Disorders And Administration Site	5	2.8	3	1.7	4	2.4
Hepatobiliary Disorders	1	0.6	0	0.0	0	0.0
Immune System Disorders	2	1.1	4	2.3	4	2.4
Infections And Infestations	18	10.1	17	9.8	15	8.9
Injury, Poisoning And Procedural Complications	7	3.9	7	4.0	8	4.8
Investigations	52	29.1	57	32.9	53	31.5
IOP Increased	50	27.9	56	32.4	50	29.8
Metabolism and Nutrition Disorders	4	2.2	7	4.0	7	4.2
Musculoskeletal and Connective Tissue Disorders	3	1.7	10	5.8	11	6.5
Neoplasms	9	5.0	5	2.9	4	2.4
Nervous System Disorders	9	5.0	12	6.9	6	3.6
Headache	3	1.7	5	2.9	0	0.0
Psychiatric Disorders	5	2.8	1	0.6	6	3.6
Renal and Urinary Disorders	1	0.6	2	1.2	3	1.8
Reproductive System And Breast	0	0.0	3	1.7	2	1.2
Respiratory, Thoracic and Mediastinal Disorders	5	2.8	5	2.9	7	4.2
Skin and Subcutaneous Tissue Disorders	1	0.6	1	0.6	5	3.0
Vascular Disorders	11	6.1	13	7.5	14	8.3
Hypertension	10	5.6	9	5.2	13	7.7

[1]Data relating to cataracts, and to the SOC *Eye Disorders*, are not shown but are presented in Table 38.

Cataract AEs are shown in Table 38.

Table 38: Cataracts in the study eye, Baseline status and AEs, Re-treated population, Study 206207-009

Preferred Term	DEX 700/700	DEX 350/700 N = 173	Sham/DEX 700 N =168
Baseline			
cataract	110 (61.5%)	98 (56.6%)	98 (58.3%)
cataract subcapsular	5 (2.8%)	3 (1.7%)	3 (1.8%)
cataract nuclear	20 (11.2%)	20 (11.6%)	19 (11.3%)
cataract cortical	10 (5.6%)	8 (4.6%)	4 (2.4%)
any cataract	134 (74.9%)	119 (68.8%)	117 (69.6%)
Initial Treatment Only			
cataract	11 (6.1%)	5 (2.9%)	4 (2.4%)
cataract subcapsular	3 (1.7%)	2 (1.2%)	4 (2.4%)
cataract nuclear	3 (1.7%)	2 (1.2%)	4 (2.4%)
cataract cortical	2 (1.1%)	2 (1.2%)	5 (3.0%)
any cataract	18 (10.1%)	10 (5.8%)	12 (7.1%)
IT and OL Extension			
cataract	29 (16.2%)	17 (9.8%)	10 (6.0%)
cataract subcapsular	24 (13.4%)	9 (5.2%)	11 (6.5%)
cataract nuclear	6 (3.4%)	5 (2.9%)	6 (3.6%)
cataract cortical	7 (3.9%)	2 (1.2%)	8 (4.8%)
any cataract	57 (31.8%)	33 (19.1%)	26 (15.5%)

For the reason given above, data for the open label extension only are not shown in this table.

AEs reported in the single treatment population during the whole study are shown in Table 39. AEs reported for the single treatment population in the OL period and classified as treatment related were as follows:

Dex 700 group: 4 IOP increased; 2 ocular hypertension; 1 cataract subcapsular; 1 lenticular opacities.

Dex 350 group: 2 cataract subcapsular; 2 ocular hypertension; 1 visual disturbance.

Sham group: 1 cataract subcapsular and cataract cortical and cataract nuclear; 1 cataract cortical; 1 cataract.

Biomicroscopy and ophthalmoscopy findings for the combined IT+OL periods are summarised as follows:

Re-treated population

A total of 170/179 patients in the Dex 700/700 group, 164/173 in the Dex 350/700 group, and 157/168 in the Sham/Dex 700 group had biomicroscopy/ophthalmoscopy findings with ≥ 1 grade deterioration from IT baseline in the study eye. The most common (≥ 20% in any group) were conjunctival haemorrhage, retinal haemorrhage, conjunctival hyperaemia and conjunctival oedema. There were no notable differences between groups.

Single treatment population

A total of 39/46 patients in the Dex 700 group, 39/42 in the Dex 350 group, and 37/53 in the Sham group had biomicroscopy/ophthalmoscopy findings with ≥ 1 grade deterioration from IT baseline in the study eye. The most common (≥ 10% in any group) were

conjunctival haemorrhage, retinal haemorrhage, conjunctival hyperaemia and conjunctival oedema. Only conjunctival haemorrhage was notably different among groups, with 29/46, 19/42 and 12/53 in the 3 groups, respectively.

Table 39: AEs by SOC, IT+OL periods, Single treatment population, Study 206207-009

	Dex 700 N=46		Dex 350 N=42		Sham N=53	
	n	%	n	%	n	%
Patients with one or more clinical adverse experiences	39	84.8	34	81.0	30	56.6
Blood And Lymphatic System Disorders	1	2.2	0	0.0	0	0.0
Cardiac Disorders	2	4.3	1	2.4	0	0.0
Ear And Labyrinth Disorders	0	0.0	0	0.0	1	1.9
Endocrine	1	2.2	0	0.0	0	0.0
Eye Disorders	25	54.3	22	52.4	28	52.8
Conjunctival hyperaemia	4	8.7	2	4.8	1	1.9
Conjunctival haemorrhage	8	17.4	6	14.3	4	7.5
Eye Pain	4	8.7	3	7.1	1	1.9
Ocular hypertension	4	8.7	3	7.1	0	0.0
Retinal vein occlusion	4	8.7	2	4.8	0	0.0
Maculopathy	2	4.3	3	7.1	3	5.7
Vitreous floaters	2	4.3	1	2.4	2	3.8
VA reduced	1	2.2	0	0.0	0	0.0
Gastrointestinal Disorders	4	8.7	1	2.4	1	1.9
General Disorders And Administration Site Conditions	2	4.3	1	2.4	0	0.0
Immune System Disorders	1	2.2	0	0.0	2	3.8
Infections And Infestations	6	13.0	6	14.3	6	11.3
Injury, Poisoning And Procedural Complications	2	4.3	2	4.8	4	7.5
Investigations	17	37.0	10	23.8	2	3.8
IOP Increased	16	34.8	10	23.8	2	3.8
Metabolism and Nutrition Disorders	1	2.2	3	7.1	2	3.8
Musculoskeletal and Connective Tissue Disorders	5	10.9	1	2.4	0	0.0
Neoplasms	0	0.0	1	2.4	1	1.9
Nervous System Disorders	3	6.5	3	7.1	5	9.4
Psychiatric Disorders	0	0.0	2	4.8	3	5.7
Renal and Urinary Disorders	1	2.2	0	0.0	1	1.9
Respiratory, Thoracic and Mediastinal Disorders	4	8.7	0	0.0	2	3.8
Skin and Subcutaneous Tissue Disorders	2	4.3	1	2.4	1	1.9
Vascular Disorders	6	13.0	4	9.5	4	7.5

Summary of safety results from the whole study (IT + OL periods)

The results were the same as for Study 206207-008, except for the following:

1. The most frequently reported AEs (incidence > 10% in any treatment group) in the re-treated population over the 12 month period were intraocular pressure increase, conjunctival haemorrhage, cataracts, subcapsular cataracts, conjunctival hyperaemia and eye pain.
2. IOP ≥ 25 mmHg or ≥ 35 mmHg, and IOP increases ≥ 10 mmHg peaked at Day 60 and declined to near baseline levels by 6 months following the first or second injection of

Dex. The majority of elevations were managed with standard IOP lowering medications; 3 re-treated patients and 4 single treatment patients required surgery in the study eye. Approximately 70% of re-treated patients entered the study with a history of cataracts. Cataract AEs of any kind in the study eye over the 1 year follow up were reported for 31.8% of patients in the Dex 700/700 group and 19.1% in the Dex 350/700 group compared to 15.5% in the Sham/Dex 700 group. Surgery was required for 3 re-treated patients in the study eye and 1 in the non-study eye. In the single treatment population, surgery was required for 2 patients in the study eye.

3. Based on retroillumination photography, there were no differences in the incidence of cortical opacities in the study eye among the 3 treatment groups in the re-treated population. For posterior subcapsular opacities, the prevalence at 1 year was similar with Dex 700/700 (13.1%) and Dex 350/700 (14.9%), though notably higher compared to Sham/Dex 700 (3.8%).

Safety summary

The new data extend the follow up period from first injection of the product to 12 months, and also provide some experience with multiple dosing. Pooled exposure in the 2 pivotal studies is shown in Table 40.

Table 40: Pooled exposure in the two pivotal trials

Description of population group	Nature of exposure	Dosage	Duration of follow-up (months)	Number
Re-treated population, excluding those who started with sham treatment	6 monthly treatment	Dex 700/700	12	341
		Dex 350/700	12	329
		Any	12	670
Single treatment population, excluding patients who started with sham treatment	single dose	Dex 700	12	80
		Dex 350	12	83
		Any	12	163
Patients in re-treated population who started with sham treatment	single dose	Dex 700	6	327

For the two pivotal studies, pooled ocular AEs in the study eye reported by > 2% of patients in any treatment group, for the whole period of the studies (12 months) are shown in Tables 41 and 42 for the re-treated and single treatment populations, respectively.

No new AEs were identified in the OL extensions. In particular, no case of endophthalmitis was reported and there was no evidence of systemic toxicity.

It appears that the incidence of cataract was higher after the second injection than after the first.

IOP elevation was reported at comparable rates following first and second treatments. Pressures tended to peak at Day 60, then decline to near baseline at 6 months.

Table 41: Ocular AEs in the study eye, reported by > 2% of patients in any treatment group, IT+OL periods, Re-treated population, Pooled studies 206207-008 and 206207-009

System Organ Class Preferred Term	Initial Treatment plus Open-label Extension Dex 700/700 N = 341	 Dex 350/700 N = 329	 Sham/Dex 700 N = 327
Overall	265 (77.7%)	261 (79.3%)	235 (71.9%)
Investigations (study eye)			
intraocular pressure increased	109 (32.0%)	119 (36.2%)	88 (26.9%)
Eye Disorders (study eye)			
conjunctival haemorrhage	84 (24.6%)	73 (22.2%)	73 (22.3%)
cataract subcapsular	44 (12.9%)	20 (6.1%)	11 (3.4%)
cataract	39 (11.4%)	26 (7.9%)	9 (2.8%)
eye pain	33 (9.7%)	24 (7.3%)	25 (7.6%)
conjunctival hyperaemia	29 (8.5%)	30 (9.1%)	26 (8.0%)
macular oedema	24 (7.0%)	21 (6.4%)	25 (7.6%)
retinal haemorrhage	19 (5.6%)	14 (4.3%)	18 (5.5%)
ocular hypertension	18 (5.3%)	16 (4.9%)	16 (4.9%)
maculopathy	18 (5.3%)	22 (6.7%)	20 (6.1%)
vitreous detachment	18 (5.3%)	17 (5.2%)	10 (3.1%)
vitreous floaters	15 (4.4%)	12 (3.6%)	13 (4.0%)
retinal exudates	14 (4.1%)	8 (2.4%)	20 (6.1%)
vitreous haemorrhage	12 (3.5%)	13 (4.0%)	16 (4.9%)
foreign body sensation in eyes	12 (3.5%)	11 (3.3%)	13 (4.0%)
conjunctival oedema	11 (3.2%)	17 (5.2%)	15 (4.6%)
cataract cortical	10 (2.9%)	5 (1.5%)	9 (2.8%)
cataract nuclear	10 (2.9%)	8 (2.4%)	5 (1.5%)
visual acuity reduced	9 (2.6%)	12 (3.6%)	17 (5.2%)
optic disc vascular disorder	9 (2.6%)	9 (2.7%)	11 (3.4%)
dry eye	8 (2.3%)	5 (1.5%)	11 (3.4%)
vision blurred	8 (2.3%)	3 (0.9%)	6 (1.8%)
eye irritation	7 (2.1%)	4 (1.2%)	8 (2.4%)
photopsia	7 (2.1%)	8 (2.4%)	2 (0.6%)
conjunctivitis	7 (2.1%)	4 (1.2%)	4 (1.2%)
eye pruritus	6 (1.8%)	9 (2.7%)	3 (0.9%)
anterior chamber cell	6 (1.8%)	7 (2.1%)	2 (0.6%)
blepharitis	5 (1.5%)	8 (2.4%)	12 (3.7%)
retinal neovascularisation	5 (1.5%)	5 (1.5%)	8 (2.4%)
retinal pigment epitheliopathy	5 (1.5%)	2 (0.6%)	8 (2.4%)
ocular discomfort	4(1.2%)	8 (2.4%)	7 (2.1%)
retinal vascular disorder	4(1.2%)	5 (1.5%)	8 (2.4%)

Table 42: Ocular AEs in the study eye, reported by > 2% of patients in any treatment group, IT+OL periods, Single treatment population, Pooled studies 206207-008 and 206207-009

System Organ Class Preferred Term	Cumulative 1-Year Dex 700 N = 80	 Dex 350 N = 83	 Sham N = 96
Overall	57 (71.3	51 (61.4	46 (47.9
Investigations (study eye)			
intraocular pressure increased	28 (35.0	22 (26.5	2 (2.1%
Eye Disorders (study eye)			
conjunctival haemorrhage	11 (13.8	11 (13.3	11 (11.5
conjunctival hyperaemia	8 (10.0	5 (6.0%	2 (2.1%
eye pain	6 (7.5%	5 (6.0%	2 (2.1%
ocular hypertension	5 (6.3%	7 (8.4%	0 (0.0%
maculopathy	4 (5.0%	3 (3.6%	4 (4.2%
conjunctivitis	4 (5.0%	1 (1.2%	2 (2.1%
vitreous floaters	4 (5.0%	1 (1.2%	2 (2.1%
retinal haemorrhage	4 (5.0%	0 (0.0%	2 (2.1%
lacrimation increased	3 (3.8%	1 (1.2%	0 (0.0%
visual acuity reduced	3 (3.8%	0 (0.0%	2 (2.1%
cataract subcapsular	2 (2.5%	3 (3.6%	1 (1.0%
retinal vein occlusion	2 (2.5%	2 (2.4%	0 (0.0%
visual disturbance	2 (2.5%	1 (1.2%	2 (2.1%
eye pruritus	2 (2.5%	1 (1.2%	1 (1.0%
macular oedema	2 (2.5%	1 (1.2%	1 (1.0%
vitreous opacities	2 (2.5%	1 (1.2%	1 (1.0%
optic disc vascular disorder	2 (2.5%	1 (1.2%	0 (0.0%
corneal oedema	2 (2.5%	0 (0.0%	0 (0.0%
photophobia	2 (2.5%	0 (0.0%	0 (0.0%
vitritis	2 (2.5%	0 (0.0%	0 (0.0%
retinal neovascularisation	1 (1.3%	3 (3.6%	7 (7.3%
vitreous haemorrhage	1 (1.3%	3 (3.6%	3 (3.1%
iris neovascularisation	1 (1.3%	2 (2.4%	5 (5.2%
cataract	1 (1.3%	2 (2.4%	3 (3.1%
glaucoma	1 (1.3%	2 (2.4%	1 (1.0%
anterior chamber cell	1 (1.3%	2 (2.4%	0 (0.0%
conjunctival oedema	1 (1.3%	2 (2.4%	0 (0.0%
cataract cortical	1 (1.3%	1 (1.2%	2 (2.1%
photopsia	1 (1.3%	1 (1.2%	2 (2.1%
retinal vascular disorder	1 (1.3%	1 (1.2%	2 (2.1%
foreign body sensation in eyes	1 (1.3%	0 (0.0%	2 (2.1%
vitreous detachment	0 (0.0%	4 (4.8%	3 (3.1%
blepharitis	0 (0.0%	3 (3.6%	1 (1.0%
retinal degeneration	0 (0.0%	2 (2.4%	1 (1.0%
retinal exudates	0 (0.0%	1 (1.2%	2 (2.1%
macular hole	0 (0.0%	0 (0.0%	3 (3.1%
macular cyst	0 (0.0%	0 (0.0%	2 (2.1%

Concerning other ocular toxicity, the numbers of patients with ≥ 1 grade increase from IT baseline, study eye are shown in Table 43.

Table 43: Retinal detachment and tears in pooled studies

Re-treated population			Single treatment population		
Dex 700/700	**Dex 350/700**	**Sham/Dex 700**	**Dex 700**	**Dex 350**	**Sham**
Retinal detachment					
2/341	2/329	2/327	0/80	1/83	0/96
Retinal tears					
4/341	4/329	4/327	0/80	1/83	0/96

Final Clinical Summary and Conclusions

In the opinion of the evaluator, deficiencies in the available data were as follows:

- Dosage has not been adequately justified.
- There are no efficacy and safety data comparing the product with treatments using other modes of corticosteroid administration.
- The pivotal studies did not demonstrate significant efficacy, as judged from the pre-specified primary efficacy analysis.
- It is envisaged that treatment will be repeated an indefinite number of times but maximum reported experience of treatment is twice.

Accordingly, the evaluator recommended against registration on the basis of the available data.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator noted that dexamethasone is formulated into numerous single active and fixed combination medicinal products including ophthalmic drops, ear drops, dental pastes, injection solutions and an aerosol inhaler. Ozurdex is a solid implant that comprises dexamethasone and the balance is a polymer matrix, a mixture of two different poly (D,L-lactide-co-glycolide) polymers. The active is liberated from this dose form by hydrolysis of the polymer matrix within the eye.

No bioavailability data were provided and plasma concentrations are consistent with low systemic exposure.

The evaluator was satisfied with chemistry, quality control and device aspects.

Nonclinical

The data package was limited: no safety pharmacology, reproductive toxicity, genotoxicity or carcinogenicity studies were submitted. The evaluator considered this to be acceptable for a drug with a long history of clinical use and given the low expected systemic exposure. Drug distribution after insertion of the implants was throughout the eye, relatively higher in the vitreous and retina.

Studies in rabbits and cynomolgus monkeys suggested that intraocular insertion and the presence of the foreign body accounted for some of the toxicities. No clear effects on intraocular pressure were seen but "opacities in the central area of the posterior cortex of the lens" were consistent with a risk in humans of cataracts.

The Delegate noted that both the implants used and the method of insertion were different from the proposed Ozurdex. He also noted that the study in rabbits supported inhibition of VEGF induced changes but the exposure levels were considered to be fivefold above clinical levels and indeed neither study included extensive dose finding. Exposure (based on AUC) to dexamethasone following a single ocular implantation in rabbits (350 or 700 µg/eye) was approximately dose proportional. In addition, systemic toxicity was seen in the rabbit studies.

Clinical

There was an initial evaluation report that was followed by a supplementary evaluation consequent upon the submission of supplementary data. The Delegate noted that the dose form and the delivery system of the product materially changed during drug development.

Initial Clinical evaluation

Pharmacokinetic data

The pivotal Study 206207-008 contributed pharmacokinetic data on the "for marketing" dose form from six patients who had received the 700 µg implant and 4 who had received the 350 µg implant. Of the former, two individuals had a single sample that was above the limit of quantification at Day 60; one at Day 7 and another at both Days 7 and 60. Of the latter, two individuals had one plasma sample above the limit of quantification at Days 7 and 30.

The pivotal Study 206207-009 contributed pharmacokinetic data on the "for marketing" dose form from seven patients who had received the 700 µg implant and 4 who had received the 350 µg implant. Of the former, three individuals had a single sample that was above the limit of quantification at Day 60 and one at Day 7. Of the latter, none had one plasma sample above the limit of quantification at Days 7 and 30.

The evaluator concluded that conventional pharmacokinetic data could not be obtained from the eye but this did not mitigate the need for adequate data.

Dose finding

Study DC103-06 used the tablet formulation and it was largely conducted in a different indication: "PME, defined as clinically observable ME associated with diabetic retinopathy, uveitis, retinal vein occlusion, or Irving-Gass syndrome, persisting ≥ 90 days after laser treatment or medical management by a physician." A minority of the patients had CRVO or BRVO. The study was of a prospective, randomised, controlled, examiner masked, dose ranging, parallel group design (dexamethasone 305 or 750 µg or observation only). Efficacy was monitored to Day 90 and safety at Day 180 also. There was a significant result for sham treatment and a dose related treatment effect for the two doses shown. The evaluator concluded that: "a dose response relationship was demonstrated. The

proportion of patients responding was not great, but to a considerable extent the admission criteria covered cases that could be regarded as refractory…" but noted that the products used were different from those proposed for registration.

The Delegate noted that there was little basis from this study to launch into Phase III studies with a new formulation and only two set doses for two of the indications that were studied.

Efficacy and safety

There were two similar pivotal studies (206207-008 and 206207-009) that had a double blind phase that lasted for six months and that used the proposed dose form and device. The initial evaluation was based on the six month blinded period of each of these two studies. The primary outcome variable was to be the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. The primary efficacy analyses included: "the comparisons between the 700 µg DEX PS DDS Applicator System ... and Sham DEX PS DDS Applicator System ... groups and between the 350 DEX PS DDS Applicator System ... and Sham groups on the primary efficacy variable at initial treatment day 180. The ITT population will be used for the analysis." That is, it seemed that the higher dose was to be tested first against sham.

Study 206207-008

At Day 180, the proportion of subjects showing the BCVA improvement of 15 or more letters from baseline in the study eye was similar [but treatment effects are seen at earlier time points. For time points prior to Day 180, it is arguable that no definite dose dependency was seen.]

The evaluator reported that: "the null hypothesis stipulated in the Protocol (no difference in proportion of patients with BCVA improvement of ≥ 15 letters compared to baseline, between the 700 µg and Sham groups) was not rejected at the p=0.05 level. However, on the basis of other measures, efficacy was demonstrated." That is, the study was a failed study that showed suggestions of a treatment effect on secondary endpoints, not always dose-dependently.

Few discontinuations occurred due to lack of efficacy.

Study 206207-009

At Day 180, the proportion of subjects showing the BCVA improvement of 15 or more letters from baseline in the study eye was similar, with a small treatment effect seen for both doses of dexamethasone [but somewhat more notable, non-dose dependent treatment effects are seen at earlier time points].

The evaluator reached similar efficacy conclusions as for Study 008 above.

Again, few discontinuations occurred due to lack of efficacy.

Evaluator's Conclusions Regarding Efficacy

Each pivotal study failed to show statistical benefit in terms of the primary endpoint.

Signs of efficacy were seen at earlier time points (Table 9) and despite a failed primary endpoint, statistical significance was claimed by the sponsor. The evaluator concluded that: "A degree of efficacy was demonstrated, based on a variety of measures other than the primary efficacy variable. However, the level of response was only moderate (admittedly, in a population which could be described as refractory cases), and by 90 days post-treatment, it had started to diminish."

With respect to adverse effects, the pivotal studies showed a dose dependent trend to posterior subcapsular opacities by Day 180. It was notable that raised intraocular pressure was very common in the active treatment groups; intraocular hypertension was common whereas these adverse reactions (not events) were almost not a feature of the sham treated groups.

The evaluator considered that a two year period was needed to assess the potential for the formation of cataracts.

No study suggested systemic toxicity.

The evaluator was concerned that dose ranging was inadequate. A higher dose might have been more effective. Rejection was recommended. The evaluator noted that:

"In particular, further information is required on

- Justification of dosage; and
- Comparison with other modes of ocular corticosteroid treatments, in terms of safety and efficacy."

Supplementary Clinical Evaluation

The submission was based on a response by the sponsor to the initial clinical evaluation report and open label extensions of the pivotal studies 008 and 009. In regard to the extension to the pivotal studies, there were observations taken at various time points to Day 180 of the open label extension.

The evaluator was cautious concerning valid conclusions regarding efficacy in these two extension studies but suggested that a second injection was likely to be as effective as the first, perhaps with greater persistence of effect.

Adverse effects in study 008 were as previously noted: "The most frequently reported AEs (incidence > 10% in any treatment group) in the re-treated population over the 12 month period were intraocular pressure increase, conjunctival haemorrhage and subcapsular cataracts...". Concerning cataracts, the evaluator noted that: "… at the end of the study, the prevalence of cataract AEs was higher in patients who had received 2 doses of Dex than in those who had initially received Sham." Intraocular pressure rose after each active injection and may have peaked around Day 60. Cataracts had a higher incidence after the second than after the first injection.

There is a suggestion that retinal tears and retinal detachments are procedure related. Unresolved matters include the potential for late endophthalmitis.

The evaluator was still of the view that exposure was not adequate to identify other than common adverse events with confidence. In his opinion, the two pivotal studies cannot be used to justify the routine retreatment approach outlined by the sponsor.

The evaluator's views were not changed by the submission of the extension studies:

"Deficiencies in the available data are as follows:

- Dosage has not been adequately justified.
- There are no efficacy and safety data comparing the product with treatments using other modes of corticosteroid administration.
- The pivotal studies did not demonstrate significant efficacy, as judged from the pre-specified primary efficacy analysis.

- It is envisaged that treatment will be repeated an indefinite number of times, but maximum reported experience of treatment is twice. "

Accordingly, the evaluator recommended against registration on the basis of the data now available.

Sponsor's Response to Supplementary Evaluation Report

The Delegate noted that a wider indication, macular oedema, is mentioned and that the goal of the developmental program is claimed to have been the early and maximal reduction of macular oedema and to prevent damage to the retinal structure. All of this has to be compared with the primary endpoint of the pivotal studies and the fact that triamcinolone (which was not used as an active comparator but which has a very large usage via the Special Access Scheme) was not used in the clinical trial program. It was pointed out that improvement in the sham treated group caused loss of statistically significant efficacy at the 180 Day time point. This may be so but the difference in proportions is small. Suggestions of consequences of delay of treatment have not been tested.

The main problem with the response was the lack of direct evidence from purposefully designed studies.

The sponsor provided a discussion of available alternative treatments for retinal vein occlusion including laser therapy, VEGF inhibitors and triamcinolone and offered some practical comments about the advantages and disadvantages of each. Unfortunately, neither direct comparisons nor specific add-on studies are available although some studies such as the ranibizumab studies did allow laser therapy as a rescue treatment.

Risk Management Plan

There was no requirement for a Risk Management Plan at the time of submission.

Risk-Benefit Analysis

Delegate Considerations

The Delegate was of the opinion that the evaluator was in some ways generous. There is only a suggestion of efficacy on secondary endpoints yet dose dependent adverse effects have been shown. A shorter dosing interval is also suggested but has not been tested.

It might simply be that dexamethasone is not particularly effective in this indication. However, this is not certain.

It is certain that trying a higher dose of dexamethasone will risk even more dose dependent corticosteroid related local toxic effects.

Ranibizumab is now the correct active comparator in any new study. It might also be worthwhile exploring additive effects of dexamethasone added to ranibizumab.

After submission, the trade name was changed from Posurdex to Ozurdex but there may still be concerns, for example, by means of potential confusion with Cosudex, Otodex, Sofradex, Tomudex and Zoladex. It would seem that there are numerous trisyllabic trade marks ending in "dex". If anything, the change from Posurdex to Ozurdex makes matters worse.

No offer has been made to undertake further studies however, the existence of other studies in other indications is declared in an investigator's brochure:

The data package suggests that dexamethasone implants offer some transient benefits over a period of less than 180 days, at both doses studied. The longer term benefit

mentioned in the response has not been shown and predictable corticosteroid related local toxicities have been elicited. The studies are thus adequate to explore short term effects at only two doses.

The two submitted studies are inadequate with respect to dose finding and that they rely on *post hoc* efficacy analysis to claim benefit whilst dismissing the failure of the primary research question. The critical issue is the validity of the claims made in the sponsor's response document that an earlier response will lead to better visual outcomes. The Delegate was unsure that this can be established in the context of this application. Perhaps a regulatory package for one of the alternatives that were mentioned might be able to address this. Even a study against "no treatment" can include rescue therapy.

The proposed indication has been changed to:

Ozurdex is indicated for the treatment of macular oedema due to retinal vein occlusion (RVO).

The Delegate asked the following questions asked of the Advisory Committee on Prescription Medicines (ACPM):

If registration proceeds, is the trade name that incorporates the trademark Ozurdex sufficiently distinctive? If the sponsor will not agree to change this trademark, is no trademark a reasonable choice?

In the response to the clinical evaluator's reports the sponsor raises the issue of alternative therapies. To what extent are these relevant to mitigating the deficiencies in this data package?

If registration proceeds, are any ongoing studies warranted in RVO patients? Should the sponsor be asked to conduct more combination studies in various indications including RVO?

Is it reasonable to assign plausibility to the claim made in the sponsor's response document that an earlier response will lead to better visual outcomes?

The Delegate proposed to reject the application. The sponsor was encouraged to submit for evaluation longer term safety data and to conduct a dose finding study including a reference therapy arm.

Response from Sponsor

The sponsor disagreed with the recommendation of the Delegate to reject the application. It requested that the Delegate and ACPM give due consideration to the significant burden of retinal vein occlusion (RVO) disease and that there are currently no registered pharmacologic therapies. It was also pertinent to consider that the unmet medical need is greater in patients with central retinal vein occlusion (CRVO) as laser treatment is at best a palliative therapy. Clinically relevant treatment benefits have been observed with Ozurdex, along with the therapeutic advantage of a relatively long duration of effect that can reduce the burden of treatment. The safety profile of Ozurdex is acceptable, being consistent with ophthalmic steroid therapy, with an overall favourable benefit risk profile.

The sponsor made the following responses with respect to the efficacy of Ozurdex, justification of dose, and clinical benefit.

Efficacy

The clinical evaluator and Delegate stated that the two pivotal studies failed. This is incorrect. The pivotal Phase III study 206207-008 met a prospectively defined primary endpoint which was the proportion of patients with 15 or more letters improvement in

best-corrected visual acuity (BCVA) from baseline at Day 90. The response rate was 22.4% with Ozurdex compared to 12.4% with Sham (p = 0.008).

The Delegate has questioned whether this analysis was *post hoc*. The sponsor attested that the analyses for the primary efficacy endpoint for study 008, as well as for the integrated summary of efficacy, were prespecified in the statistical analysis plans prior to database lock.

The companion study 206207-009 was supportive, but did not meet its primary endpoint which was assessed at Day 180. The response rate was 23.5% with Ozurdex compared to 17.0% with Sham (p = 0.087). At Day 90 however, responses were comparable to study 008 and statistically significant: 21.2% with Ozurdex and 13.8% with Sham (p = 0.039). The sponsor agreed that the results from this analysis for study 009 can be viewed as *post hoc* and therefore can only be considered as supportive evidence, even though the p-value was < 0.05. However, together the consistency of the two studies confirms the clinical relevance and persistence of efficacy with Ozurdex up to 90 days. No other currently approved intravitreal injection reaches this duration of effect from a single injection.

Although a 15 letter improvement in visual acuity at 180 days was the original development goal, it should not be regarded as the only definitive time point for a single dose of a product intended to treat macular oedema resulting from retinal vein occlusion. Rather 180 days was considered the maximum duration of effect estimated from studies used to predict human ocular pharmacokinetics and the design limitations of an ocular implant of this type. The Phase III studies demonstrated that treatment with Ozurdex attains a clinically meaningful and statistically significant 15 letter improvement in visual acuity at 90 days (21.8%) with a similar response rate at Day 180 (21.5%). In addition, there was a statistically significant 14 letter improvement at 180 days. Vision gains of 14 letters are clinically similar to a 3 line improvement and represent a true visual acuity benefit in the clinical setting.

The Delegate stated that there is only a suggestion of efficacy from secondary endpoints and also postulated that "it might simply be dexamethasone may not be particularly effective in this indication". The sponsor disagreed with these statements. Robust efficacy was demonstrated in the Phase III studies of more than 1200 patients over a broad range of efficacy variables as previously described in the sponsor's *Posurdex Summary*. The beneficial effects of Ozurdex compared to Sham were clearly shown not only in terms of vision improvement but also in the prevention of vision loss. At each visit through Day 180, statistically significantly lower percentages of patients in the Ozurdex group than Sham experienced ≥ 15 letters worsening, representing up to a threefold reduction. Taken together, the various analyses provide compelling corroborative evidence for the efficacy of Ozurdex in the treatment of macular oedema due to retinal vein occlusion.

The Delegate stated that it is uncertain whether the benefit of early treatment can be established. The sponsor disagreed. The benefit of early treatment with Ozurdex was confirmed in the 12 month data from studies 008 and 009. There was a greater proportion of responders in those patients who received Ozurdex immediately compared to those patients who were initially on Sham and thereby had treatment delayed by 6 months. Although patients initially receiving Sham who received Ozurdex in the second 6 months showed an increased response, their rates never reached the improvements found in patients who received 2 injections of Ozurdex. Similarly, a significantly higher proportion of patients who initially received Sham showed ≥ 15 letter worsening compared to patients who were immediately treated with Ozurdex.

The earlier treatment response observed with Ozurdex compared to Sham is clinically important to both the patient and the treating physician. Long standing macular oedema

results in progressive retinal changes (for example, photoreceptor loss, retinal pigment epithelial atrophy) and loss of retinal function (BVOSG, 1984; Machemer 1968, Report BIO-08-709).[13,14] Prevention of these pathological changes, with accompanying permanent vision loss are as clinically meaningful as the actual visual acuity at Day 90 or 180.

In addition, a small proportion of Sham patients (approximately 8%) spontaneously improved without therapeutic intervention, reflecting the natural history of the disease. Patients who may spontaneously respond cannot, however, be prospectively identified, and deferring treatment can impact vision improvement. While patients initially receiving Sham can show a positive response following delayed treatment with Ozurdex, the degree of improvement in visual acuity never achieves the same level as in patients initially treated with Ozurdex. There is growing recognition among physicians that rather than continuing observation, as recommended by earlier trials, it is critical to treat patients as early as possible, in order to prevent irreversible photoreceptor damage to the retina and avert vision loss.

Justification of dosage

The clinical development program for Ozurdex evaluated the DEX PS DDS Applicator System containing 350 µg or 700 µg dexamethasone. The sponsor noted the clinical evaluator was concerned that the dose ranging was inadequate and that a higher dose might have been more effective.

In the Allergan Phase II study DC103-06, the 700 µg dose demonstrated consistently greater efficacy than 350 µg, with a longer duration of effect. As the safety profile was similar between the 2 doses, the benefit risk ratio is optimal for 700 µg. These findings were confirmed in the Phase III studies of patients with macular oedema due to retinal vein occlusion.

Demonstrated risks of ophthalmic corticosteroids include increased intraocular pressure (IOP), glaucoma with possible damage to the optic nerve, defects in visual acuity and posterior subcapsular cataract formation. Such effects are more likely if the steroids are administered in greater frequency, at higher doses, or for a longer period of time. Therefore treatment with the minimal effective dose is desirable. In fact, with respect to dexamethasone, the Delegate noted that trying a higher dose will risk even more dose dependent corticosteroid related local toxicities.

As such, Ozurdex with 700 µg dexamethasone provided clinically relevant treatment benefits as measured by 15 letter improvement in BCVA and prevention of 15 letter loss, with an acceptable safety profile consistent with ophthalmic steroid therapy.

Clinical Benefit

Despite the burden of the disease, there are currently no licensed pharmacologic therapies and no agreed standard of care for macular oedema caused by branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Clinicians need therapies for retinal vein occlusion with meaningful efficacy, low treatment burden and an acceptably low rate of adverse events, that is, a “safer” steroid. Traditionally the mainstay of treatment has been either laser photocoagulation (only demonstrated for BRVO, apart from palliative therapy in CRVO to ameliorate severe rubeotic glaucoma), or off label intravitreal triamcinolone acetonide; vascular endothelial growth factor (VEGF) inhibitors are increasingly being used off label for macular oedema. Off label triamcinolone has a major adverse event burden of both glaucoma or ocular hypertension and the relatively rapid development and progression of posterior subscapular cataracts requiring surgery.

[13] Branch Vein Occlusion Study Group. Am J Ophthalmol 1984; 98: 271-282.
[14] Machemer R. Am J Ophthalmol 1968; 66: 396-410.

Ranibizumab (Lucentis) or bevacizumab (Avastin) show good visual outcomes but are associated with a major treatment burden as they require between 6 and 12 injections in the first year (typically around 9), with intensive monitoring and frequent follow up to achieve these outcomes.

Ozurdex is a corticosteroid with dual anti-angiogenic and antiinflammatory actions that by design, has a longer duration of effect and a less frequent injection regimen than other treatment options. Ozurdex offers a new therapeutic option in the treatment of macular oedema. The unique drug delivery applicator system was designed to overcome ocular delivery barriers and prolong duration of the dexamethasone effect in the eye. Dexamethasone is 5 times more potent than triamcinolone. Ozurdex has demonstrated a release profile that, while maximal at 60 days, is sustained up to 180 days. This release profile translates to improved tolerability.

In patients with BRVO, improvements in visual acuity with laser (standard care) or triamcinolone are similar to those with Ozurdex. More importantly however, Ozurdex demonstrates a greater protective effect on vision. In addition, there is a fast response to Ozurdex in contrast to laser therapy which has a slow response time and is generally delayed for 3 months after diagnosis to allow spontaneous resolution and clearing of intra-retinal haemorrhage.

There is currently no available therapy for CRVO until severe complications occur. At that point, treatment with extensive laser is purely palliative. There is no effect on vision which, in the majority of cases, becomes markedly reduced. More effective treatments are needed that provide rapid and substantial restoration of vision from the earliest possible time following the occlusive episode. Ozurdex provides a benefit to this subgroup of patients as demonstrated by the clinically and statistically significant improvements in BCVA. Response rates were consistently higher with Ozurdex than with Sham from Day 30 to the end of the initial treatment period. In addition, the proportion of patients experiencing ≥ 15 letter loss was consistently lower with Ozurdex compared to Sham. Overall, the benefit:risk profile of Ozurdex is positive. Clinically relevant treatment benefits have been observed as measured by 15 letter improvement in BCVA and importantly, the prevention of 15 letter vision loss, which is typically permanent. The safety profile is acceptable, being consistent with ophthalmic steroid therapy but substantially better than triamcinolone. Triamcinolone is not approved for the treatment of BRVO and CRVO. Ozurdex however is recommended as a treatment option for both per the Royal College of Ophthalmologists Interim Guidelines for Management of Retinal Vein Occlusion (December 2010).[15] In addition, the National Institute of Clinical Excellence (NICE) draft guidance recommends Ozurdex for the treatment of BRVO and CRVO when laser photocoagulation is neither beneficial nor appropriate (8 June 2011).[16]

Conclusion

The sponsor disagreed with the Delegate's decision to reject this application. It should be approved based on the following:

- In the Phase II study, the 700 µg dose demonstrated consistently greater efficacy than 350 µg, with a longer duration of effect. As the safety profile was similar between the 2 doses, the benefit risk ratio is optimal for 700 µg. Higher doses will risk even more dose dependent corticosteroid related local toxicities. Thus 700 µg is the appropriate dose.

[15] Royal College of Ophthalmologists. Interim guidelines for management of retinal vein occlusion. December 2010. Available at www.rcophth.ac.uk.

[16] The National Institute for Health and Clinical Excellence (NICE). Final draft guidance published 6th June 2011.

- The Phase III studies demonstrated that treatment with Ozurdex attains a clinically meaningful and statistically significant 15 letter improvement in visual acuity at 90 days with up to a 14 letter improvement at 180 days. Vision gains of 14 letters are clinically similar to a 3 line improvement, and represent a true alteration in visual acuity in the clinical setting. Thus sustained efficacy has been demonstrated.
- In addition, the proportion of patients with a ≥ 15 letter worsening among the Sham treated patients was approximately double that of patients treated with Ozurdex. Prevention of further vision loss is a critical aim in treating RVO.
- There were a greater proportion of responders in those patients who received Ozurdex immediately compared to those patients who were initially on Sham, thereby demonstrating the benefit of early treatment.
- Despite the burden of disease, there are currently no licensed pharmacologic therapies and no agreed standard of care for macular oedema caused by BRVO and CRVO. Various treatments are used off label however these can have either major adverse events or major treatment burden. Therefore Ozurdex can address this unmet clinical need in these disease states.

The design of the implant and the Phase III studies sought to reduce macular oedema as early and maximally as possible and for as long as possible to minimise the number of intravitreal injections and therefore burden of treatment. The 2 pivotal studies with over 1200 patients were well designed and conducted according to Good Clinical Practice (GCP) guidelines. Results from these studies provide consistent and convincing evidence for drug safety and efficacy.

Clinically relevant treatment benefits have been observed as measured by 15 letter improvement in BCVA and prevention of 15 letter loss. Ozurdex allows for early treatment of the oedema due to BRVO or CRVO, combined with the therapeutic advantage of a relatively long duration of effect (lasting longer than 3 months and up to approximately 6 months). In contrast, laser therapy cannot be implemented early in the disease and VEGF-inhibitors may be limited by their short term effectiveness, the requirement for frequent retreatment, high recurrence rate and potential systemic ischemic side effects related to VEGF inhibition. The safety profile of Ozurdex is acceptable, being consistent with ophthalmic steroid therapy, and thus the overall benefit:risk profile is positive.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the application on the basis that the submitted studies demonstrated only marginal efficacy and over a short time frame, whereas treatment would be expected to continue for longer than the 2 doses for which there are some data. In expressing its view that the submitted studies did not provide evidence of a positive risk benefit, the ACPM considered the following matters:

Efficacy: The ACPM agreed that a statistical benefit in terms of the modified primary endpoint (at 90 days) had been demonstrated in the single pivotal study. There was also limited support for efficacy based on secondary measures. It was agreed that a dose response relationship was demonstrated though the level of response was only modest and the proportion of patients responding was not great. Also, the placebo response increased over time and was little different from the treated group by Day 180.

The committee considered that the application had several deficiencies in the data set which may prevent registration including:

- An inadequate definition of the optimal dose. It was noted that the dose finding study submitted was conducted in a different indication and a minority of patients had the requisite conditions for the indication proposed. Also, dose doubling was common. This was considered to be inadequate as a basis for Phase III study of only 2 doses and with a different formulation. In these circumstances the fact that the dose form and the delivery system of the product materially changed during drug development was considered a serious deficiency.
- The absence of data on when retreatment is required. There is a need to do a further study examining the optimal time point for retreatment.
- The lack of definition of the patient subset likely to benefit from treatment. Both ischaemic central vein occlusion and non-ischaemic central vein occlusion were studied despite no benefit being expected for ischaemic central vein occlusion. Patients with central retinal vein occlusion (CRVO) appear to respond better to treatment than those with branch retinal vein occlusion (BRVO).
- CRVO appeared to respond better but it is certain that the non-ischaemic subgroup will do better than the ischaemic subgroup. BRVO will have a differential prognoses further affected by which branch is obstructed.

Safety: It was noted that no study suggested systemic toxicity and while no clear effects on intraocular pressure were seen in any nonclinical studies, opacities in the central area of the posterior cortex of the lens (in rabbits) were consistent with a risk in humans of cataracts. This signal was strengthened in the pivotal studies, which showed a dose dependent trend to posterior subcapsular opacities by Day 180. The ACPM agreed with the clinical evaluator that a two year period is needed to assess the potential for the formation of cataracts.

The ACPM also agreed with the Delegate's concern with the rate of raised intraocular pressure in the active treatment groups while the reporting rates of these adverse reactions were low in the sham treated groups.

Overall, the ACPM was of the opinion that although the data provided evidence of efficacy on the reduced primary endpoint there has been very limited exploration of optimal dose and yet dose dependent adverse effects have been shown. In addition, although treatment for this condition is likely to be of medium to long term, there are no data beyond 2 doses and the timing for the second dose is uncertain.

The committee noted the query from the Delegate on the vexed question of trade name and reiterated its concerns over the potential for patient and prescriber confusion with "look-alike sound-alike" names as an issue of quality use of medicines.

Should registration be approved the committee encouraged postmarketing studies on the risk of cataract development and on the optimal dispersal mechanism within the eye. In addition, the committee suggested that posterior uveitis should be removed from the PI/CMI given that no data were submitted to support efficacy in this subset of patients.

Outcome

The application was withdrawn before a decision was made.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

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