NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion

Single technology appraisal (STA)

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List of abbreviations

AE	Adverse event
BCVA	Best corrected visual acuity
BSE	Better-seeing eye
BRVO	Branch retinal vein occlusion
BVOS	Branch Vein Occlusion Study
CHMP	Committee for Medicinal Products for Human Use
CRVO	Central retinal vein occlusion
DEX	Dexamethasone
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GENEVA	Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macular Oedema
HRQL	Health related quality of life
IOP	Intraocular pressure
IVTA	Intravitreal triamcinolone acetonide
MAH	Marketing Authorisation Holder
ME	Macular oedema
NICE	National Institute for Health and Clinical Excellence
OCT	Optical coherence tomography
RCO	Royal College of Ophthalmologists
RVO	Retinal vein occlusion
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
TPs	Transition probabilities
VA	Visual acuity
WSE	Worse-seeing eye

Executive summary

Retinal vein occlusion (RVO) is the second most common vascular cause of reduced vision (1) and typically occurs in the middle-aged and elderly population (1, 2). Branch RVO (BRVO) and central RVO (CRVO) are the two main classifications of RVO. Macular oedema (ME) is a common complication of RVO (3, 4) and is the primary cause of vision loss in patients with BRVO (5) and one of the leading causes of vision loss in patients with CRVO (6).

Current therapeutic choices for ME depend on the cause and severity of RVO. Currently, there are no approved pharmacologic therapies for ME and clinical evidence supporting the use of any particular treatment for RVO is limited (3, 4). Laser photocoagulation may improve vision in a proportion of patients with non-ischaemic BRVO, but not in patients with any form of CRVO (7, 8). Laser treatment is not considered appropriate for patients with macular haemorrhage following BRVO (7-9). Observation is typically the standard of care for patients with ME following CRVO and patients with ME following BRVO considered not suitable for laser treatment (including patients with retinal haemorrhage affecting the macular or foveal ischaemia).

Healthcare professionals may regard it necessary to prescribe or advise on the use of an unlicensed medicine through the so-called 'specials' regime when no licensed suitable alternative is available (10). A lack of licensed pharmacological therapies has led to the off-license use of triamcinolone or bevacizumab in the treatment of ME following RVO. The safety and efficacy of triamcinolone and bevacizumab as intravitreal injections has yet to be established and formulations of these therapies are not designed for ocular use (11, 12). Triamcinolone (Kenalog) is formally contraindicated for intraocular use within its Summary of Product Characteristics (SPC) (12) and Genentech/Roche have raised concerns regarding the compounding of bevacizumab into smaller doses for intraocular use (11).

Ozurdex (dexamethasone 700 µg intravitreal implant in applicator) is indicated for the treatment of adult patients with ME following either BRVO or CRVO (13). Ozurdex provides a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for laser photocoagulation, such as those with macular haemorrhage. Patients affected by ME following BRVO who have not previously responded to laser treatment should also be offered treatment with Ozurdex.

Ozurdex is the first and only licensed pharmacological treatment for ME following BRVO and CRVO in the UK. The main comparator for the condition under review is therefore observation (best supportive care), as there are currently no other licensed pharmacological interventions for ME following BRVO or CRVO and laser photocoagulation is not considered appropriate for the subgroups considered within this submission (CRVO, BRVO with MH, and BRVO previously treated with laser).

Ozurdex biodegradable intravitreal implant in applicator delivers 700 µg of the corticosteroid dexamethasone (DEX) through a solid polymer drug delivery system to the posterior segment of the eye. Dexamethasone is a potent corticosteroid which suppresses inflammation via the inhibition of oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response (13). Expression of the cytokine Vascular Endothelial Growth (VEGF) is increased in ME and it acts as a potent promoter of vascular permeability (13). Corticosteroids, such as DEX, inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid ME (13).The use of DEX has previously had limited success in treating retinal disorders including ME, due to the inability to deliver and maintain adequate quantities of the drug to the posterior segment. The innovative drug delivery system of Ozurdex overcomes this limitation by delivering a sustained dose of DEX to target ME over a period of up to six months.

The recommended dose of Ozurdex is one implant to be administered to the affected eye by a qualified ophthalmologist (experienced in intravitreal injections) (13). Administration to both eyes concurrently is not recommended (13). Repeat doses of Ozurdex 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.

European marketing authorisation for Ozurdex was based on the results of two identical Phase III, masked, randomised, sham-controlled studies (GENEVA). These pivotal trials form the basis of the clinical evidence provided within this submission. The GENEVA studies were designed with an initial six-month masked treatment period and a follow on, open label extension period during which eligible patients received Ozurdex. The populations considered within the GENEVA studies included patients with ME following RVO, BRVO or CRVO.

Two clinically relevant subgroups reflecting those patients with ME following BRVO considered most suitable for Ozurdex treatment were identified post-hoc: BRVO with macular haemorrhage (BRVO with MH) (first-line position) and BRVO previously treated with laser (second-line position). Duration of ME at baseline was also considered within post-hoc analyses. The longer the duration of ME, the less likely it is to resolve spontaneously and the presence of chronic ME may lead to a poorer overall visual prognosis in BRVO (14, 15). It has also been suggested that chronic ME results in irreversible photoreceptor damage and that early treatment is necessary for optimal improvements in vision (16).

The primary goal of treating BRVO and CRVO is to improve or prevent further loss of visual acuity (VA) and reduce ME (17, 18). In the pivotal Phase III GENEVA studies, a single treatment of Ozurdex produced significantly greater improvements in VA when compared with Sham over a variety of efficacy measures, including time to achieve a 15 letter improvement from baseline BCVA, proportion of patients achieving ≥ 15 letter improvement, proportion of patients achieving ≥ 15 letter worsening and mean change from baseline BCVA. Statistically significant differences between Ozurdex and Sham were apparent as early as day 30 after treatment. Ozurdex demonstrated similar efficacy in BRVO and CRVO subgroups.

[redacted]

The main adverse events reported with Ozurdex in the GENEVA studies were increases in IOP and a higher incidence of cataracts. Intravitreal injections of steroids, such as DEX, are well-recognised to induce elevations in IOP with different steroids exhibiting a varying propensity to induce this effect. Therefore increases in IOP were anticipated and either did not require treatment or were generally

successfully managed with topical IOP lowering medications (19, 20). The incidence of cataract AEs was considered low with only 3/341 patients requiring surgery in the Ozurdex retreated population.

The GENEVA studies (19-22) demonstrate that in patients with ME following BRVO or CRVO, Ozurdex offers long-lasting improvements in VA from a single injection and is well tolerated with an acceptable safety profile.

The cost-effectiveness of Ozurdex was determined using a Markov model developed in Microsoft® Excel. This approach was used to estimate lifetime outcomes and costs for patients with ME and vision loss following All RVO, BRVO or CRVO. Specific analyses were conducted to examine subgroups of patients for whom immediate laser photocoagulation may not have been appropriate, patients with BRVO with macular haemorrhage (BRVO-MH) and patients with BRVO who had previously received laser photocoagulation (BRVO-previous laser).The evaluation was conducted from the perspective of the NHS and personal and social services in England and Wales. Discounting was performed at 3.5% for both costs and benefits. The Markov approach used within this submission has been adopted in previous economic evaluations of interventions used in the treatment of conditions affecting VA (23, 24). This approach provides an appropriate structure with which to model changes in VA over time and the associated resource use and costs.

Pivotal assumptions used in the model surrounded the percentage of patients treated in their better-seeing (BSE) or worse-seeing eye (WSE), length of time to stabilisation in VA, re-injection intervals and length of overall treatment, extrapolation of outcomes beyond available trial data, the risk of fellow eye occurrence, and the cost of blindness.

The results of the base-case analyses in patients with RVO, BRVO, CRVO, BRVO with macular haemorrhage (BRVO-MH) and BRVO with previously laser treatment are provided in Table 1.

Table 1: Base-case results

Patient group	Incremental cost	Incremental QALYs	ICER
All RVO	£1,667	0.23	£7,368
CRVO	£1,836	0.31	£6,008
BRVO-MH	£1,510	0.19	£7,953
BRVO-previous laser	-£1,218	0.31	Dominant

The results of the base-case analyses in subgroups of BRVO patients with a duration of ME ≤ 90 days and ≥ 90 days are provided in Table 2

Table 2: Base-case analyses in BRVO subgroups of patients with a duration of ME ≤ 90 days and ≥ 90 days

Patient group	Incremental cost	Incremental QALYs	ICER
Duration of ME ≤ 90 days	-£493	0.27	Dominant
Duration of ME > 90 days	£1,929	0.17	£11,418

The economic analysis within this submission demonstrates that Ozurdex is cost-effective compared with observation, with base-case incremental cost per quality

adjusted life years (ICERs) below £20,000 for all patient populations proposed in this submission.

Ozurdex provides a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage. Patients affected by ME following BRVO who have not previously responded to laser treatment should also be offered treatment with Ozurdex.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Ozurdex®; approved name: dexamethasone 700 µg intravitreal implant in applicator; therapeutic class: ophthalmologicals, anti-inflammatory agents.

1.2 What is the principal mechanism of action of the technology?

Ozurdex biodegradable intravitreal implant in applicator delivers 700 µg of the corticosteroid dexamethasone (DEX) through a solid polymer drug delivery system to the posterior segment of the eye. Dexamethasone is a potent corticosteroid which suppresses inflammation via the inhibition of oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response (13). Expression of the cytokine Vascular Endothelial Growth Factor (VEGF) is increased in macular oedema (ME) and it acts as a potent promoter of vascular permeability (13). Corticosteroids, such as DEX, inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid ME (13).

The Ozurdex biodegradable intravitreal implant slowly releases 700 µg of DEX into the eye over a period of up to six months (25). In clinical trials, Ozurdex offered long lasting improvements in BCVA in patients with ME following Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) and furthermore reduced the risk of vision loss (25). Ozurdex is the first and, at present, only licensed pharmacological treatment for ME following CRVO and BRVO.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Marketing authorisation was granted on July 27th 2010 for the indication detailed in this submission

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The CHMP considered that the risk-benefit balance of Ozurdex in the treatment of adult patients with ME following BRVO or CRVO was favourable based on a review of safety and efficacy data (26).

The CHMP suggested that after treatment with Ozurdex, a maintained effect with regards to improvements in VA was observed which lasted up to six months. This effect was replicated following administration of a second implant. The CHMP

considered the efficacy of Ozurdex sufficiently established as the criteria for re-implantation have been clearly defined in the summary of product characteristics (SPC).

It was stated in the European Public Assessment Report (EPAR) that the safety profile of Ozurdex in patients with ME following BRVO or CRVO did not show any unexpected effects related to the intravitreal administration of a corticosteroid. The occurrence of non-serious ocular adverse events (AEs) such as increases in intraocular pressure (IOP) and cataracts were considered manageable. For example, very few patients (<1%) experienced a raised IOP that was not sufficiently controlled by IOP lowering medications and thus required a surgical intervention. Suitable warnings are included in the SPC.

The CHMP considered that there was a lack of experience with administration of Ozurdex beyond more than two implantations. Therefore, Allergan has committed to conducting a post-approval observational study in patients requiring more than two implants with the aim of collecting long-term efficacy and safety data in such patients.

Ozurdex is subject to restricted medical prescription; Ozurdex may only be administered by physicians experienced in the administration of intravitreal injections.

Allergan has also committed to additional risk minimisation activities in line with standard CHMP requests associated with the introduction of all current intravitreal therapies. These include provision of a number of educational materials for physicians and patients to ensure that the correct injection technique is used to minimise both procedure related adverse events and those attributable to the use of the active ingredient (dexamethasone). These materials also serve to inform the patient and physician as to the adverse events that may occur and what to look out for. The CHMP require that these educational materials are provide to and agreed with National Regulatory Authorities prior to launch. The MHRA has already provided such approval for all these materials as part of its pre-vetting procedure for new products entering the UK market.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Ozurdex is indicated for the treatment of adults with ME following BRVO or CRVO. Ozurdex is registered as a pharmaceutical (drug device combination) and therefore does not carry a CE mark.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

None.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Ozurdex was launched in the UK on August 5th 2010.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Ozurdex was assessed in Europe through a centralised procedure and so has received marketing authorisation across all member states. In addition, Ozurdex was granted regulatory approval in the United States by the Food and Drug Administration (FDA) on the 17^{h} June 2009. Ozurdex has also received regulatory approval in Brazil (19 July 2010).

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A submission to the Scottish Medicines Consortium (SMC) was made in August 2010. It is anticipated that advice will be issued to NHS Scotland in November 2010 and published on the SMC website in December 2010.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 3: Unit costs of technology being appraised

Pharmaceutical formulation	Intravitreal implant in applicator; one implant contains 700 µg of DEX
Acquisition cost (excluding VAT)	£870 per unit
Method of administration	Intravitreal injection
Doses	700 µg
Dosing frequency	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.
Average length of a course of treatment	It is anticipated that patients will receive treatment for a maximum of 2-3 years based on the natural history of RVO.
Average cost of a course of treatment	£870 per unit (£1740 per year)
Anticipated average interval between courses of treatments	It is anticipated that patients will receive treatment at intervals of up to six months.
Anticipated number of repeat courses of treatments	Between 1-6 implants
Dose adjustments	N/A

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

n/a

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

As with all current intravitreal therapies, Ozurdex must be administered in controlled aseptic conditions by a qualified ophthalmologist experienced in intravitreal injections. Intravitreal injection is a common ocular procedure within the NHS; therefore these conditions are already established. No special storage conditions are required for Ozurdex.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Ozurdex is currently the only licensed agent for the treatment of ME following BRVO or CRVO. Any intravitreous injection can be associated with endophthalmitis, intraocular inflammation, increased IOP and retinal detachment, therefore monitoring is required after the procedure. The Ozurdex SPC states that monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients of ≤ 45 years of age are more likely to experience increases in IOP. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post-injection as needed. It is of note that during clinical trials assessing the safety and efficacy of Ozurdex (GENEVA studies) the majority of eyes treated with Ozurdex did not experience a substantial increase in IOP (25). Observed increases in IOP during the GENEVA studies were predictable, transient and mainly required no treatment or were managed successfully with standard topical IOP-lowering medications (25).

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

As with all intravitreal injections, both antimicrobial cover and topical anaesthesia will be required as part of the course of treatment.

A broad spectrum topical antimicrobial should be given prior to and on the day of the injection procedure and should be continued after the treatment. A topical anaesthetic agent should also be applied to the eye, immediately prior to Ozurdex implantation.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Vision impairment is associated with significant costs to the individual, healthcare systems and society (27, 28). In the UK, retinal vein occlusion (RVO) is a leading cause of vision impairment (1) and is the second most common form of retinal vascular disorder after diabetic retinopathy (15). RVO typically occurs in the middle-aged and the elderly population (1, 2).

The two main classifications of RVO are branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Macular oedema (ME) is a common complication of RVO (3, 4). It is the primary cause of vision loss in patients with BRVO (5) and one of the leading causes of vision loss in patients with CRVO (6). The primary goal of treating BRVO and CRVO is to improve or prevent further loss of visual acuity (VA) and reduce ME (17, 18).

In BRVO and CRVO, the longer the duration of ME, the less likely it is to resolve spontaneously. It is reported that approximately 26% of eyes with BRVO improve spontaneously without treatment, however 65% of BRVO cases develop persistent or chronic ME (14). There are no clear indicators at baseline to suggest which patients are more likely to experience spontaneous improvements. The prognosis for untreated CRVO is poor. The majority of patients with CRVO progress to become legally blind in their affected eye; over half of CRVO cases result in BCVA < 6/60 in the affected eye (9).

It is important to treat ME early. In patients with chronic ME (> 8 months duration) (29), permanent retinal damage and vision loss may occur (14, 16, 29, 30). Haemorrhages into the vitreous from neovascularisations are more likely to affect eyes with chronic ME and often result in poor final VA and a less favourable prognosis (15). As such, the longer the duration of ME, the more challenging the treatment (31). Data from randomised controlled trials in patients with ME following BRVO support the need for immediate treatment. In the Branch Vein Occlusion Study (BVOS), patients in the observation group with duration of BRVO > 12 months had a significantly lower chance of gaining ≥ 2 lines at year 1 versus those with a duration < 12 months (8% vs. 60%, $p < 0.01$) (7). Similarly, patients in the laser group of the BVOS study with duration of disease > 12 months were less likely to gain two lines or more in BCVA after one year of laser treatment than those with a duration less < 12 months (53% vs. 78%, $p = 0.11$)(7). Such studies demonstrate that in order to achieve optimal improvements in VA or to prevent further vision loss, it is important to treat ME promptly.

Adults experiencing sight loss incur an associated loss in quality of life (QoL) (28). It is generally accepted that RVO is associated with decreased patient-reported visual functioning (32). Patients report difficulties with many aspects of daily life, distance vision, driving and general health (32, 33). The National Eye Institute Visual Functioning Questionnaire 25 (NEI-VFQ 25) is commonly used to assess the impact of treatment on patient-reported binocular visual functioning. In clinical practice, it is

generally considered that visual performance is dictated by the better-seeing eye (BSE) (34). However, although improvements in visual functioning may be greater when the treated eye is considered 'better-seeing', treatment is warranted even when the affected eye is the worse-seeing eye (WSE) (35). Improving VA in the WSE may be beneficial for a patient's vision-related functioning (35) and HRQL. A further rationale for treatment in a patient's WSE is to preserve vision in the WSE in the event of a loss in VA in the BSE (35).

Ozurdex is the first and, at present, only licensed pharmacological treatment for ME following CRVO or BRVO.

2.2 How many patients are assumed to be eligible? How is this figure derived?

The number of incident patients per annum with BRVO or CRVO assumed to be eligible for treatment in the UK is 14,443 and 8,987, respectively. These figures were derived using the following approach.

The population of England and Wales was taken as 54,809,100 (mid-2009 estimates from the Office for National Statistics; with the age distribution [≥ 40 years] derived from the same source) (36). The incidence of BRVO or CRVO in patients aged ≥ 40 years is 0.12% (n = 32,096) and 0.04% (n = 10, 699), respectively (determined from Klein et al, 2000) (37). The proportion of patients with ME following BRVO is estimated to be 50% (n = 16,048) (derived from Margolis et al, 2006) (5) and following CRVO is estimated to be 84% (n = 8,987) (based upon the Central Vein Occlusion Study, 1993) (38). Finally, the proportion of patients with ME following BRVO or CRVO who require treatment was estimated to be 90% (14,443) and 100% (n = 8,987).

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

No guidance relating to the use of pharmacological treatments for ME following BRVO or CRVO have been produced by NICE. However, NICE has published guidance relating to the use of arteriovenous crossing sheathotomy for BRVO. The guidance did not recommend its use in BRVO, stating that it should only be used in the context of research (39).

A future NICE technology appraisal is proposed in the 23rd wave for ranibizumab in the treatment of ME with RVO; dates have yet to be confirmed.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

No NICE guidelines currently exist for the use of pharmacological agents in the treatment of ME following BRVO or CRVO. However interim guidelines for the treatment of RVO have been produced by the Royal College of Ophthalmologists (RCO) (1). The management of BRVO and CRVO is considered separately within the RCO guidelines (1).

The RCO guidelines state that in CRVO there is no proven treatment for ME and no VA benefit in the use of laser therapy (1). The use of intravitreal triamcinolone acetonide (IVTA) to treat ME may produce anatomical and functional improvement of ME related to CRVO. However, the RCO considered that such effects are short-lived. It is important to note that IVTA is not licensed for this use and that the formulation available in the UK (Kenalog) is specifically contraindicated for use in the eye (12).

Ozurdex clinical studies were discussed within the interim RCO guidelines issued in February 2009; it was commented that Ozurdex treatment was found to be associated with significant improvements in vision and less ME versus controls in patients with CRVO (1). No recommendations could be made by the RCO regarding intravitreal VEGF therapy or experimental therapies such as chorio-retinal anastomosis for the treatment of ME following CRVO (1).

Patients with CRVO are typically observed. However, only a small proportion of patients resolve without treatment (40) and over half of CRVO cases result in BCVA < 6/60 in the affected eye (9).

In the treatment of ME in BRVO, a grid pattern of laser photocoagulation was recommended by the RCO after a period of three to six months following the initial event and following absorption of the majority of haemorrhage (as evidenced from clinical trials) (1). The RCO guidelines indicated that the use of pharmacological agents such as IVTA, Ozurdex and intravitreal bevacizumab may be beneficial in the treatment of ME following BRVO. However, clinical data was not sufficient at the time of drafting and therefore no recommendations could be made. Arteriovenous sheathotomy was not recommended by the RCO due to the known complication rate of vitreo-retinal procedures and evidence from trials that the clinical benefits were similar to IVTA treatment (1). It is anticipated that RCO guidelines will be updated now that a licensed treatment option is available in the UK.

Laser photocoagulation is therefore the only recommended interventional treatment for patients with BRVO prior to the availability of Ozurdex however it is associated with a number of limitations. Patients with ME following BRVO > 1 year in duration and with VA of ≤ 6/60 are unlikely to benefit (3) and patients with macular haemorrhage involving the centre point are unsuitable for immediate treatment (7-9). In these circumstances, typical management presently comprises observation, as discussed above, delaying intervention has been shown to reduce the VA outcomes.

In UK clinical practice, triamcinolone (Kenalog), bevacizumab, and ranibizumab may be used in the treatment of ME following BRVO or CRVO. However, none of these interventions are licensed for this indication. The safety and efficacy of triamcinolone and bevacizumab as intravitreal injections has yet to be established and formulations of these therapies are not designed for ocular use (as advised by the manufacturers) (11, 12). Indeed, triamcinolone (Kenalog formulation) is actively contraindicated for intraocular use.

Ozurdex represents the only licensed pharmacological intervention available for the treatment of ME following BRVO or CRVO. Ozurdex provides a first-line pharmacological treatment option for all patients affected by ME following CRVO and

those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage. Ozurdex also provides a treatment option for patients affected by ME following BRVO who have not previously responded sufficiently to laser treatment.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Due to paucity of evidence based treatment options for RVO there is uncertainty around the best pharmacological approach with off-license use of pharmacotherapies that are not designed for ocular use. Observation represents the mainstay of current management for patients with ME following CRVO and in patients with ME following BRVO, who are unsuitable for immediate laser treatment. Patients unsuitable for immediate laser treatment include those with macular haemorrhage in whom treatment is currently delayed for three to six months following the initial event to allow for the absorption of the majority of the haemorrhage (1). Evidence suggests that delaying intervention has been shown to reduce final visual acuity outcomes for patients (3).

Only a small proportion of CRVO patients resolve without treatment (40) and over half of CRVO cases result in BCVA < 6/60 in the affected eye (9). In addition, any delays in treatment, where treatment is given, can lead to a poor final VA and a less favourable prognosis (15).

Evidence from the recently published SCORE-BRVO study demonstrates the potential harm to VA of delaying treatment (41). In the SCORE-BRVO study at month 12, patients in the standard of care group with a duration of ME < 3 months at baseline gained 7.8 letters compared with an average loss of 0.6 letters in those with a duration of ME > 3 months at baseline (41). In addition, patients with > than 3-months duration of ME at baseline were less likely to gain ≥ 15 or more letters of BCVA at month 12 compared with those patients with < 3 months duration of ME at baseline (15% versus 38%, respectively) (41).

Ozurdex provides a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage. Ozurdex also provides a treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment

2.6 Please identify the main comparator(s) and justify their selection.

Despite the burden of disease, there are currently no other licensed pharmacological treatment options for ME following CRVO or BRVO. According to the MHRA, healthcare professionals may regard it necessary to prescribe or advise on the use of an unlicensed medicine through the so-called ‘specials’ regime when no licensed suitable alternative is available (10). This has led to the use in clinical practice of therapies not developed or indicated for the treatment of RVO (off-license interventions).

An evaluation of the three most commonly used therapeutic interventions (laser photocoagulation, off-label use of VEGF inhibitors and corticosteroids) was provided by Allergan (data available on request) to the European Medicines Agency (EMA). This evaluation was taken into account in the CHMP assessment report for Ozurdex (26). Ozurdex is the only licensed pharmacological intervention for the treatment of ME following CRVO or BRVO.

In clinical practice intravitreal injections of triamcinolone (a corticosteroid) or bevacizumab (a VEGF inhibitor) may be used to treat ME following RVO. However, the safety and efficacy of triamcinolone and bevacizumab as intravitreal injections has yet to be established and these treatments are not currently licensed in the UK for the treatment of ME following BRVO or CRVO. Clinically available formulations for triamcinolone and bevacizumab are not designed for ocular use (as stated by the manufacturers). Genentech/Roche have raised concerns regarding the compounding of bevacizumab into smaller doses for intraocular use as it is not designed, manufactured or approved for such use (11).

Significantly, the prescribing information for the injectable suspension of triamcinolone (Kenalog, manufactured by Bristol Myers Squibb in a formulation for intra-articular injection) states that intraocular injection is contraindicated (12). Adequate studies to demonstrate the safety of Kenalog as intraocular (intravitreal) injections have not been performed and endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances, including vision loss, have been reported with the intravitreal administration of Kenalog (12). In addition, intraocular injection of corticosteroid formulations containing benzyl alcohol, such as Kenalog, is not recommended because of potential toxicity to the eye from the benzyl alcohol (12).

Modified Grid Laser photocoagulation is not considered as an appropriate comparator in the specific patient subgroups described within this submission: i) CRVO, ii) BRVO with macular haemorrhage (BRVO with MH), and iii) BRVO previously treated with laser. Laser photocoagulation can improve vision in some patients with non-ischaemic BRVO, but not in patients with any form of CRVO (7, 8). In patients with BRVO > 1 year in duration and VA of ≤ 6/60, grid laser treatment is unlikely to be of benefit (3) and it is not considered an immediate option in patients with macular haemorrhage (7-9). The Royal College of Ophthalmologists (RCO) previous guidance suggest that laser photocoagulation is only recommended in patients with BRVO after a period of three to six months following the initial event and following the absorption of the majority of the haemorrhage (1). The RCO guidelines are currently being fully updated to reflect current evidence and scientific advances since the original guidance in March 2004.

The main comparator for the condition under review is therefore observation (best supportive care), as there are currently no licensed pharmacological interventions for ME following BRVO or CRVO and laser photocoagulation is not considered appropriate for the subgroups considered within this submission (CRVO, BRVO with MH, and BRVO previously treated with laser). As indicated above, observation will only benefit a minority of patients who would spontaneously improve (approximately 25%) where as the remaining majority will suffer reduced VA outcomes based on

delaying an intervention. Therefore, in clinical practice, as it is not possible to predict which patients with significant vision impairment from their vein occlusion are likely to spontaneously improve, observation is not an appropriate management option for any patient with a visual acuity of ≤ 6/12 or 6/9 with significant ME.

Ozurdex provides clinicians with a licensed pharmacological option for the treatment of ME following CRVO or BRVO.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Broad spectrum antibiotics may be prescribed to manage any risk of eye infections. Elevations in IOP may be observed after intravitreal injection of a steroid, therefore effective topical IOP-lowering medicinal products may be prescribed where indicated.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The introduction of Ozurdex would not require any significant changes to the selection and monitoring of patients currently undertaken with observation. The administration of Ozurdex is by intravitreal injection, whereas observation is a non-invasive process. However, the infrastructure for the administration of intravitreal injections is already in place within the NHS and no significant service changes would be necessary with the introduction of Ozurdex. In the budget impact assessment proposed, the impact of any additional visits required for the monitoring of IOP changes will be captured appropriately.

2.9 Does the technology require additional infrastructure to be put in place?

No, the infrastructure for the administration of intravitreal injections is already in position within the NHS.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

The NHS Constitution confirms the right of patients to be able to access clinical services based on clinical need. Patients have the right not to be discriminated against on the grounds of disability and should receive safe and effective treatment to meet their clinical need. Patients have a right to drugs and treatments recommended by NICE, however, as yet no recommended pharmacological treatment exists for patients with ME following RVO (42).

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No specific equity and equality issues.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A – no equity or equality issues.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with macular oedema caused by RVO	People with macular oedema caused by RVO; including all RVO, CRVO, BRVO with MH, and BRVO previously treated with laser.	Ozurdex is intended to provide a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage. Ozurdex also provides a second-line treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment.
Intervention	Dexamethasone intravitreal implant	Dexamethasone intravitreal implant	N/A
Comparator(s)	For CRVO: • Triamcinolone acetonide (IVTA; 'Kenalog' formulation or equivalent) • Bevacizumab • Best supportive care For BRVO: • Triamcinolone acetonide (IVTA; 'Kenalog' formulation or equivalent) • Bevacizumab • Best supportive care (ischaemic only) • Grid pattern photocoagulation	For CRVO and BRVO: Best supportive care (observation)	See Section 2.6;. The safety and efficacy of triamcinolone and bevacizumab as intravitreal injections has yet to be established and these treatments are not currently licensed in the UK for the treatment of ME following BRVO or CRVO. Clinically available formulations for triamcinolone and bevacizumab are not designed for ocular use (as stated by the manufacturers) (11, 12). An alternative formulation of triamcinolone acetonide (Trivaris™) was developed and studied in the treatment of ME following RVO, however, studies failed to meet their primary endpoint and this formulation is not available in clinical practice. It was agreed at the NICE scoping meeting that data for comparators should relate to the specific

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			formulations available in the UK; therefore no data for Trivaris is admissible for review as this formulation is not, and will not be, available in the UK Laser photocoagulation is not considered as an appropriate comparator in the specific patient subgroups described within this submission. in CRVO there is no VA benefit in the use of laser therapy (1). In patients with BRVO > 1 year in duration and VA of ≤ 6/60, grid laser treatment is unlikely to be of benefit (3) and it is not considered an immediate option in patients macular haemorrhage (1, 7-9).
Outcomes	The outcome measures to be considered include: • Visual acuity (the affected eye) • Visual acuity (the whole person) • Contrast sensitivity • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Visual acuity (the affected eye) • Adverse effects of treatment • Health-related quality of life	Data derived from clinical studies for Ozurdex consider visual acuity in the study eye. As RVO is predominantly a monocular disease at first presentation, BCVA in the affected eye is the most important measure of health-related benefit. Visual acuity in the whole person is not considered as although improvements in overall visual functioning may be greater when the treated eye is considered 'better-seeing', treatment is warranted even when the affected eye is the worse-seeing eye (WSE) (35). Contrast sensitivity (CS) is not routinely measured in UK clinical practice. Where CS is measured, the Pelli-Robson chart is generally used. However, it should be noted that although this measure has been adopted in a research setting, the Pelli-Robson chart is not widely used in

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			clinical practice (43). It has been suggested that use of the Pelli-Robson chart is limited when an assessment of each eye individually or repeated measures of CS (e.g. in longitudinal studies) is required (44). The reliability /validity of CS as an outcome measure in retinal disease is open to debate (45).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	N/A
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: BRVO and CRVO; the presence or absence of ischaemia; baseline visual acuity; baseline structural damage to the central fovea; degree of perfusion at the back of the eye duration of	Retinal vein occlusion (RVO) as a total group will be considered as well as specific subgroups: CRVO, BRVO with macular haemorrhage (MH), and BRVO previously treated with laser. Additionally, duration of ME (time since diagnosis) will be considered.	N/A

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	macular oedema (time since diagnosis). Guidance will only be issued in accordance with the marketing authorisation.		
Special considerations, including issues related to equity or equality	None	None	N/A

5 Clinical evidence

Summary

- Ozurdex is indicated for the treatment of adult patients with macular oedema (ME) following retinal vein occlusion (RVO).
- Ozurdex provides a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage (MH). Ozurdex also provides a treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment.
- Ozurdex (dexamethasone [DEX] 700 µg intravitreal implant in applicator) is specifically designed to overcome challenges associated with drug delivery to the posterior segment of the eye in terms of administration frequency and targeted deposition. The biodegradable implant delivers a 700 µg total dose of DEX to the vitreous with gradual release over time (up to six months) - allowing for sustained levels of DEX in the target areas.
- Ozurdex is the only pharmacological therapy for the treatment of ME following BRVO or CRVO that has received European marketing authorisation. Approval was based on the results of two identical Phase III masked, randomised, sham-controlled studies (GENEVA).
- The GENEVA studies were designed with an initial 6 month masked treatment period and a follow on, open label (OL) extension period during which all eligible patients received Ozurdex.
- In the GENEVA studies, Ozurdex offered long lasting and significant improvements in BCVA in patients with ME following BRVO or CRVO, and furthermore reduced the risk of vision loss (25). Improvements in BCVA lasted for up to 6 months after a single intravitreal injection and were reproduced following a second intravitreal injection at 6 months.
- The populations considered within the GENEVA studies included patients with ME following BRVO or CRVO. Two clinically relevant subgroups reflecting those patients with ME following BRVO considered most suitable for Ozurdex treatment were identified post-hoc - BRVO with macular haemorrhage (BRVO with MH) (first line position) and BRVO previously treated with laser (second line position).
- The GENEVA studies were originally designed to achieve Food and Drug Administration (FDA) regulatory approval for Ozurdex. The FDA requested that the primary outcome for the first study (009) should be the proportion of eyes achieving an improvement in BCVA of ≥ 15 letters from baseline at day 180. The FDA later agreed that the prospective primary outcome measure for the second study (008) should be the time to achieve an improvement of BCVA of ≥ 15 letters from baseline (25). This submission to NICE focuses on the primary efficacy endpoint of the pooled GENEVA studies required by the European Medicines Agency (EMA) - the proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in the study eye at day 90.
- In the Phase II dose-ranging study (46) used to inform dose selection within the GENEVA studies, the Ozurdex treatment effect was sustained for up to six months. Therefore, efficacy outcomes in the GENEVA studies were measured beyond the primary timepoint (day 90) to day 180 in order to demonstrate

sustainability of treatment effect prior to retreatment.

- During the initial treatment period, efficacy outcomes generally favoured Ozurdex versus Sham:
    - The cumulative response rate for time to achieve ≥ 15 letters BCVA improvement was consistently and distinctly higher at all time points with Ozurdex versus Sham (P ≤ 0.001), with differential improvements in VA apparent as early as day 30
    - The proportion of patients achieving ≥ 15 letters BCVA improvement was significantly higher at all time points (P ≤ 0.039) with Ozurdex versus Sham in all groups, excluding day 180 (and day 90 in patients with CRVO)
        - The window for scheduled post-implant visits was quite wide, with the day 180 assessment occurring as late as 210 days after implantation in some patients. In a post-hoc analysis the exclusion of patients whose day 180 visit was greater than 180 after implantation resulted in a statistically significantly higher proportion of patients with an improvement of ≥ 15 letters BCVA at all time points (including day 180) with Ozurdex versus Sham (P ≤ 0.017)
    - In BRVO and CRVO, the longer the duration of ME, the less likely it is to resolve spontaneously. In a post-hoc analysis of the GENEVA studies, a significantly higher proportion of patients with a longer duration of ME (> 90 days) achieved ≥ 15 letters BCVA improvement at all time points during the initial treatment period with Ozurdex versus Sham (P ≤ 0.033), excluding day 180.
    - Mean change from baseline BCVA was greater at all time points with Ozurdex versus Sham (P ≤ 0.016), excluding day 180 in patients with CRVO
    - The proportion of patients achieving ≥ 10 letters BCVA improvement was significantly higher at all time points with Ozurdex versus Sham (P ≤ 0.041), excluding day 180 in patients with CRVO
    - Significantly more patients treated with Ozurdex versus Sham achieved a ≥ 1-grade improvement in general vision at days 30, 60 and 90 (as measured binocularly by the NEI-VFQ 25) (P ≤ 0.015), even though the majority of patients (97.4%) were treated in their WSE
- During the OL extension, efficacy outcomes generally favoured Ozurdex/Ozurdex versus Sham/Ozurdex:
    - The cumulative response rate for time to achieve ≥ 15 letters BCVA improvement remained consistently and distinctly higher at all time points for patients treated with Ozurdex/Ozurdex versus Sham/Ozurdex (P ≤ 0.005 [P < 0.001 for all RVO pooled])
    - The beneficial effects of Ozurdex versus Sham were demonstrated not only by a ≥ 15-letter improvement in BCVA, but also via the prevention of a ≥ 15-letter worsening
    - During early visits (days 210 and 240), the mean change from baseline BCVA was statistically significantly greater with Ozurdex/Ozurdex versus Sham/Ozurdex (P ≤ 0.034 [P ≤ 0.004 for all RVO pooled]), excluding day 240 in patients with BRVO
    - During early visits (days 210 and 240), an improvement in BCVA of

≥ 10-letters from baseline was achieved in a statistically significantly greater proportion of all patients treated with Ozurdex/Ozurdex versus Sham/Ozurdex (P ≤ 0.025); with a similar trend observed in BRVO and CRVO subgroups

- Similar results between treatment groups were reported for the proportion of patients achieving an improvement in BCVA of ≥ 15 letters from baseline in the retreated population.

- The GENEVA studies demonstrated that, in comparison with Sham, treatment with Ozurdex was associated with long-lasting and significant improvements in the BCVA of patients with ME following BRVO or CRVO.

5.1 Identification of studies

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of DEX for the treatment of ME following RVO. Searches were conducted that combined terms (including MESH headings as appropriate) for 1) macular oedema and retinal vein occlusion, 2) interventions and comparators, and 3) RCT design. Section 9.2 contains further details relating to the search (including search strings).

5.2 Study selection

Inclusion and exclusion selection criteria are shown in Table 4. A total of 139 potentially relevant publications were identified for inclusion in the systematic review, of which 102 were excluded on the basis of title and abstract and were allocated an exclusion code to document rationale for exclusion. The majority of papers were excluded at this stage as they referred to a study type which was not considered relevant. Papers included at this stage were then assessed based on full text. After review of 37 full text papers, a further 36 were excluded. Non-randomised trials that were identified were noted for later assessment. As a result, one paper was identified as appropriate for inclusion (25). This was supplemented with unpublished data for relevant RCTs (clinical study reports) from the manufacturer.

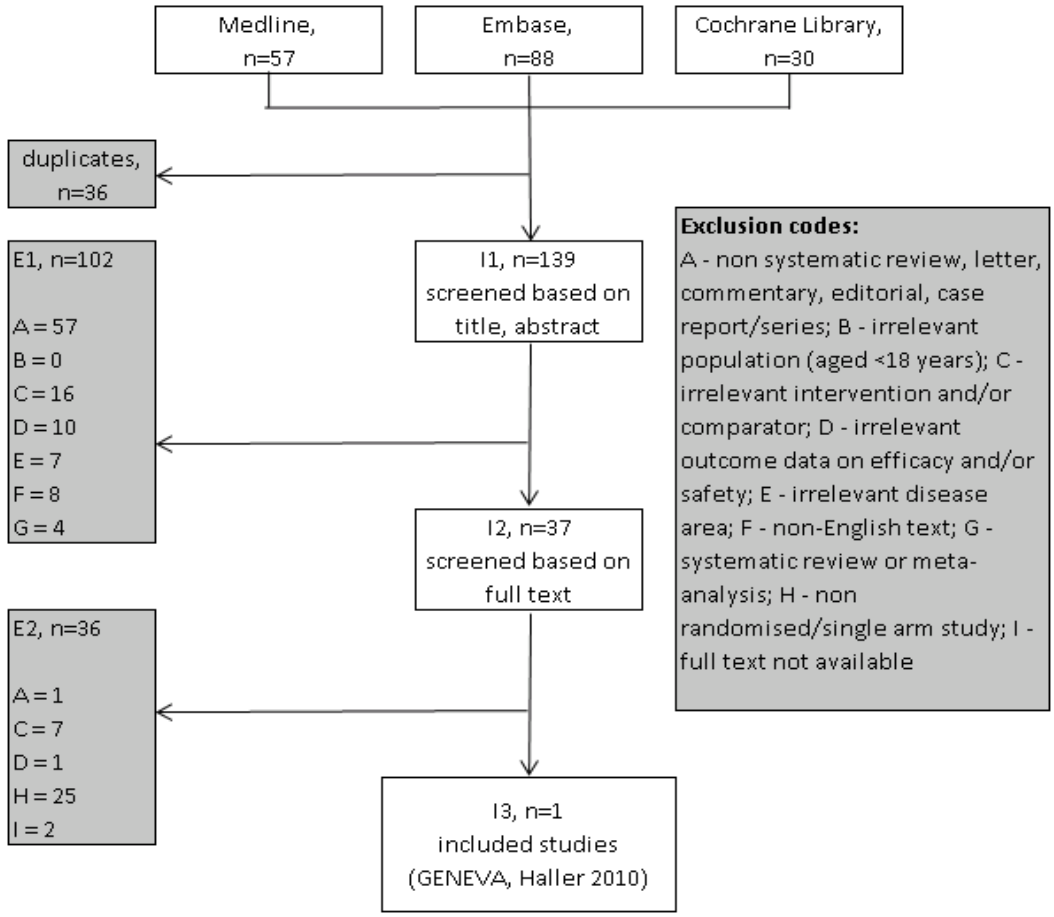
Table 4: Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	
Population	Adults aged 18 and over with vision loss due to macular oedema associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
Interventions	Comparison of two or more of the following interventions: dexamethasone, sham treatment/placebo, triamcinolone acetonide, bevacizumab or ranibizumab
Outcomes	Outcomes of interest included: • 15 letter gain from baseline in best corrected visual acuity (BCVA) • 15 letter loss from baseline in BCVA • mean change from baseline in retinal thickness (micrometres)
Study design	Randomised controlled trials evaluating the efficacy and safety of dexamethasone. Non-randomised evidence (e.g. observational data, open label clinical trial) were also identified by the search. During first round exclusion, these studies were labelled for subsequently review (see Figure 1)

	Clinical effectiveness
Exclusion criteria	
Population	Adults not aged 18 and over with vision loss due to macular oedema not associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
Interventions	Any of those not listed in the included interventions.
Outcomes	Any of those not listed in the included outcomes
Study design	Non systematic reviews, letters, commentaries, case report/series, surveys

5.2.2 *Flow diagram of included and excluded studies*

Figure 1: CONSORT flow diagram of clinical systematic review search



5.2.3 *When data from a single RCT have been drawn from more than one source and/or when trials are linked, this should be made clear.*

The systematic review identified a single Phase III randomised study comparing dexamethasone and Sham (Haller 2010), which describes the GENEVA study (25). The clinical study reports (CSR) for the GENEVA study were provided by the manufacturer and were used to provide efficacy and safety data for this submission (19-22).

5.2.4 Complete list of relevant RCTs

An overview of the Ozurdex clinical trial programme is provided in Table 5. The RCTs considered relevant to this submission, and described within the following sections, are summarised in Table 6

Table 5: Overview of Ozurdex Phase II and III trials

Study	Phase	Study title	Intervention	Study Length	Number of patients	Primary study ref.
Phase II						
DC103-06	II	A Phase II randomised, multicenter, dose-ranging, controlled, parallel-group trial to assess the safety and efficacy of Dexamethasone Posterior Segment Drug Delivery System in the treatment of persistent macular edema	Ozurdex (n = 105) Observation (n = 105) DEX 350 µg (n = 105)	6 months	Ozurdex (n = 105) Sham (n = 105) DEX 350 µg (n = 105)	Kupperman et al, 2007 (46)
Phase III						
GENEVA 008	III	A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion	Ozurdex (n = 201) Sham (n = 202) DEX 350 µg (n = 196)	12 months	Ozurdex (n = 427) Sham (n = 426) DEX 350 µg (n = 414)	Clinical study reports (19-22) and Haller et al, 2010 (25)
GENEVA 009	III		Ozurdex (n = 226) Sham (n = 224) DEX 350 µg (n = 218)			

Table 6: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
GENEVA 008 and 009	Ozurdex (n = 427 [008: n = 201, 009: n = 226])	Sham (n = 426 [008: n = 202, 009: n = 224]) DEX 350 µg (n = 414 [008: n = 196, 009: n = 218])	Patients with ME following BRVO or CRVO	Clinical study reports (19-22) and Haller et al, 2010 (25)

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

GENEVA 008 and 009 compare Ozurdex with a Sham procedure (as a proxy for observation). No studies comparing Ozurdex with an active-control have been conducted as Ozurdex is the only licensed pharmacotherapy for the treatment of ME following BRVO or CRVO.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Study DC103-06 (46) has been excluded from further discussion as this was a Phase II dose-ranging trial in a mixed population of patients with persistent ME (> 90 days after laser treatment or medical management). The population included patients with ME associated with Diabetic Retinopathy, RVO, Uveitis, and Irvine-Gass syndrome. The primary endpoint of the study was the proportion of patients with ≥ 10 letters improvement in BCVA at day 90. Statistical significance for the primary endpoint (in the mixed patient population) was observed for the Ozurdex (36.7%) versus the observation group (19.0%), P = 0.005. The Phase II study DC103-06 was used to inform the doses under investigation in the pivotal Phase III GENEVA studies and is not discussed further within this submission (data is available upon request).

5.2.7 List of relevant non-RCTs

No non-RCTs were identified.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, ***the information should be tabulated.***

5.3.2 Methods

The methodology of the relevant RCTs is summarised in Table 7.

Table 7: Comparative summary of methodology of the RCTs

Trial no. (acronym)	GENEVA 008	GENEVA 009
Location	85 study centres in 13 countries (Australia, Austria, Canada, Czech Republic, France, Germany, Israel, Mexico, Philippines, Portugal, South Africa, Taiwan, USA)	82 study centres in 13 countries (Brazil, Canada, Colombia, Hong Kong, India, Italy, New Zealand, Poland, Singapore, South Korea, Spain, UK, USA)
Design	Masked, randomised, sham-controlled, three-arm, parallel-group design.	
Duration of study	Initial six month (day 0-180) treatment period, followed by a further six month (day 180-360) open label extension period	
Method of randomisation	Patients were randomised using a 1:1:1 allocation ratio. Randomisation was performed centrally (using an interactive voice response system) and stratified by the underlying cause of RVO (BRVO or CRVO).	
Method of blinding (care provider, patient and outcome assessor)	Patients were masked with regard to the initial study treatment, and the key efficacy variables were collected and evaluated by treating investigators who were also masked with regard to study treatment. In order to maintain treatment masking, patients assigned to Sham had a needleless applicator pressed against the conjunctiva and actuated so patients were able to hear the audible click to simulate the actual procedure.	
Intervention(s) (n =) and comparator(s) (n =)	Ozurdex (n = 427 [008: n = 201, 009: n = 226]) Sham (n = 426 [008: n = 202, 009: n = 224]) DEX 350 µg (n = 414 [008: n = 196, 009: n = 218])	
Primary outcome	Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in the study eye (ITT population) at day 90 (measured using the ETDRS chart at each follow-up visit) (EMA endpoint). The GENEVA studies were originally designed to achieve FDA regulatory approval for Ozurdex. The FDA requested that the primary outcome for the first study (009) be the proportion of eyes achieving an improvement in BCVA of ≥ 15 letters from baseline at day 180. The FDA later agreed that the prospective primary outcome measure for the second study (008) should be the time to achieve an improvement of BCVA of ≥ 15 letters from	

Trial no. (acronym)	GENEVA 008	GENEVA 009
	baseline (33). However, this submission to NICE considers the primary endpoint required by the EMA – the proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in the study eye.	
Additional outcomes relevant to the decision problem	Proportion of patients with BRVO or CRVO with an improvement in BCVA of ≥ 15 letters from baseline (study eye, measured using the ETDRS chart at each follow-up visit).	
	Time to achieve an improvement in BCVA of ≥ 15 letters from baseline (study eye, measured using the ETDRS chart at each follow-up visit).	
	Time to achieve an improvement in BCVA of ≥ 15 letters from baseline in patients with BRVO or CRVO (study eye, measured using the ETDRS chart at each follow-up visit).	
	Mean change from baseline BCVA (study eye, measured using the ETDRS chart at each follow-up visit).	
	Mean change from baseline BCVA in patients with BRVO or CRVO (study eye, measured using the ETDRS chart at each follow-up visit).	
	Categorical change from baseline BCVA (≥ 15 letters improvement, ≥ 15 letters worsening) (study eye, measured using the ETDRS chart at each follow-up visit).	
	Categorical change from baseline BCVA (≥ 15 letters improvement, ≥ 15 letters worsening) in patients with BRVO and CRVO (study eye, measured using the ETDRS chart at each follow-up visit).	
	Proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (study eye, measured using the ETDRS chart at each follow-up visit).	
	Proportion of patients with BRVO or CRVO with an improvement in BCVA of ≥ 10-letters from baseline (study eye, measured using the ETDRS chart at each follow-up visit).	
	Contrast sensitivity at baseline, IT day 180 and OL day 180/exit (study eye, measured using the Pelli-Robson chart).	
	Retinal thickness (study eye, measured by optical coherence tomography [OCT] at baseline, days 90, 180, 270, and 360)	
	Retinal thickness in patients with BRVO or CRVO (study eye, measured by OCT at baseline, days 90, 180, 270, and 360)	
	Proportion of patients with at least a 1-grade improvement from baseline in VFQ-25 response for	

Trial no. (acronym)	GENEVA 008	GENEVA 009
	general vision (measured at each follow-up visit in ITT population).	
	Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline (patients with longer duration of ME > 90 days) (study eye, measured using the ETDRS chart at each follow-up visit, post-hoc analysis).	

Abbreviations: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment of Diabetic Retinopathy Study; FDA, Food and Drug Administration; RVO, retinal vein occlusion

5.3.3 Participants

Inclusion and exclusion criteria for the relevant RCTs are summarised in Table 8.

Table 8: Eligibility criteria of the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria	Eligibility criteria for injection with Ozurdex (day 180)†
GENEVA studies (008 and 009)	Patients eligible for the studies met all of the following criteria: • ≥ 18 years of age. • ME due to CRVO at least 6 weeks to 9 months prior to study entry. • ME due to BRVO at least 6 weeks to 12 months prior to study entry. • ME involving the centre of the macular. • BCVA score between 34 and 68 letters by ETDRS in the study eye. • Retinal thickness of ≥ 300 µm by optical coherence tomography (OCT).	Patients were excluded from the studies for any of the following: • An ocular condition that would prevent a 15-letter improvement in VA. • Presence of an epiretinal membrane in the study eye which is the primary cause of ME or is severe enough to prevent improvement in VA despite reduction in ME. • Ocular hypertension (IOP > 23 mm Hg, > 21 mm Hg without or without anti-glaucoma medication, respectively or use of ≥ 2 anti-glaucoma medications); aphakia or anterior chamber intraocular lens; diabetic retinopathy; retinal or disc or choroidal neovascularisation; rubeosis iridis; active ocular infection; toxoplasmosis; visible scleral thinning or ectasia; media opacity. • Intraocular surgery including cataract surgery, and/or laser of any type in the study eye within 90 days prior to qualification/baseline. • Anticipated requirement for ocular surgery or laser in the study eye during the 12-month study period. • Haemodilution (within 3 months); periocular depot (within 6 months) or systemic steroids (within 1 month); use of carbonic anhydrase inhibitors steroids (within 1 month), immunosuppressants/modulators, antimetabolites, alkylating agents steroids (within 6 months),	BCVA was < 84 letters or the retinal thickness by OCT was > 250 µm in the central 1 mm macular subfield and, in the investigator's opinion, the procedure would not put the patient at significant risk.

Trial no. (acronym)	Inclusion criteria	Exclusion criteria	Eligibility criteria for injection with Ozurdex (day 180)†
		topical ophthalmic steroids or topical NSAIDs (within 1 month or anticipated during 12 month study period), warfarin, heparin or enoxaparin (within 2 weeks). • History of IOP elevation in response to steroids. • Glaucoma or optic nerve head change (patients with a history of previous angle-closure successfully treated with either a laser or surgical peripheral iridotomy were not excluded providing the visual fields were stable for > 1 year prior to study entry and the patient had been and could be safely dilated). • Herpetic infection or adnexa. • Central serous chorioretinopathy. • Pars plana vitrectomy. • History of use of intravitreal steroids or any intravitreal injectable drug in the study eye. • BCVA score< 34 letters in the non-study eye using the ETDRS method.	

Abbreviations: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment of Diabetic Retinopathy Study; IOP, intraocular pressure; OCT, optical coherence tomography; RVO, retinal vein occlusion; VA, visual acuity; † At day 180 of the initial treatment period, patients were eligible to receive OL treatment with Ozurdex (whilst remaining masked to the initial treatment).

5.3.4 Baseline characteristics

ITT population

Patient characteristics at baseline for the ITT population are summarised in Table 9 and Table 10. The majority of patients in the GENEVA studies presented with BRVO (> 65%). The majority of patients had a duration of ME > 90 days (with the most frequently reported duration of ME between 90 to 170 days). Over 100 patients in the pooled GENEVA studies had a duration of ME ≥ 270 days. The longer the duration of ME, the less likely it is to resolve spontaneously and it has been demonstrated that the presence of chronic ME may lead to a poorer overall visual prognosis in patients with BRVO (14, 15). It has also been suggested that chronic ME results in irreversible photoreceptor damage and that early treatment is necessary for optimal improvements in vision (16).

In GENEVA 008 and 009, 12.4% (74/599) and 8.5% (57/668) of patients, respectively, reported prior procedures for the treatment of ME in the study eye. In GENEVA 008, the majority of these patients (93.2% [69/74]) had undergone retinal laser coagulation, however, haemodilution was reported for 5.4% (4/74) of the patient population and one patient had previously received an intra-ocular injection of triamcinolone on two separate occasions. In GENEVA 009, all previously treated patients had undergone retinal laser coagulation, with the exception of one patient who had received an intra-ocular injection. In GENEVA 008 and 009, respectively, prior medications for the treatment of ME were reported by 5.6% (22/394) and 5.5% (24/436) of patients with BRVO, and 8.8% (18/205) and 6.5% (15/232) of patients with CRVO. Prior to study entry, the use of medications other than those prescribed for the treatment of ME were reported in a total of 18.2% (109/599) and 17.5% (117/668) of patients in the GENEVA 008 and 009 studies, respectively.

Table 9: Patient demographics and baseline characteristics (- 180 days)

Characteristic	GENEVA 008 (n = 599)	GENEVA 009 (n = 668)	Pooled (n = 1267)
Age (years)	65.5	63.6	64.5
Mean (range)	(32 to 91)	(31 to 96)	(31 to 96)
Sex			
Male	327 (54.6%)	350 (52.4%)	677 (53.4%)
Female	272 (45.4%)	318 (47.6%)	590 (46.6%)
Race			
Caucasian	502 (83.8%)	449 (67.2%)	951 (75.1%)
Black	18 (3.0%)	31 (4.6%)	49 (3.9%)
Asian	26 (4.3%)	92 (13.8%)	118 (9.3%)
Japanese	0 (0.0%)	3 (0.4%)	3 (0.2%)
Hispanic	44 (7.3%)	47 (7.0%)	91 (7.2%)
Other	9 (1.5%)	46 (6.9%)	55 (4.3%)
Iris Colour			
Dark	344 (57.6%)	406 (60.8%)	750 (59.3%)
Light	253 (42.4%)	262 (39.2%)	515 (40.7%)
Diagnosis in study eye			
BRVO	394 (65.8%)	436 (65.3%)	830 (65.5%)
CRVO	205 (34.2%)	232 (34.7%)	437 (34.5%)

Characteristic	GENEVA 008 (n = 599)	GENEVA 009 (n = 668)	Pooled (n = 1267)
Diagnosis by treatment group: CRVO			
Ozurdex treatment group (n)	59	74	133
Sham treatment group (n)	72	75	147
Diagnosis by treatment group: BRVO with macular haemorrhage			
Ozurdex treatment group (n)	118	137	255
Sham treatment group (n)	124	136	260
Diagnosis by treatment group: BRVO with previous laser treatment			
Ozurdex treatment group (n)	21	15	36
Sham treatment group (n)	20	16	36
Diagnosis by BSE/WSE: CRVO (%)	BSE: 1.5 WSE: 98.5	BSE: 2.7 WSE: 97.3	BSE: 2.1 WSE: 97.9
Diagnosis by BSE/WSE: BRVO with previous laser treatment (%)	BSE: 0.0 WSE: 100.0	BSE: 3.2 WSE: 96.8	BSE: 1.4 WSE: 98.6
Diagnosis by BSE/WSE: BRVO with MH (%)	BSE: 1.7 WSE: 98.4	BSE: 3.3 WSE: 96.7	BSE: 2.5 WSE: 97.5
Duration of macular oedema			
< 90 days	92 (15.4%)	119 (17.8%)	211 (16.7%)
90 to 179 days	306 (51.1%)	351 (52.5%)	657 (51.9%)
180 to 269 days	141 (23.5%)	139 (20.8%)	280 (22.1%)
≥ 270 days	60 (10.0%)	59 (8.8%)	119 (9.4%)
Baseline BCVA in the study eye (mean number of letters read correctly)			
Ozurdex treatment group	54.5	54.1	54.3
Sham treatment group	54.4	55.0	54.7

Abbreviations: BCVA, Best corrected visual acuity; BRVO, Branch retinal vein occlusion; BSE, Better-seeing eye; CRVO, Central retinal vein occlusion; MH, macular haemorrhage; WSE, Worse-seeing eye

Table 10: Baseline BCVA by patient cohorts (pooled data)

ETDRS score (Snellen equivalent)	CRVO		BRVO with MH		BRVO with previous laser treatment	
	Ozurdex (n = 133)	Sham (n = 147)	Ozurdex (n = 255)	Sham (n =260)	Ozurdex (n = 36)	Sham (N = 36)
> 69 letters (≥ 20/40)	0	0.7	0	1.2	0	0
59-68 letters (20/50-20/63)	35.3	37.4	42.0	40.4	27.8	36.1
54-68 letters (20/80)	18.0	23.8	16.9	20.4	19.4	25.0
44-53 (20/100-20/125)	18.0	15.0	25.1	22.3	27.8	22.2
39-43 letters (20/160-20/200)	12.0	6.1	6.7	8.5	16.7	11.1
≤ 38 letters (≤ 20/200)	16.5	17.0	9.4	7.3	8.3	5.6
Mean (SD)	52.4 (10.6)	53.3 (10.8)	54.9 (9.7)	55.3 (9.4)	52.8 (9.9)	54.6 (9.0)
Median	54	56	56	57	53	56
Range	34-69	28-69	34-68	34-80	34-68	37-67

Retreated population

The demographic and baseline characteristics of the re-treated population in the GENEVA studies are provided in Table 11. The mean age of patients was > 60 years with the majority of patients presenting with BRVO (> 64%).

Table 11: Patient demographics and baseline characteristics: Pooled re-treated population (-360 days)

Characteristic	Re-treated population	
	Ozurdex/Ozurdex (n = 341)	Sham/Ozurdex (n = 327)
Age (years)	65.2	64.7
Mean (range)	(34 to 90)	(31 to 91)
Sex		
Male	177 (51.9%)	179 (54.7%)
Female	164 (48.1%)	148 (45.3%)
Race		
Caucasian	262 (76.8%)	251 (76.8%)
Black	13 (3.8%)	16 (4.9%)
Asian	26 (7.6%)	32 (9.8%)
Japanese	0 (0.0%)	1 (0.3%)
Hispanic	29 (8.5%)	17 (5.2%)
Other	11 (3.2%)	10 (3.1%)
Iris Colour		
Dark	189 (55.4%)	192 (58.9%)
Light	152 (44.6%)	134 (41.1%)
Diagnosis in study eye		
BRVO	227 (66.6%)	210 (64.2%)
CRVO	114 (33.4%)	117 (35.8%)
Baseline BCVA (mean number of letters read correctly)	53.9	54.9

5.3.5 Outcomes

Context of primary outcomes in the GENEVA studies

The primary outcomes in the GENEVA studies focus upon the proportion of patients with improvements in BCVA (the most commonly cited measure of visual function) as measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The term BCVA refers to a person's visual acuity with their vision optically 'corrected', i.e. by wearing spectacles. Visual acuity (VA) is usually measured using a chart displaying letters arranged in rows of progressively decreasing size. The ETDRS chart and Snellen chart are standard methods of determining VA (Appendix 20: Measures of visual acuity).

The ETDRS chart consists of lines each containing 5 letters, with a halving of letter sizes every third line from top to bottom. A letter score is generated from 0 to 100 (representing the number of letters read correctly). A higher score represents better VA (~85 is 'normal' or average vision). A one-line change on the ETDRS chart corresponds to a 5 letter score change (improvement or worsening); a change of ≥ 15 letters is a common clinical trial benchmark for effectiveness of a treatment.

The Snellen chart is usually read while standing at a distance of 20 feet (6 metres). VA is represented as a fraction, with the distance at which you are standing being the numerator (top part of fraction), and the normal maximum legible viewing distance as the denominator (bottom of fraction). So if, at 20 feet (6 metres), you can read the letters on the row marked "20", this means you have normal vision (20/20 or 6/6). If at 20 feet (6 metres), you can read the letters on the row marked "40", this means you have VA of 20/40 (6/12) or better (i.e. half normal VA).

The common cut-off for driving restrictions in many Western countries is 69 letters on the ETDRS chart (Snellen equivalent of 20/40 [6/12]) (47) in the best seeing eye (BSE) of a person with binocular vision. In the UK, the legal standard required for driving a private car or motorbike (group 1 entitlement) is to be able to read a number plate at 20 metres[a] (approximately 6/10). The common threshold for legal blindness is ≤ 38 letters on the ETDRS chart (Snellen equivalent ≤ 20/200 [≤ 6/60]) in many countries including the UK (48).

In the GENEVA studies the primary efficacy measure was BCVA using the ETDRS method. A 15 letter change in BCVA is equivalent to a doubling of the visual angle and is a commonly used in clinical trials to demonstrate the effectiveness of treatment. It is considered clinically significant and reflects a true alteration in VA. A 15-letter change in BCVA using the ETDRS method considerably exceeds the amount required to have a high degree of certainty that the observed alteration is a valid change in VA and not attributable to random chance (49, 50). The primary goal of treating BRVO and CRVO is to improve or prevent further loss of visual acuity (VA) and reduce ME (17, 18).

[a] 20.5 metres if the font is pre-01/09/2001

Table 12: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
GENEVA 008 and 009	• Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in the study eye (ITT population) at day 90 (measured using the ETDRS chart at each follow-up visit) (EMA endpoint)	• Changes in BCVA were assessed using the ETDRS chart – a standard testing procedure for more than 20 years (49).The standardised format of ETDRS chart overcomes some of the limitations posed by the Snellen chart (51). A 15-letter change in BCVA using the ETDRS method considerably exceeds the amount required to have a high degree of certainty that the observed alteration is a valid change in VA and not attributable to random chance (49, 50).	• Proportion of patients with BRVO or CRVO with an improvement in BCVA of ≥ 15 letters from baseline • Time to achieve an improvement in BCVA of ≥ 15 letters from baseline (in all patients and in patients with BRVO or CRVO) • Mean change from baseline BCVA (in all patients and in patients with BRVO or CRVO) • Categorical change from baseline BCVA (≥ 15 letters improvement, ≥ 15 letters worsening) (in all patients and in patients with BRVO or CRVO) • Proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (in all patients and in patients with BRVO or CRVO) • Contrast sensitivity measured using the Pelli-Robson chart • Retinal thickness measured by OCT (in all patients and in patients with BRVO or CRVO) • Proportion of patients with at least a 5-point improvement and at least a 1-grade improvement from baseline in VFQ-25 • Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline (patients with duration of ME > 90 days)	• BCVA outcomes: As described for primary outcome. • The Pelli-Robson chart (to measure contrast sensitivity) is not widely used in clinical practice (43). It has been suggested that use of the Pelli-Robson chart is limited when an assessment of each eye individually or repeated measures of CS (e.g. in longitudinal studies) is required (44). • OCT imaging is a sensitive method for detecting and quantifying macular thickening regardless of its cause (31). • VFQ-25: RVO is associated with decreased patient-reported visual functioning (32). The NEI-VFQ-25 is a shortened version of the 51-item NEI-VFQ Field Test Version and consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. A 1-grade improvement using the NEI-VFQ-25 is considered to be the minimum level of change that can be assessed by a patient in their visual functioning as a result of vision in both eyes.

5.3.6 Statistical analysis and definition of study groups

Table 13: Summary of statistical analyses in RCTs

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
GENEVA 008 and 009	To assess the treatment difference in the proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline.	A Pearson's chi-square test at the 0.05 significance level and a 2-sided 95% CI using the normal approximation for a binary variable was performed to test the primary hypothesis.	Assuming a 9% improvement rate for Sham and α = 0.05 with 165 patients per group the power was 81% to detect a between-group absolute difference of 11 percentage points in the improvement rate. For a three-arm study with a 1:1:1 ratio for treatment allocation, a total of 495 patients were needed for each study. Accounting for a 10% dropout rate, approximately 550 patients were to be enrolled in each study.	In general, the last observation carried forward method was used to replace missing post-baseline data unless the response variable for changes from baseline was unambiguously determined based on the available information.

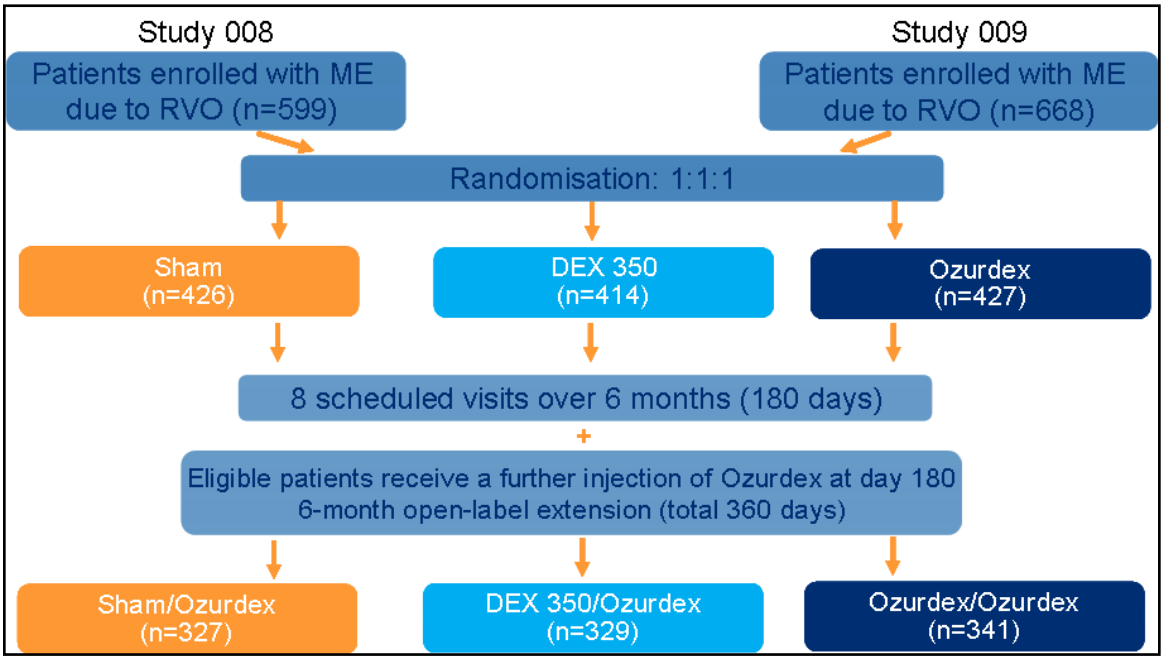
5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup analyses were undertaken for patients with BRVO or CRVO and were pre-planned. Subgroup analyses of patients with BRVO with macular haemorrhage (MH) or patients with BRVO previously treated with laser were post-hoc. Subgroup analyses are considered within the results section for the GENEVA clinical trials where applicable.

5.3.8 Participant flow

GENEVA 008 and 009 adopted the same, masked, randomised, sham-controlled, three-arm, parallel-group design. The studies incorporated an initial six month (day 0-180) masked treatment period treatment period, followed by a further six month (day 180-360) OL extension period during which all eligible patients received Ozurdex (dexamethasone 700 µg intravitreal implant in applicator)(Figure 2).

Figure 2: GENEVA study design

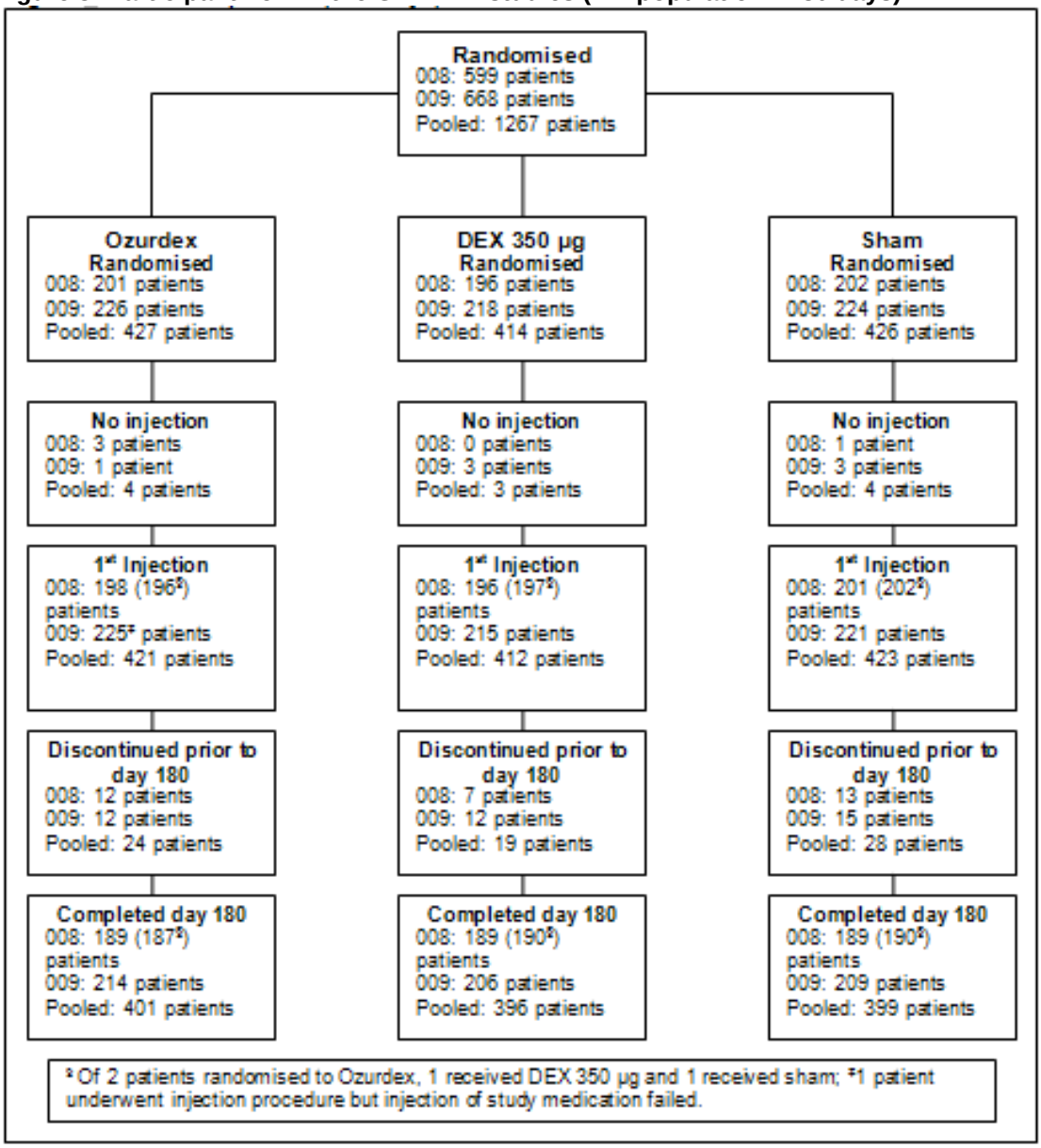


ME:Macular Oedema, RVO:Retinal Vein Occlusion

Details of the numbers of patients who were eligible to enter the GENEVA studies and were randomised and allocated to each treatment are presented in Figure 3 and Figure 4.

A total of 1,267 patients were enrolled in the two studies (GENEVA 008: n = 599, GENEVA 009: n = 668) and were randomly assigned 1:1:1 to Ozurdex, DEX 350 µg or Sham (Figure 3).

Figure 3: Participant flow in the GENEVA studies (ITT population - 180 days)



In the ITT population (pooled analysis), 24 patients (5.6%) in the Ozurdex group and 28 patients (6.6%) in the Sham group discontinued prior to day 180 (Table 14).

Table 14: Reasons for discontinuation in the pooled GENEVA studies (- 180 days)

Reasons for discontinuation	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Discontinued prior to day 180	12 (6.0%)	13 (6.4%	12 (5.3%)	15 (6.7%)	24 (5.6%)	28 (6.6%)
Adverse event	3 (1.5%)	3 (1.5%)	5 (2.2%)	5 (2.2%)	8 (1.9%)	8 (1.9%)
Lack of efficacy	0 (0%)	2 (1.0%)	0 (0%)	2 (0.9%)	0 (0%)	4 (0.9%)
Administrative	7 (3.5%)	4 (2.0%)	2 (0.9%)	3 (1.3%)	9 (2.1%)	7 (1.6%)
Protocol violation	2 (1.0%)	2 (1.0%)	2 (0.9%)	0 (0%)	4 (0.9%)	2 (0.5%)
Other	0 (0%)	2 (1.0%)	3 (1.3%)	5 (2.2%)	3 (0.7%)	7 (1.6%)

At day 180 of the initial treatment period, patients were eligible to receive OL treatment with Ozurdex (whilst remaining masked to the initial treatment) if BCVA was < 84 letters or the retinal thickness by optical coherence tomography (OCT) was > 250 µm in the central 1 mm macular subfield and, in the investigator's opinion, the procedure would not put the patient at significant risk. An injection of Ozurdex at day 180 of the initial treatment period was administered to 341, 329 and 327 patients in the Ozurdex, DEX 350 µg and Sham groups, respectively (re-treated population) (Figure 4) (21, 22, 52).

A total of 199 patients did not receive an injection at day 180 of the initial treatment period. In patients treated with Ozurdex at baseline but who were not given a second injection at day 180 (single-treated population, n = 80), reasons for not receiving retreatment are shown in Table 15. Patients who did not receive retreatment were classified as resolved (OCT < 250 µm) or not resolved (OCT > 250 µm) for economic modelling purposes (further described in Section 6). Table 16 shows the distribution of patients classed as not resolved by subgroup at day 180 based on the number of patients in each sub-population.

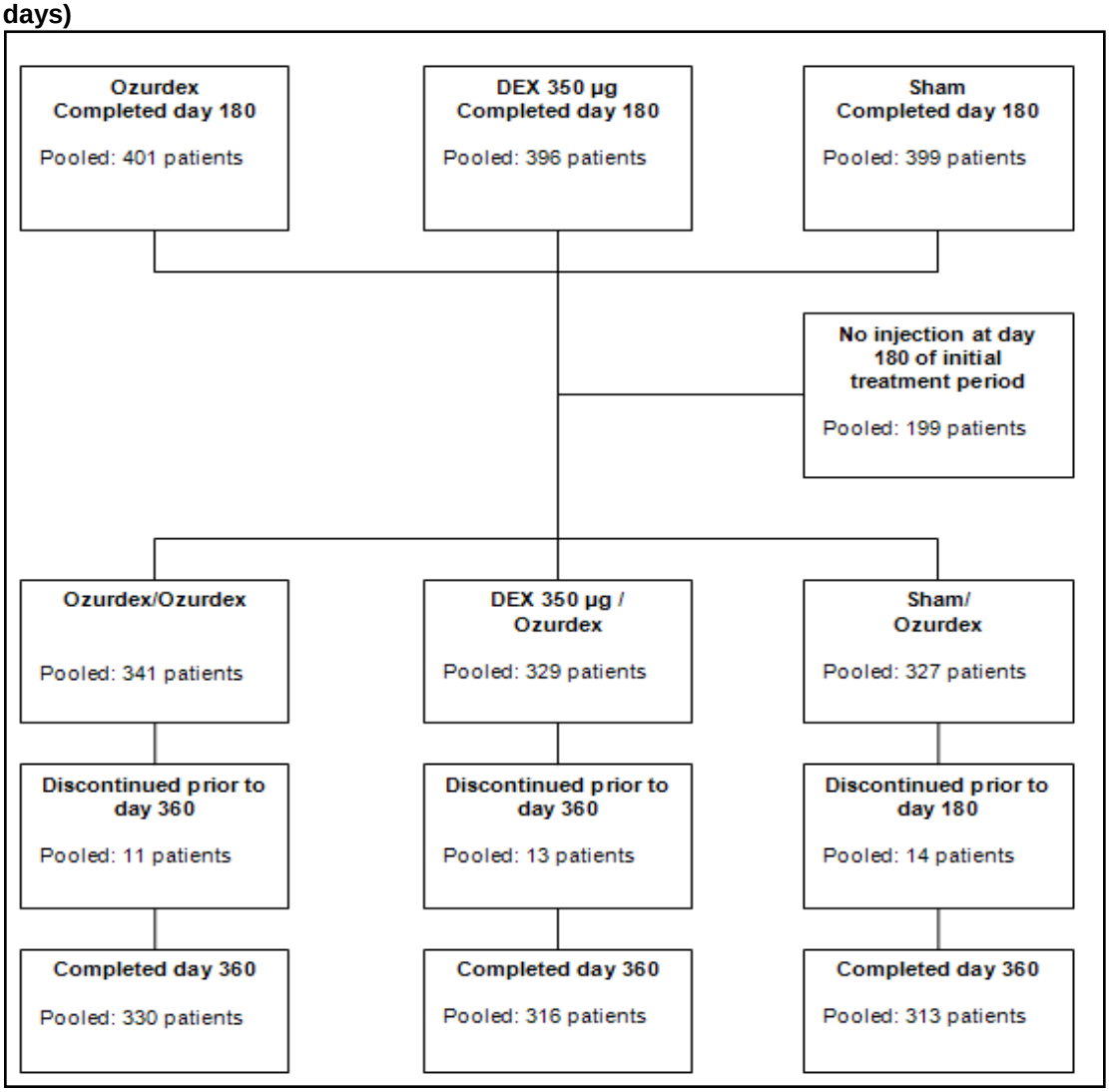
Table 15: Reasons for not receiving retreatment

Reasons for not receiving retreatment	Pooled GENEVA studies	
	Single-treated population	
	BRVO (n = 61)	CRVO (n = 19)
Discontinued prior to day 180	11 (18.0%)	9 (47.4%)
Did not meet retreatment criteria	30 (49.2%)	2 (10.5%)
Safety reasons	6 (9.8%)	4 (21.1%)
Other	14 (23.0%)	4 (21.1%)

Table 16: Single-treated population: patients considered not resolved (OCT > 250µm) by subgroup analysis (- day 180)

Subgroup analysis	Pooled GENEVA studies	
	BRVO	CRVO
Day 180		
All patients	23/61 (37.7%)	11/19 (57.9%)
Duration of ME > 90 days	19/47 (40.4%)	8/15 (53.3%)
Duration of ME ≤ 90 days	4/14 (28.6%)	3/4 (75.0%)
Previous laser (BRVO only)	1/5 (20.0%)	N/A
BRVO with macular haemorrhage	21/53 (39.6%)	N/A

Figure 4: Participant flow in the GENEVA studies (pooled retreated population - 360 days)



In the re-treated population, 11 patients (3.2%) in the Ozurdex/Ozurdex group and 14 patients (4.3%) in the Sham/Ozurdex group discontinued prior to day 360 but subsequent to day 180 (Table 17).

Table 17: Reasons for discontinuation: Pooled re-treated population (- 360 days)

Reasons for discontinuation	Pooled GENEVA studies	
	Re-treated population	
	Ozurdex/Ozurdex (n = 341)	Sham/Ozurdex (n = 327)
Discontinued prior to day 360	11 (3.2%)	14 (4.3%)
Adverse event	4 (1.2%)	3 (0.9%)
Lack of efficacy	2 (0.6%)	1 (0.3%)
Administrative	1 (0.3%)	6 (1.8%)
Protocol violation	3 (0.9%)	3 (0.9%)
Other	1 (0.3%)	1 (0.3%)

5.4 Critical appraisal of relevant RCTs

Critical appraisals of the relevant RCTs are presented in Table 18.

Table 18: Quality assessment results for RCTs

GENEVA 008 and 009	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Patients were randomised using a 1:1:1 allocation ratio. Randomisation was performed centrally (using an interactive voice response system).	Yes
Was the concealment of treatment allocation adequate?	In order to maintain treatment masking, patients assigned to Sham had a needleless applicator pressed against the conjunctiva and actuated so patients were able to hear the audible click to simulate the actual procedure.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No clinically relevant differences between groups were observed for demographic and disease characteristics at baseline	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Patients were masked with regard to study treatment, and the key efficacy variables were collected and evaluated by follow-up investigators who were also masked with regard to study treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups?	No unexpected imbalances.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Outcomes were presented in the CSRs; only those relevant to the decision problem are presented within this submission	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population was included in the primary analysis. In general, the last observation carried forward (LOCF) method was used to replace missing post-baseline data unless the response variable for changes from baseline was unambiguously determined based on the available information.	Yes

5.5 Results of the relevant RCTs

Introduction – GENEVA studies (008 and 009)

GENEVA 008 and 009 were Phase III multicentre studies with the same, masked, randomised, sham-controlled, three-arm, parallel-group design. The studies incorporated an initial six month (day 0-180) treatment period, followed by a further six month (day 180-360) open-label (OL) extension period.

The first masked injection of the randomised treatment was administered at day 0 of the initial treatment period, with all randomised patients included in the intent-to-treat (ITT) population. Treatment was administered in one eye only (referred to as the study eye). If both eyes were eligible for treatment, then the eye with the shorter duration of ME was selected as the study eye. The study eye was identified at the qualification/baseline visit and remained the same throughout the entire study duration. In the GENEVA studies, 97.4% (1234/1267) patients received treatment in their worst-seeing eye (WSE) (53). The exclusion criteria for the GENEVA studies prevented patients with a BCVA < 34 in the non-study eye from entering the study. Therefore, the proportion of patients treated in their WSE was higher in the GENEVA studies than expected in clinical practice (90%, expert opinion (54)). The active treatment, DEX (350 µg or 700 µg) was delivered via an injectable implant. Patients were monitored over the six month initial treatment period via eight scheduled visits (qualification/baseline, randomisation/day 0, days 1, 7, 30, 60, 90, and 180).

On entering the OL extension period (day 180) eligible patients received an unmasked injection of Ozurdex (DEX 700 µg) in the study eye (referred to throughout this submission as the 're-treated' population) and were followed primarily for safety outcomes. Patients were eligible to receive OL treatment with Ozurdex (whilst remaining masked to the initial treatment) if BCVA was < 84 letters and/or the retinal thickness by optical coherence tomography (OCT) was > 250 µm in the central 1 mm macular subfield and, in the investigator's opinion, the procedure would not put the patient at significant risk. Patients that did not receive re-treatment ('single-treated' population) are not considered within this element of the submission; these patients did not receive an injection of Ozurdex at day 180 and are captured within the ITT and safety populations for the initial treatment period. During the OL extension period, patients were monitored via a further six scheduled visits (days 1, 7[b], 30, 60, 90 and 180 of the OL extension period).

The OL extension period was primarily for safety; however, the pooled 12-month efficacy data for the re-treated population are presented within this section for completeness. Efficacy results presented within this submission focus on the UK licensed dose of DEX-PS-DDS (700 µg, Ozurdex) compared with Sham.

[b] This visit only applied if re-treatment had occurred.

GENEVA studies – Initial treatment period (-180 days)

Executive Summary – Initial treatment period

- The following efficacy outcomes favoured Ozurdex versus Sham:
    - The cumulative response rate for time to achieve ≥ 15 letters BCVA improvement was consistently and distinctly higher at all time points with Ozurdex versus Sham ($P < 0.001$), with differential improvements in BCVA apparent as early as day 30.
    - The proportion of patients achieving ≥ 15 letters BCVA improvement was significantly higher at all time points with Ozurdex versus Sham ($P \leq 0.039$), excluding day 180 (and day 90 in patients with CRVO)
        - The window for scheduled post-implant visits varied, with some patients assessed after day 180. The exclusion of these patients from the analysis resulted in a statistically significantly higher proportion of patients with an improvement of ≥ 15 letters BCVA at all time points (including day 180) with Ozurdex versus Sham ($P \leq 0.017$)
    - The mean change from baseline BCVA was significantly higher at all time points with Ozurdex versus Sham ($P \leq 0.016$), excluding day 180 in patients with CRVO.
    - The proportion of patients achieving ≥ 10 letters BCVA improvement was significantly higher at all time points with Ozurdex versus Sham ($P \leq 0.041$), excluding day 180 in patients with CRVO.
- A ≥ 1-grade improvement in general vision (as measured binocularly by the NEI-VFQ 25 scale) at days 30, 60 and 90 was achieved in significantly more patients treated with Ozurdex versus Sham ($P \leq 0.015$), even though the majority of patients (97.4%) in the GENEVA studies were treated in their WSE.
- Throughout the GENEVA studies, the beneficial effects of Ozurdex versus Sham were demonstrated not only by a ≥ 15-letter improvement in BCVA but also via the prevention of a ≥ 15-letter worsening – i.e. more patients improved and fewer patients declined when compared with Sham, resulting in a mean change in BCVA of 9.8, 10.3 and 8.7 letters at peak effect in pooled analyses of all RVO, BRVO, and CRVO, respectively.
- Even in patients with a longer duration of ME (> 90 days), a significantly greater proportion of those treated with Ozurdex versus Sham achieved a ≥ 15 letters BCVA improvement at all time points (excluding day 180) ($P \leq 0.033$).
- A single injection of Ozurdex was associated with long-lasting and significant improvements in the BCVA of patients with ME following BRVO or CRVO.

Primary outcome: initial treatment period (- 180 days)

This submission focuses on the primary efficacy endpoint of the pooled GENEVA studies required by the European Medicines Agency (EMA) - the proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in the study eye at day 90. The Ozurdex treatment effect was sustained for up to six months in the Phase II dose-ranging study (46) used to inform dose selection within the GENEVA studies. Therefore, efficacy outcomes in the ITT population are presented beyond the primary timepoint of day 90, and up to day 180, in order to show the proportion of patients with a sustained treatment effect after a single injection of Ozurdex. In clinical practice repeated doses of Ozurdex would be considered when a patient experiences a response to treatment followed subsequently by a loss in VA and in the physician's opinion may benefit from retreatment without being exposed to significant risk (13).

Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days) (19, 20, 55)

Individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with an improvement of ≥ 15 letters BCVA from baseline (in the study eye) was statistically significantly higher at days 30, 60 and 90 (P ≤ 0.039) with Ozurdex versus Sham. Significant between-group differences in the pooled analysis were 13.8% [95% CI: 9.2%, 18.4%] at day 30, 18.0% [95% CI: 12.7%, 23.3%] at day 60, and 8.6% [95% CI: 3.6%, 13.7%] at day 90. A similar trend was observed at day 180 (Table 19).

The window for scheduled post-implant visits varied, which is of potential significance. Approximately half of all patients had their day 180 study visit considerably later than day 180 (197 patients treated with Ozurdex and 219 patients in the Sham group were assessed after day 180 of the ITT period). The exclusion of these patients in a post-hoc analysis resulted in a statistically significantly higher proportion of patients with an improvement of ≥ 15 letters BCVA at all time points, including day 180, with Ozurdex versus Sham (P ≤ 0.017).

Table 19: Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Day 30	19.9%†	7.4%	22.6%†	7.6%	21.3%†	7.5%
Day 60	28.9%†	10.4%	29.6%†	12.1%	29.3%†	11.3%
Day 90	22.4%§	12.4%	21.2%‡	13.8%	21.8%†	13.1%
Day 180	19.4%	18.3%	23.5%	17.0%	21.5%	17.6%

† (P < 0.001); ‡ (P = 0.039); § (P = 0.008)

Further relevant outcomes (- 180 days)

Proportion of patients with BRVO or CRVO with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days) (19, 20, 55)

Pooled analysis of the GENEVA studies demonstrated that the proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline was statistically significantly greater at days 30, 60 and 90 (P ≤ 0.006) for patients with BRVO and at days 30 and 60 (P < 0.001) for patients with CRVO, Ozurdex versus Sham (Table 20 and Table 21). Significant between-group differences in the pooled analysis for patients with BRVO were 13.4% [95% CI: 7.8%, 19.1%] at day 30, 17.0% [95% CI: 10.5%, 23.5%] at day 60, and 9.0% [95% CI: 2.6%, 15.4%] at day 90. Significant between-group differences in the pooled analysis for patients with CRVO were 14.5% [95% CI: 6.5%, 22.5%] at day 30, and 19.8% [95% CI: 11.0%, 28.7%] at day 60.

Table 20: Proportion of patients with BRVO with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 140)	Sham (n = 130)	Ozurdex (n = 151)	Sham (n = 149)	Ozurdex (n = 291)	Sham (n = 279)
Day 30	21.4%†	6.9%	21.2%§	8.7%	21.3%†	7.9%
Day 60	31.4%†	9.2%	27.8%¶	15.4%	29.6%†	12.5%
Day 90	25.0%‡	13.8%	22.5%	15.4%	23.7%††	14.7%
Day 180	22.9%	20.8%	23.2%	20.1%	23.0%	20.4%

† (P < 0.001); ‡ (P = 0.021); § (P = 0.002); ¶ (P = 0.009); †† (P = 0.006)

Table 21: Proportion of patients with CRVO with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n = 136)	Sham (n = 147)
Day 30	16.4%	8.3%	25.3%†	5.3%	21.3%†	6.8%
Day 60	23.0%	12.5%	33.3%†	5.3%	28.7%†	8.8%
Day 90	16.4%	9.7%	18.7%	10.7%	17.6%	10.2%
Day 180	11.5%	13.9%	24.0%‡	10.7%	18.4%	12.2%

† (P < 0.001); ‡ (P = 0.031)

Ozurdex provides a first-line pharmacological treatment option for those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with MH. Ozurdex also provides a treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment. Therefore, two clinically relevant subgroups reflecting those patients with ME following BRVO considered most suitable for Ozurdex treatment were identified post-hoc - BRVO with MH and BRVO previously treated with laser. In the pooled analysis the proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline was statistically significantly greater at days 30, 60 and 90 (P ≤ 0.028) in both of these subgroups, Ozurdex versus Sham. Significance was also reached at day 180 (P = 0.022) in patients with ME following BRVO previously treated with laser. (Table 22 and Table 23).

Significant between-group differences in the pooled analysis for patients with ME following BRVO with MH were 13.1% [95% CI: 7.0%, 19.3%] at day 30, 18.3% [95% CI: 11.2%, 25.4%] at day 60, and 11.3% [95% CI: 4.4%, 18.1%] at day 90. Significant

between-group differences in the pooled analysis for patients with ME following BRVO previously treated with laser were 19.4% [95% CI: 4.8%, 34.0%] at day 30, 27.8% [95% CI: 13.1%, 42.4%] at day 60, 22.2% [95% CI: 5.8%, 38.7%] at day 90, and 19.4% [95% CI: 3.4%, 35.4%] at day 180.

Table 22: Proportion of patients with BRVO with MH with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 118)	Sham (n = 124)	Ozurdex (n = 137)	Sham (n = 136)	Ozurdex (n = 255)	Sham (n = 260)
Day 30	22.9%†	8.1%	21.2%§	9.6%	22.0%†	8.8%
Day 60	35.6%†	9.7%	28.5%¶	16.9%	31.8%†	13.5%
Day 90	28.0%‡	12.9%	24.1%	16.2%	25.9%†	14.6%
Day 180	23.7%	21.8%	24.1%	21.3%	23.9%	21.5%

† (P ≤ 0.001); ‡ (P = 0.004); § (P = 0.008); ¶ (P = 0.023); †† (P = 0.006)

Table 23: Proportion of patients with BRVO with previous laser treatment with an improvement in BCVA of ≥ 15 letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 21)	Sham (n = 20)	Ozurdex (n = 15)	Sham (n = 16)	Ozurdex (n = 36)	Sham (n = 36)
Day 30	28.6%†	0.0%	13.3%	6.3%	22.2%§	2.8%
Day 60	38.1%‡	0.0%	13.3%	0.0%	27.8%¶	0.0%
Day 90	33.3%	10.0%	20.0%	0.0%	27.8%††	5.6%
Day 180	28.6%	10.0%	20.0%	0.0%	25.0%‡‡	5.6%

† (P =0.021); ‡ (P = 0.003); § (P = 0.028); ¶ (P < 0.001); †† (P = 0.011); ‡‡ (P = 0.022)

Time to achieve an improvement in BCVA of ≥ 15 letters from baseline (- 180 days) (19, 20, 55)

Individual and pooled data from the GENEVA studies demonstrated that the cumulative response rate to achieve ≥ 15 letters BCVA improvement from baseline was statistically significantly different for Ozurdex versus Sham (P ≤ 0.001) (Figure 5, Figure 6 and Figure 7). Kaplan-Meier analysis showed that Ozurdex was associated with a consistently higher response rate versus Sham; with a distinction apparent as early as day 30, with no crossover during the initial 180 day treatment period.

Figure 5: Time to achieve an improvement in BCVA of ≥ 15 letters from baseline (GENEVA 008 - 180 days)

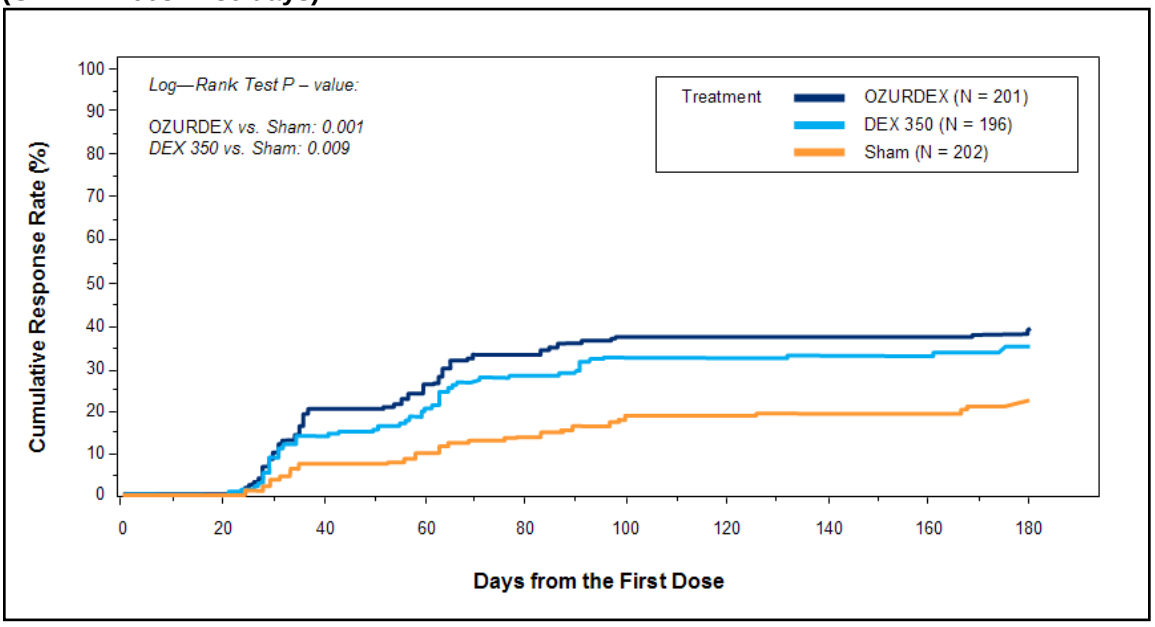


Figure 6: Time to achieve an improvement in BCVA of ≥ 15 letters from baseline (GENEVA 009 - 180 days)

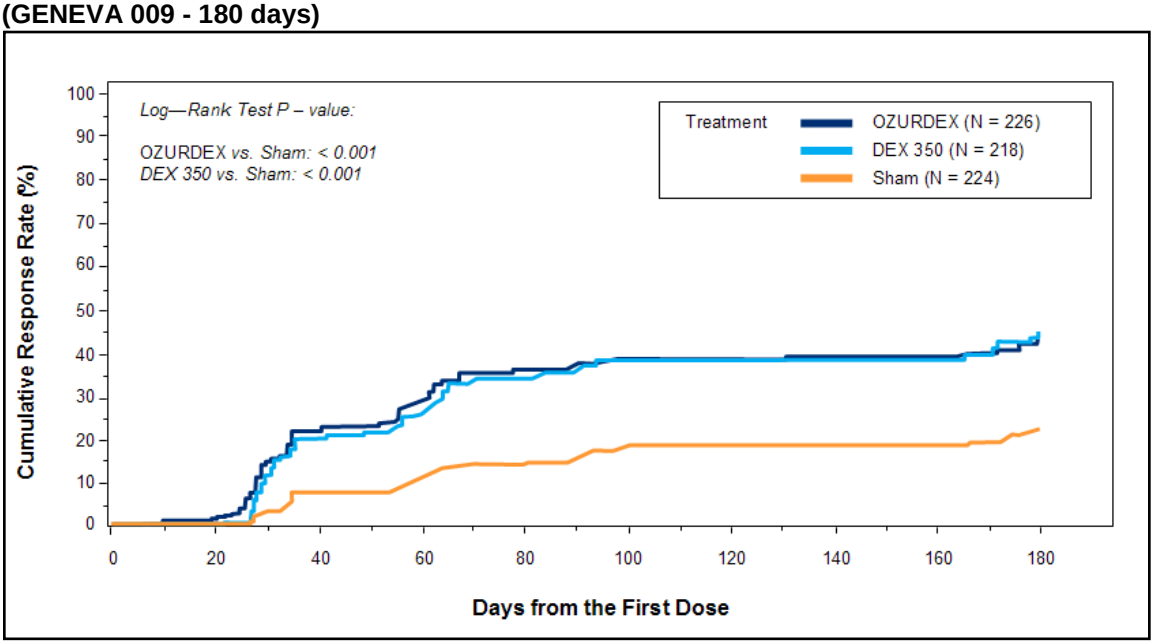
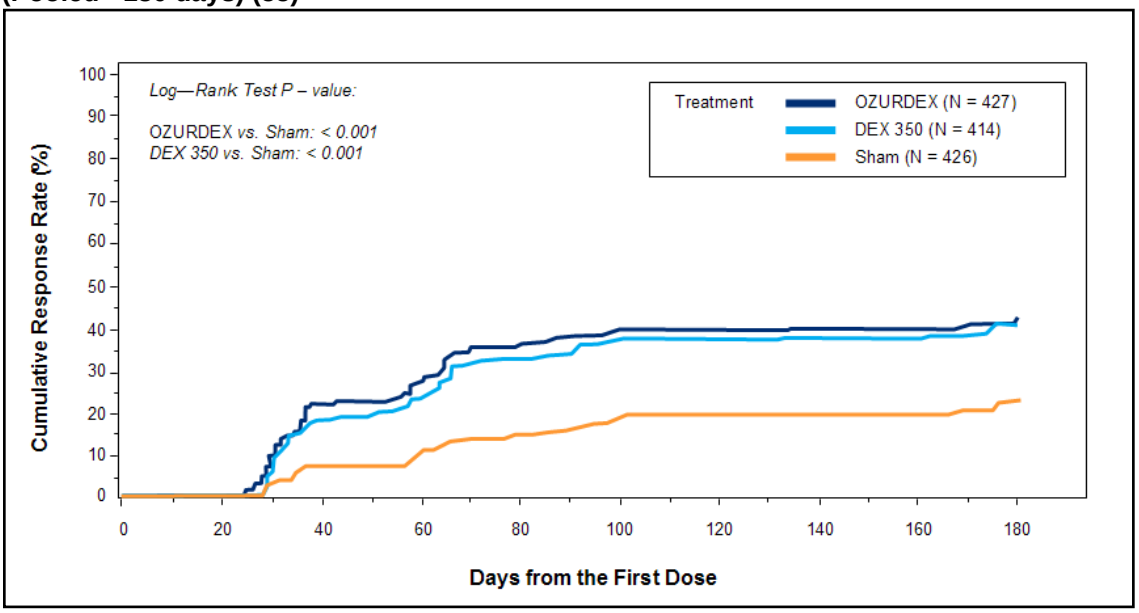


Figure 7: Time to achieve an improvement in BCVA of ≥ 15 letters from baseline (Pooled - 180 days) (55)



Pooled analysis of the GENEVA studies demonstrated that, in patients with BRVO or CRVO, the cumulative response rate was statistically significantly different for Ozurdex versus Sham ($P < 0.001$). Kaplan-Meier analyses showed that response rates in patients with BRVO or CRVO were consistently higher for Ozurdex versus Sham from day 30 to the end of the initial treatment period (day 180) (Figure 8 and Figure 9 respectively).

Figure 8: Time to an improvement in BCVA of ≥ 15 letters from baseline in patients with BRVO (Pooled - 180 days)

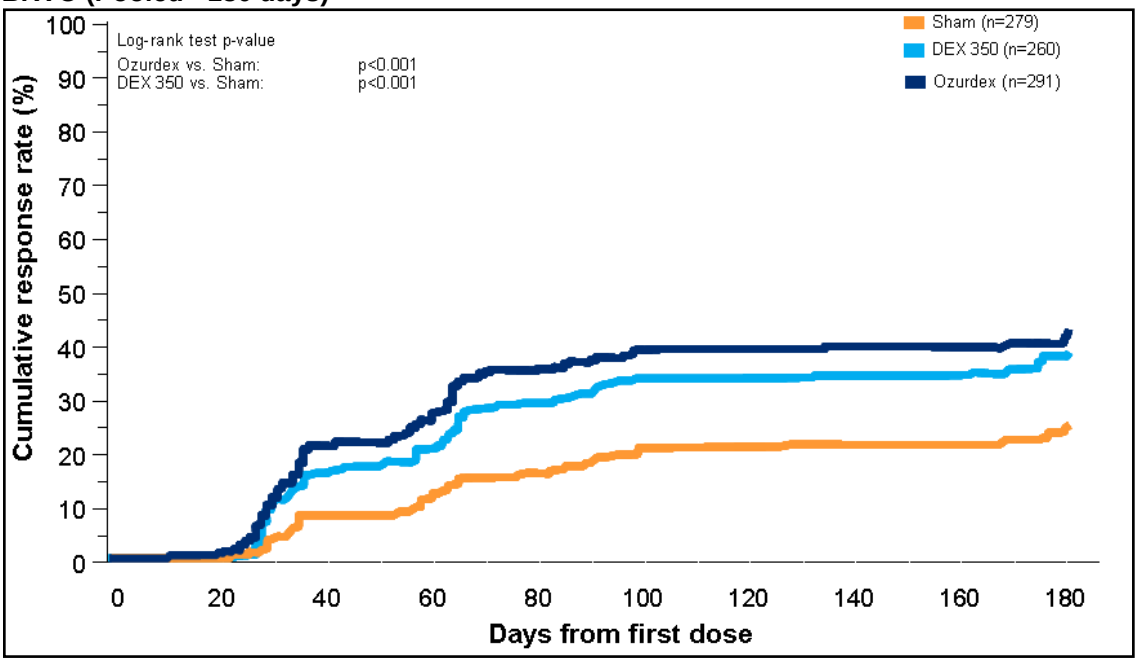
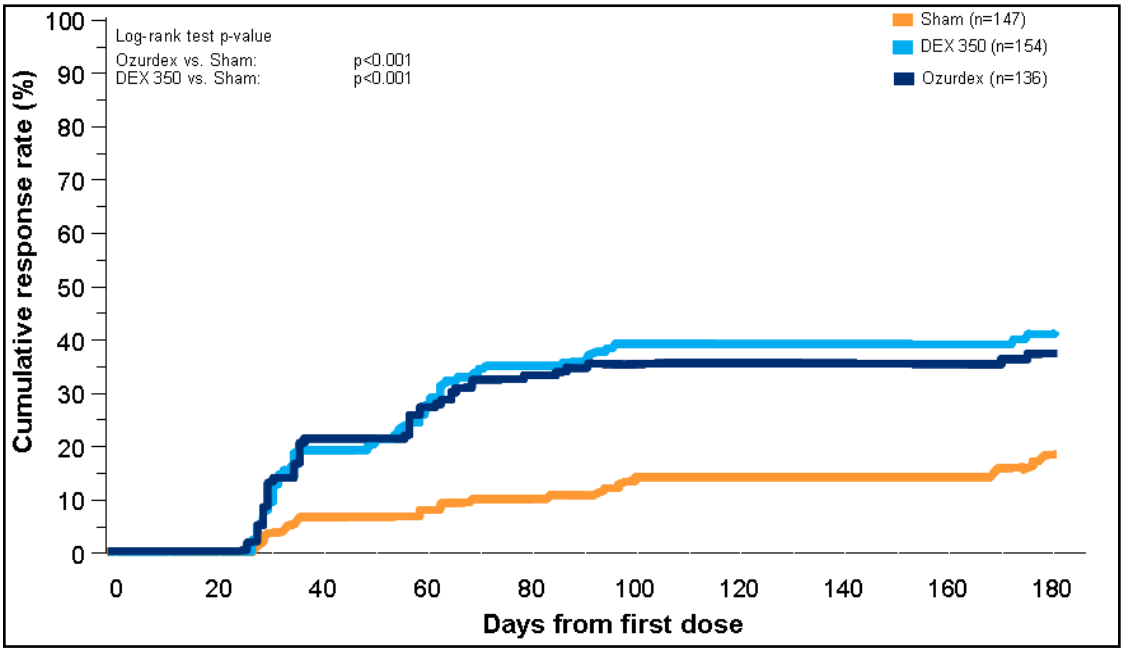


Figure 9: Time to an improvement in BCVA of ≥ 15 letters from baseline in patients with CRVO (Pooled - 180 days)



Mean change from baseline BCVA (- 180 days) (19, 20, 55)

Individual and pooled data from the GENEVA studies demonstrated that the mean change from baseline BCVA in the number of letters read correctly was statistically significantly greater at days 30, 60 and 90, P < 0.001 and day 180 in GENEVA 009 and pooled analysis, P ≤ 0.016) with Ozurdex versus Sham (Table 24). Significant between-group differences in the pooled analysis were 5.5 [95% CI: 4.3, 6.7] at day 30, 6.7 [95% CI: 5.3, 8.1] at day 60, 4.1 [95% CI: 2.6, 5.6] at day 90, and 2.5 [95% CI: 0.7, 4.3] at day 180.

Improvements in the number of letters read correctly peaked at day 60, with a mean increase of ≥ 9.5 letters reported with Ozurdex versus approximately a 3 letter improvement with Sham. At day 90, increases of approximately 7 letters were maintained with Ozurdex, versus a change of approximately 3 letters at every visit with Sham (Table 24).

Table 24: Mean change from baseline BCVA (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Day 30	7.6†	2.5	8.5†	2.7	8.1†	2.6
Day 60	9.5†	3.1	10.1†	3.2	9.8†	3.1
Day 90	7.2†	2.8	7.3†	3.5	7.2†	3.2
Day 180	4.6	2.7	5.5‡	2.5	5.1††	2.6

† (P < 0.001); ‡ (P = 0.016); †† (P = 0.006); ‡‡ (P = 0.005)

Pooled analysis of the GENEVA studies demonstrated that in patients with BRVO, the mean change from baseline BCVA in the number of letters read correctly was statistically significantly greater at days 30, 60, 90, and 180 (P ≤ 0.008) with Ozurdex

versus Sham (Table 25). Significant between-group differences in the pooled analysis were 4.7 [95% CI: 3.4, 6.0] at day 30, 5.3 [95% CI: 3.8, 6.7] at day 60, 3.6 [95% CI: 2.1, 5.2] at day 90, and 2.5 [95% CI: 0.6, 4.3] at day 180.

Table 25: Mean change from baseline BCVA in patients with BRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 140)	Sham (n = 130)	Ozurdex (n = 151)	Sham (n = 149)	Ozurdex (n = 291)	Sham (n = 279)
Day 30	8.4†	3.4	8.6†	4.2	8.5†	3.8
Day 60	10.0†	4.4	10.6†	5.6	10.3†	5.1
Day 90	8.0†	4.1	9.2‡	5.8	8.7†	5.0
Day 180	6.8	4.8	8.0§	5.0	7.4¶	4.9

† (P < 0.001); ‡ (P = 0.001); § (P = 0.018); ¶ (P = 0.008)

Pooled analysis of the GENEVA studies demonstrated that in patients with CRVO, the mean change from baseline BCVA in number of letters read correctly was statistically significantly greater at days 30, 60 and 90 (P ≤ 0.005) with Ozurdex versus Sham (Table 26). Significant between-group differences in the pooled analysis were 6.9 [95% CI: 4.5, 9.3] at day 30, 9.3 [95% CI: 6.5, 12.1] at day 60, and 4.6 [95% CI: 1.4, 7.8] at day 90.

Table 26: Mean change from baseline BCVA in patients with CRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n = 136)	Sham (n = 147)
Day 30	5.9‡	0.9	8.3†	-0.1	7.2†	0.4
Day 60	8.2†	0.7	9.2†	-1.6	8.7†	-0.5
Day 90	5.2§	0.5	3.5¶	-1.2	4.2††	-0.4
Day 180	-0.3	-0.9	0.4	-2.7	0.1	-1.8

† (P < 0.001); ‡ (P = 0.006); § (P = 0.046); ¶ (P = 0.044); †† (P = 0.005)

Categorical change from baseline BCVA, ≥ 15 letters improvement, ≥ 15 letters worsening (- 180 days) (19, 20, 55)

Individual and pooled data from the GENEVA studies demonstrated that a statistically significant categorical change from baseline BCVA was apparent at day 30, 60 and 90 (P < 0.001); additionally in GENEVA 009 and the pooled analysis at day 180 (P ≤ 0.002) with Ozurdex versus Sham (P-values represent change across all categories) (Table 27). A vision loss of ≥ 3-line (15 letters) from baseline was reported in a statistically significantly lower percentage of patients treated with Ozurdex versus Sham at day 30 in the pooled analysis (P = 0.036), day 60 in GENEVA 008 and the pooled analysis (P ≤ 0.037), and days 90 and 180 in GENEVA 009 and the pooled analysis (P ≤ 0.048).

Table 27: Categorical change from baseline BCVA, ≥ 15 letters improvement, ≥ 15 letters worsening (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Day 30	P < 0.001†		P < 0.001†		P < 0.001†	
≥ 15 letters improvement	19.9%	7.4%	22.6%	7.6%	21.3%	7.5%
≥ 5 and < 15 letters improvement	41.8%	32.7%	48.7%	32.6%	45.4%	32.6%
Between -5 to +5 letters	32.3%	46.0%	22.6%	45.1%	27.2%	45.5%
≥ 5 and < 15 letters worsening	5.0%	9.9%	4.9%	12.1%	4.9%	11.0%
≥ 15 letters worsening	1.0%	4.0%	1.3%	2.7%	1.2%	3.3%
Day 60	P < 0.001†		P < 0.001†		P < 0.001†	
≥ 15 letters improvement	28.9%	10.4%	29.6%	12.1%	29.3%	11.3%
≥ 5 and < 15 letters improvement	41.3%	34.2%	47.3%	34.8%	44.5%	34.5%
Between -5 to +5 letters	24.9%	37.6%	19.0%	36.2%	21.8%	36.9%
≥ 5 and < 15 letters worsening	4.5%	13.9%	1.8%	11.2%	3.0%	12.4%
≥ 15 letters worsening	0.5%	4.0%	2.2%	5.8%	1.4%	4.9%
Day 90	P < 0.001†		P < 0.001†		P < 0.001†	
≥ 15 letters improvement	22.4%	12.4%	21.2%	13.8%	21.8%	13.1%
≥ 5 and < 15 letters improvement	39.8%	34.2%	45.1%	37.1%	42.6%	35.7%
Between -5 to +5 letters	27.4%	34.7%	25.7%	29.9%	26.5%	32.2%
≥ 5 and < 15 letters worsening	7.0%	13.4%	4.4%	11.2%	5.6%	12.2%
≥ 15 letters worsening	3.5%	5.4%	3.5%	8.0%	3.5%	6.8%
Day 180	NS		P = 0.002†		P <0.001†	
≥ 15 letters improvement	19.4%	18.3%	23.5%	17.0%	21.5%	17.6%
≥ 5 and < 15 letters improvement	34.8%	27.7%	35.0%	28.6%	34.9%	28.2%
Between -5 to +5 letters	29.4%	30.2%	27.0%	28.6%	28.1%	29.3%
≥ 5 and < 15 letters worsening	10.9%	14.9%	8.0%	13.8%	9.4%	14.3%
≥ 15 letters worsening	5.5%	8.9%	6.6%	12.1%	6.1%	10.6%

Abbreviations: NS, Not statistically significantly different; † Categorical change from baseline statistically significantly greater with Ozurdex compared with Sham

Pooled analysis of the GENEVA studies demonstrated that a statistically significant categorical change from baseline BCVA was apparent at day 30, 60, 90 and 180 with Ozurdex versus Sham in patients with BRVO and day 30, 60 and 90 in patients with CRVO (Table 28 and Table 29, respectively). A vision loss of ≥ 3-line (15 letters) from baseline was reported in a similar percentage of patients treated with Ozurdex versus Sham.

Table 28: Categorical change from baseline BCVA, ≥ 15 letters improvement, ≥ 15 letters worsening in patients with BRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 140)	Sham (n = 130)	Ozurdex (n = 151)	Sham (n = 149)	Ozurdex (n = 291)	Sham (n = 279)
Day 30	-		-		P< 0.001	
≥ 15 letters improvement	21.4%	6.9%	21.2%	8.7%	21.3%	7.9%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	47.4%	36.9%
Between -5 to +5 letters	NR	NR	NR	NR	25.8%	44.1%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	5.5%	9.7%
≥ 15 letters worsening	0.0%	2.3%	0.0%	0.7%	0.0%	1.4%
Day 60	-		-		P< 0.001	
≥ 15 letters improvement	31.4%	9.2%	27.8%	15.4%	29.6%	12.5%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	45.4%	38.0%
Between -5 to +5 letters	NR	NR	NR	NR	22.7%	38.0%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	2.1%	9.7%
≥ 15 letters worsening	0.0%	1.5%	0.7%	2.0%	0.3%	1.8%
Day 90	-		-		P< 0.001	
≥ 15 letters improvement	25.0%	13.8%	22.5%	15.4%	23.7%	14.7%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	46.4%	40.1%
Between -5 to +5 letters	NR	NR	NR	NR	24.1%	31.5%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	4.5%	10.4%
≥ 15 letters worsening	2.1%	2.3%	0.7%	4.0%	1.4%	3.2%
Day 180	-		-		P= 0.002	
≥ 15 letters improvement	22.9%	20.8%	23.2%	20.1%	23.0%	20.4%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	41.6%	30.8%
Between -5 to +5 letters	NR	NR	NR	NR	26.8%	29.7%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	6.2%	13.6%
≥ 15 letters worsening	3.6%	3.8%	1.3%	6.7%	2.4%	5.4%

Abbreviations: NR, Not reported

Table 29: Categorical change from baseline BCVA, ≥ 15 letters improvement, ≥ 15 letters worsening in patients with CRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n = 136)	Sham (n = 147)
Day 30	-		-		P < 0.001	
≥ 15 letters improvement	16.4%	8.3%	25.3%	5.3%	21.3%	6.8%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	41.2%	24.5%
Between -5 to +5 letters	NR	NR	NR	NR	30.1%	48.3%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	3.7%	13.6%
≥ 15 letters worsening	3.3%	6.9%	4.0%	16.7%	3.7%	6.8%
Day 60	-		-		NS	
≥ 15 letters improvement	23.0%	12.5%	33.3	5.3%	28.7%	8.8%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	42.6%	27.9%
Between -5 to +5 letters	NR	NR	NR	NR	19.9%	34.7%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	5.1%	17.7%
≥ 15 letters worsening	1.6%	8.3%	5.3%	13.3%	3.7%	10.9%
Day 90	-		-		P = 0.003	
≥ 15 letters improvement	16.4%	9.7%	18.7	10.7%	17.6%	10.2%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	34.6%	27.2%
Between -5 to +5 letters	NR	NR	NR	NR	31.6%	33.3%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	8.1%	15.6%
≥ 15 letters worsening	6.6%	11.1%	9.3%	16.0%	8.1%	13.6%
Day 180	-		-		NS	
≥ 15 letters improvement	11.5%	13.9%	24.0%	10.7%	18.4%	12.2%
≥ 5 and < 15 letters improvement	NR	NR	NR	NR	20.6%	23.1%
Between -5 to +5 letters	NR	NR	NR	NR	30.9%	28.6%
≥ 5 and < 15 letters worsening	NR	NR	NR	NR	16.2%	15.6%
≥ 15 letters worsening	9.8%	18.1%	17.3%	22.7%	14.0%	20.4%

Abbreviations: NR, Not reported; NS, Not statistically significantly different

Proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days) (19, 20, 55)

Individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline was statistically significantly higher at days 30, 60 and 90 (P ≤ 0.010); and additionally in GENEVA 009 and the pooled analysis at day 180 (P ≤ 0.037) with Ozurdex versus Sham (Table 30). Significant between-group differences in the pooled analysis were 26.2% [95% CI: 20.3%, 32.1%] at day 30, 25.0% [95% CI: 18.7%, 31.3%] at day 60, 15.2% [95% CI: 8.8%, 21.5%] at day 90, and 6.7% [95% CI: 0.4%, 13.0%] at day 180.

Table 30: Proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 008		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Day 30	41.3%†	18.3%	45.6%†	16.5%	43.6%†	17.4%
Day 60	49.3%†	25.7%	52.7%†	26.3%	51.1%†	26.1%
Day 90	39.3%‡	27.2%	47.3%†	29.5%	43.6%†	28.4%
Day 180	32.3%	29.7%	40.3%§	29.9%	36.5%¶	29.8%

† (P < 0.001); ‡ (P = 0.010), § (P = 0.021); ¶ (P = 0.037)

Pooled analysis of the GENEVA studies demonstrated that the proportion of patients with BRVO with an improvement in BCVA of ≥ 10-letters from baseline was statistically significantly higher at all time points during the initial treatment period (P ≤ 0.041) with Ozurdex versus Sham (Table 31). Significant between-group differences in the pooled analysis were 22.5% [95% CI: 15.2%, 29.9%] at day 30, 22.5.% [95% CI: 14.7%, 30.3%] at day 60, 15.9% [95% CI: 8.0%, 23.8%] at day 90, and 8.3% [95% CI: 0.4%, 16.2%] at day 180.

Table 31: Proportion of patients with BRVO with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 140)	Sham (n = 130)	Ozurdex (n = 151)	Sham (n = 149)	Ozurdex (n = 291)	Sham (n = 279)
Day 30	42.9%	20.0%	42.4%†	20.1%	42.6%†	20.1%
Day 60	51.4%	28.5%	52.3%†	30.2%	51.9%†	29.4%
Day 90	42.9%	28.5%	51.0%‡	33.6%	47.1%†	31.2%
Day 180	37.9%	33.1%	44.0%§	32.9%	41.2%††	33.0%

† (P < 0.001); ‡ (P = 0.002); § (P = 0.041); ¶ (P = 0.037); †† (P = 0.041)

Pooled analysis of the GENEVA studies demonstrated that the proportion of patients with CRVO with a BCVA improvement of ≥ 10-letters from baseline was statistically significantly higher at days 30, 60 and 90 (P ≤ 0.17) with Ozurdex versus Sham (Table 32). Significant between-group differences in the pooled analysis were 33.3% [95% CI: 23.4%, 43.3%] at day 30, 29.5% [95% CI: 19.0%, 40.1%] at day 60, and 12.9% [95% CI: 2.3%, 23.5%] at day 90.

Table 32: Proportion of patients with CRVO with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n = 136)	Sham (n = 147)
Day 30	37.7%§	15.3%	52.0%†	9.3%	45.6%†	12.2%
Day 60	44.3%¶	20.8%	53.3%†	18.7%	49.3%†	19.7%
Day 90	31.1%	25.0%	40.0%††	21.3%	36.0%‡	23.1%
Day 180	19.7%	23.6%	32.0%	24.0%	26.5%	23.8%

† (P < 0.001); ‡ (P = 0.017); § (P =0.003); ¶ (P = 0.004); †† (P = 0.013)

Contrast sensitivity measured using the Pelli-Robson chart (- 180 days)(19, 20)

Individual data from GENEVA 008 and 009 demonstrated that there were no statistically significant differences between treatment groups at baseline or day 180

in both the mean number and change from baseline in the number of letters read correctly in the study eye using contrast sensitivity (Table 33, Table 35, and Table 37).

Individual data from GENEVA 008 and 009 demonstrated that > 35% of patients in both treatment groups showed a change of between -2 and +2 letters (considered no change) (Table 34, Table 36, and Table 38).

Table 33: Contrast sensitivity: mean change from baseline in number of letters read correctly (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 183)	Sham (n = 179)	Ozurdex (n = 212)	Sham (n = 202)	Ozurdex (n = 395)	Sham (n = 381)
Day 180	1.8	1.3	1.2	1.1	1.5	1.2

Table 34: Contrast sensitivity: categorical change from baseline in number of letters read correctly (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 183)	Sham (n = 179)	Ozurdex (n = 212)	Sham (n = 202)	Ozurdex (n = 395)	Sham (n =381)
Day 180						
≥ 15 letters improvement	1.6%	2.2%	1.9%	0.5%	1.8%	1.3%
≥ 9 and ≤ 14-letters improvement	8.2%	3.9%	2.8%	4.9%	5.3%	4.5%
≥ 3 and ≤ 8-letters improvement	31.1%	32.4%	27.4%	32.5%	29.1%	32.5%
Between -2 to +2 letters	42.6%	43.0%	53.8%	42.4%	48.6%	42.5%
≥ 3 and ≤ 8-letters worsening	11.5%	14.5%	10.8%	16.7%	11.1%	15.7%
≥ 9 and ≤ 14-letters worsening	3.8%	2.2%	2.4%	1.0%	3.0%	1.6%
≥ 15 letters worsening	1.1%	1.7%	0.9%	2.0%	1.0%	1.8%

Table 35: Contrast sensitivity: mean change from baseline in number of letters read correctly in patients with BRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 130)	Sham (n = 113)	Ozurdex (n = 144)	Sham (n = 134)	Ozurdex (n = 274)	Sham (n = 247)
Day 180	2.1	1.6	1.5	1.2	1.8	1.4

Table 36: Contrast sensitivity: categorical change from baseline in number of letters read correctly in patients with BRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 130)	Sham (n = 113)	Ozurdex (n = 144)	Sham (n = 134)	Ozurdex (n=274)	Sham (n=247)
Day 180						
≥ 15 letters improvement	1.5%	1.8%	2.1%	0.0%	1.8%	0.8%
≥ 9 and ≤ 14-letters improvement	10.0%	3.5%	3.5%	5.2%	6.6%	4.5%
≥ 3 and ≤ 8-letters improvement	28.5%	36.3%	24.3%	33.6%	26.3%	34.8%
Between -2 to +2 letters	45.4%	41.6%	59.0%	41.0%	52.6%	41.3%
≥ 3 and ≤ 8-letters worsening	12.3%	14.2%	10.4%	17.9%	11.3%	16.2%
≥ 9 and ≤ 14-letters worsening	0.8%	2.7%	0.7%	0.7%	0.7%	1.6%
≥ 15 letters worsening	1.5%	0.0%	0.0%	1.5%	0.7%	0.8%

Table 37: Contrast sensitivity: mean change from baseline in number of letters read correctly in patients with CRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n = 136)	Sham (n = 147
Day 180	1.1	0.7	0.4	1.0	0.7	0.8

Table 38: Contrast sensitivity: categorical change from baseline in number of letters read correctly in patients with CRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n =136)	Sham (n=147)
Day 180						
≥ 15 letters improvement	1.9%	3.0%	1.5%	1.5%	1.7%	2.2%
≥ 9 and ≤ 14-letters improvement	3.8%	4.5%	1.5%	4.4%	2.5%	4.5%
≥ 3 and ≤ 8-letters improvement	37.7%	25.8%	33.8%	30.9%	35/5%	28.4%
Between -2 to +2 letters	35.8%	45.5%	42.6%	44.1%	39.7%	44.8%
≥ 3 and ≤ 8-letters worsening	9.4%	15.2%	11.8%	14.7%	10.7%	14.9%
≥ 9 and ≤ 14-letters worsening	11.3%	1.5%	5.9%	1.5%	8.3%	1.5%
≥ 15 letters worsening	0.0%	4.5%	2.9%	2.9%	1.7%	3.7%

Retinal thickness measured by optical coherence tomography (OCT) (-180 days)(19, 20, 55, 56)

Individual and pooled data from the GENEVA studies demonstrated that mean central retinal thickness was statistically significantly less, and mean decreases in retinal thickness were significantly greater, at day 90 ($P < 0.001$) with Ozurdex versus Sham (Table 39).

Table 39: Retinal thickness measured by OCT (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Baseline	548.9 µm	534.4 µm	573.6 µm	542.5 µm	562.0 µm	538.6 µm
Day 90†	-199.3 µm‡	-78.2 µm	-215.6 µm‡	-91.1 µm	-207.9 µm‡	-85.0 µm
Day 180†	-105.0 µm	-110.3 µm	-132.1 µm	-127.4 µm	-119.3 µm	-119.3 µm

† Mean change from baseline; ‡ (P < 0.001)

Pooled analysis of the GENEVA studies demonstrated that in patients with BRVO or CRVO, mean decreases from baseline in central retinal thickness were statistically significantly greater at day 90 (P < 0.001) with Ozurdex versus Sham (Table 40 and Table 41, respectively).

Table 40: Retinal thickness measured by OCT in patients with BRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 140)	Sham (n = 130)	Ozurdex (n = 151)	Sham (n = 149)	Ozurdex (n = 291)	Sham (n = 279)
Baseline	509.4 µm	489.0 µm	534.2 µm	501.9 µm	522.3 µm	495.8 µm
Day 90†	-160.5 µm‡	-71.4 µm	-206.2 µm‡	-93.4 µm	-184.2 µm‡	-83.1 µm
Day 180†	-101.1 µm	-107.7 µm	-147.8 µm	-127.5 µm	-125.3 µm	-118.2 µm

† Mean change from baseline; ‡ (P < 0.001)

Table 41: Retinal thickness measured by OCT in patients with CRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 61)	Sham (n = 72)	Ozurdex (n = 75)	Sham (n = 75)	Ozurdex (n = 136)	Sham (n = 147)
Baseline	639.7 µm	618.0 µm	654.1 µm	621.5 µm	647.6 µm	619.8 µm
Day 90†	-288.5 µm‡	-90.8 µm	-234.9 µm‡	-86.5 µm	-259.1 µm‡	-88.6 µm
Day 180†	-113.9 µm	-115.2 µm	-99.9 µm	-127.1	-118.2 µm	-125.3 µm

† Mean change from baseline; ‡ (P < 0.001)

Proportion of patients with at least a 5-point improvement from baseline in Visual Functioning Questionnaire-25 (VFQ-25)[c] (- 180 days) (19, 20, 55)

Individual data from GENEVA 009 and pooled data from the GENEVA studies demonstrated that a statistically significantly higher proportion of patients achieved a 5-point improvement from baseline in multiple VFQ-25 subscales with Ozurdex versus Sham. There were no statistically significant differences between treatment groups in GENEVA 008. Clinically meaningful and statistically significant between-group differences in the GENEVA studies are shown in Table 42. In GENEVA 009 and the pooled analysis, the composite score was statistically significantly greater with Ozurdex versus Sham at day 90 for the 5-point improvement in VFQ-25 (P ≤ 0.05).

[c] The VFQ-25 is a shortened version of the 51-item National Eye Institute (NEI) VFQ Field Test Version and consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item.

Table 42: Statistically significant 5-Point improvements in VFQ-25

Visit	GENEVA 009	Pooled
	Ozurdex (n = 226) versus Sham (n = 224)	Ozurdex (n = 427) versus Sham (n = 426)
General Vision	P < 0.05 at days 30, 60, 90 and 180	P < 0.05 at days 30, 60 and 90
Difficulty with near vision	P < 0.05 at days 30, 60 and 90	P < 0.05 at day 90
Limitations in social functioning†	P < 0.05 at days 30, 60 and 90	P < 0.05 at days 60 and 90
Driving difficulties	P < 0.05 at day 30	NS

Abbreviations: NS, Not statistically significantly different; † due to vision

Proportion of patients with at least a 1-grade improvement from baseline in VFQ-25 response for general vision (- 180 days) (19, 20, 55)

Individual data from GENEVA 009 and pooled data from the GENEVA studies demonstrated that the proportion of patients with at least 1-grade improvement in general vision was statistically significant at days 30, 60 and 90 (P ≤ 0.015), and additionally in GENEVA 009 at day 180 (P = 0.004) with Ozurdex versus Sham. There were no statistically significant differences between treatment groups in GENEVA 008. A 1-grade improvement is considered to be the minimum level of change that can be assessed by a patient in their visual functioning as a result of vision in both eyes. In GENEVA 009, more than 40% of patients treated with Ozurdex showed at least a 1-grade improvement in general vision. This is considered clinically relevant as the majority of patients in GENEVA received treatment in their worse-seeing eye (WSE) and health-related quality of life (HRQL) is ordinarily considered to be driven by BCVA in the better seeing eye. The exclusion criteria for the GENEVA studies prevented patients with a BCVA < 34 in the non-study eye from entering the study . Therefore, the proportion of patients treated in their WSE was higher in the GENEVA studies (97.4%) than expected in clinical practice (90%, expert opinion (54)).

Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in patients with longer duration of ME > 90 days (- 180 days) (19, 20, 55)

Individual and pooled data from the GENEVA studies demonstrated that in patients with a duration of ME > 90 days, a statistically significantly higher proportion achieved a ≥ 15 letters improvement in BCVA at days 30, 60 and 90 (P ≤ 0.033); and additionally in GENEVA 009 at day 180 (P = 0.013) with Ozurdex versus Sham (Table 43).

Table 43: Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline (longer duration of ME > 90 days) (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 173)	Sham (n = 177)	Ozurdex (n = 181)	Sham (n = 183)	Ozurdex (n = 354)	Sham (n = 360)
Day 30	18.5%†	6.2%	23.2%†	6.0%	20.9%†	6.1%
Day 60	27.2%†	8.5%	27.1%†	11.5%	27.1%†	10.0%
Day 90	20.2%‡	10.7%	21.5%§	13.1%	20.9%¶	11.9%
Day 180	17.3%	17.5%	23.8%††	13.7%	20.6%	15.6%

† (P < 0.001); ‡(P = 0.014); § (P = 0.033); ¶ (P = 0.001): †† (P = 0.013);

Pooled data from the GENEVA studies and individual data from GENEVA 008 demonstrated that in patients with BRVO with a duration of ME > 90 days, a statistically significantly higher proportion achieved a ≥ 15 letters improvement in BCVA at days 30, 60 and 90 (P ≤ 0.049); and in GENEVA 009 at day 30 (P = 0.004) with Ozurdex versus Sham (Table 44).

Table 44: Proportion of patients with BRVO with an improvement in BCVA of ≥ 15 letters from baseline (longer duration of ME > 90 days) (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 120)	Sham (n = 116)	Ozurdex (n = 121)	Sham (n = 119)	Ozurdex (n = 241)	Sham (n = 235)
Day 30	19.2%†	6.0%	20.7%¶	7.6%	19.9%‡	6.8%
Day 60	29.2%‡	7.8%	24.0%	16.0%	26.6%‡	11.9%
Day 90	21.7% §	12.1%	22.3%	16.0%	22.0%††	14.0%
Day 180	20.0%	19.8%	24.0%	17.6%	22.0%	18.7%

† (P = 0.002); ‡(P < 0.001); § (P = 0.049); ¶ (P = 0.004); †† (P = 0.024)

Pooled data from the GENEVA studies and individual data from GENEVA 009 demonstrated that in patients with CRVO with a duration of ME > 90 days, a statistically significantly higher proportion achieved a ≥ 15 letters improvement in BCVA at days 30, 60 and 90 (P ≤ 0.049) (and day 180 in GENEVA 009, P = 0.007) with Ozurdex versus Sham (Table 45).

Table 45: Proportion of patients with CRVO with an improvement in BCVA of ≥ 15 letters from baseline (longer duration of ME > 90 days) (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 53)	Sham (n = 61)	Ozurdex (n = 60)	Sham (n = 64)	Ozurdex (n = 113)	Sham (n = 125)
Day 30	17.0%	6.6%	28.3%†	3.1%	23.0%†	4.8%
Day 60	22.6%	9.8%	33.3%†	3.1%	28.3%†	6.4%
Day 90	17.0%	8.2%	20.0%‡	7.8%	18.6%§	8.0%
Day 180	11.3%	13.1%	23.3%¶	6.3%	17.7%	9.6%

† (P < 0.001); ‡(P = 0.049); § (P = 0.015); ¶ (P = 0.007)

In BRVO and CRVO, the longer the duration of ME, the less likely it is to resolve spontaneously. There are no clear indicators at baseline to suggest which patients are more likely to experience spontaneous improvements; therefore it is important to treat ME early. In patients with chronic ME (> 8 months duration) (29), permanent retinal damage and vision loss may occur (14, 16, 29, 30). Haemorrhages into the vitreous from neovascularisations are more likely to affect eyes with chronic ME and

often result in poor final VA and a less favourable prognosis (15). As such, the longer the duration of ME, the more challenging the treatment (31). In order to achieve optimal improvements in VA or to prevent further vision loss, it is important to treat ME promptly.

[redacted]

Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline in patients with shorter duration of ME ≤ 90 days (- 180 days) (19, 20, 55)

Pooled data from the GENEVA studies and individual data from GENEVA 009 demonstrated that in patients with a duration of ME ≤ 90 days, a statistically significantly higher proportion achieved a ≥ 15 letters improvement in BCVA at day 60 (P ≤ 0.015) with Ozurdex versus Sham (Table 46).

Table 46: Proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline (shorter duration of ME ≤ 90 days) (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 28)	Sham (n = 25)	Ozurdex (n = 45)	Sham (n = 41)	Ozurdex (n = 73)	Sham (n = 66)
Day 30	28.6%	16.0%	20.0%	14.6%	23.3%	15.2%
Day 60	39.3%	24.0%	37.8%†	14.6%	38.4‡	18.2%
Day 90	35.7%	24.0%	20.0%	17.1%	26.0%	19.7%
Day 180	32.1%	24.0%	22.2%	29.3%	26.0%	27.3%

† (P = 0.015); ‡ (P = 0.009)

Pooled data from the GENEVA studies and individual data from GENEVA 009 demonstrated that in patients with a duration of ME ≤ 90 days, a statistically significantly higher proportion achieved a ≥ 15 letters improvement in BCVA at day 60 (P ≤ 0.020) with Ozurdex versus Sham (Table 47).

Table 47: Proportion of patients with BRVO with an improvement in BCVA of ≥ 15 letters from baseline (shorter duration of ME ≤ 90 days) (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 20)	Sham (n = 14)	Ozurdex (n = 30)	Sham (n = 30)	Ozurdex (n = 50)	Sham (n = 44)
Day 30	35.0%	14.3%	23.3%	13.3%	28.0%	13.6%
Day 60	45.0%	21.4%	40.0%†	13.3%	42.0%‡	15.9%
Day 90	45.0%	28.6%	23.3%	13.3%	32.0%	18.2%
Day 180	40.0%	28.6%	20.0%	26.7%	28.0%	27.3%

† (P = 0.020); ‡ (P = 0.006)

Individual and pooled data from the GENEVA studies demonstrated that in patients with a duration of ME ≤ 90 days, a similar proportion achieved a ≥ 15 letters improvement in BCVA at all timepoints with Ozurdex versus Sham (Table 47).

Table 48: Proportion of patients with CRVO with an improvement in BCVA of ≥ 15 letters from baseline (shorter duration of ME ≤ 90 days) (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 8)	Sham (n = 11)	Ozurdex (n = 15)	Sham (n = 11)	Ozurdex (n = 23)	Sham (n = 22)
Day 30	12.5%	18.2%	13.3%	18.2%	13.0%	18.2%
Day 60	25.0%	27.3%	33.3%	18.2%	30.4%	22.7%
Day 90	12.5%	18.2%	13.3%	27.3%	13.0%	22.7%
Day 180	12.5%	18.2%	26.7%	36.4%	21.7%	27.3%

Post-hoc pooled analysis of patients achieving a BCVA of ≥ 69-letters or ≤ 38-letters in considering specific populations used in the economic model (- 180 days) (58)

The economic model described in Section 6 considers the healthstates of specific populations of patients with CRVO, BRVO with MH and BRVO with previous laser treatment.

A post-hoc analysis was conducted to establish the proportion of patients in the GENEVA studies that achieved the following healthstates: BCVA of ≥ 69-letters (Snellen fraction ≤ 20/40) or ≤ 38-letters (Snellen fraction ≥ 20/200) at the end of initial treatment period (re-treated plus single treated population).

The post-hoc analysis of pooled data from the GENEVA studies (modified ITT) demonstrated that a statistically significantly higher proportion of patients with CRVO achieved a BCVA ≥ 69 letters (Snellen fraction ≤ 20/40) at days 30 and 60 (P ≤ 0.004) with Ozurdex versus Sham (Table 49). Furthermore, a statistically significantly lower proportion of patients with CRVO had a BCVA ≤ 38 letters (Snellen fraction ≥ 20/200) at days 30 and 60 (P ≤ 0.028) with Ozurdex versus Sham (Table 49). Significant between-group differences in the pooled analysis for BCVA ≥ 69 letters were 14.5% [95% CI: 4.6%, 24.4%] at day 30, and 15.2% [95% CI: 5.4%, 25.0%] at day 60. Significant between-group differences in the pooled analysis for BCVA ≤ 38-letters were -9.3% [95% CI: -17.4%, -1.2%] at day 30, and -14.2% [95% CI: -22.3%, -6.2%] at day 60.

Table 49: Proportion of patients with CRVO with a BCVA of ≥ 69-letters or ≤ 38-letters (- 180 days)

Visit	CRVO			
	≥ 69-letters		≤ 38-letters	
	Ozurdex (n = 133)	Sham (n = 147)	Ozurdex (n = 133)	Sham (n = 147)
Day 30	30.8%†	16.3%	9.8%§	19.0%
Day 60	30.8%‡	15.6%	7.5%¶	21.8%
Day 90	27.8%	18.4%	17.3%	23.1%
Day 180	20.3%	23.8%	22.6%	28.6%

† (P = 0.004); ‡ (P = 0.003); § (P = 0.028); ¶ (P < 0.001)

Additionally, in patients with BRVO with MH, a statistically significantly higher proportion of patients achieved a BCVA ≥ 69 letters (Snellen fraction ≤ 20/40) at days 30, 60 and 90 (P ≤ 0.001) with Ozurdex versus Sham (Table 50). A statistically significantly lower proportion of patients in this group achieved a BCVA ≤ 38 letters (Snellen fraction ≥ 20/200) at day 60 (P = 0.021) with Ozurdex versus Sham (Table 50). Significant between-group differences in the pooled analysis for BCVA ≥ 69 letters were 17.3% [95% CI: 9.5%, 25.0%] at day 30, 15.9% [95% CI: 7.6%, 24.1%] at day 60, and 14.3% [95% CI: 6.1%, 22.4%] at day 90. Significant between-group differences in the pooled analysis for BCVA ≤ 38 letters were -4.2% [95% CI: -7.7%, 0.3%] at day 60.

In the patients with BRVO who had received previous laser treatment a similar proportion of patients achieved a BCVA ≥ 69 letters (Snellen fraction ≤ 20/40) and ≤ 38 letters (Snellen fraction ≥ 20/200) with Ozurdex versus Sham (Table 50). The only exception was reported at day 60, where a statistically significantly higher proportion of patients achieved a BCVA ≥ 69 letters (Snellen fraction ≤ 20/40) (P = 0.023) with Ozurdex versus Sham (Table 50). Significant between-group differences in the pooled analysis for BCVA ≥ 69 letters were 25.0% [95% CI: 4.2%, 45.8%] at day 60.

Table 50: Proportion of patients with BRVO with MH or previous laser treatment with BCVA of ≥ 69-letters or ≤ 38-letters (- 180 days)

Visit	BRVO with MH				BRVO with previous laser treatment			
	≥ 69-letters		≤ 38-letters		≥ 69-letters		≤ 38-letters	
	Ozurdex (n=255)	Sham (n=260)	Ozurdex (n=255)	Sham (n=260)	Ozurdex (n=36)	Sham (n=36)	Ozurdex (n=36)	Sham (n=36)
Day 30	38.4%†	21.2%	3.9%	6.5%	30.6%	16.7%	8.3%	5.6%
Day 60	45.5%†	29.6%	2.4%‡	6.5%	44.4%§	19.4%	8.3%	5.6%
Day 90	41.6%†	27.3%	3.9%	7.7%	38.9%	19.4%	8.3%	8.3%
Day 180	36.5%	29.6%	5.9%	9.2%	22.2%	13.9%	13.9%	11.1%

† (P ≤ 0.001); ‡ (P= 0.021); § (P = 0.023)

GENEVA studies – Retreated population (- 360 days)

Executive Summary – retreated population

- During the OL extension, efficacy outcomes generally favoured Ozurdex/Ozurdex versus Sham/Ozurdex:
    - The cumulative response rate for time to achieve ≥ 15 letters BCVA improvement remained consistently higher at all time points with Ozurdex/Ozurdex versus Sham/Ozurdex (P ≤ 0.005).
    - Mean change from baseline BCVA was statistically significantly greater during early OL visits (days 210 and 240) with Ozurdex/Ozurdex versus Sham/Ozurdex (P ≤ 0.034 [P ≤ 0.004 all RVO pooled]), excluding day 240 in patients with BRVO.
- Throughout the GENEVA studies, the beneficial effects of Ozurdex versus Sham were demonstrated not only in terms of a ≥ 15-letter improvement in BCVA but also via the prevention of a ≥ 15-letter worsening; this drove a mean change in BCVA of 9.6 letters at peak.
- In all patients, an improvement in BCVA of ≥ 10-letters from baseline was achieved in a statistically significantly greater proportion of patients during early OL visits (days 210 and 240) with Ozurdex versus Sham (P ≤ 0.025); a similar trend was observed in patients with BRVO or CRVO.
- Ozurdex treatment was associated with long-lasting and significant improvements in the BCVA of patients with ME following BRVO or CRVO.
- [redacted]
- [redacted]

The OL extension period was primarily for safety; however, the pooled 12-month efficacy data for the re-treated population are presented within this section for completeness. Efficacy results presented within this submission focus on the UK licensed dose of DEX-PS-DDS (700 µg, Ozurdex), therefore DEX 350 µg/Ozurdex is shown only for patient disposition. The single-treated population are not considered within the clinical sections; these patients did not receive a second injection of Ozurdex at day 180, efficacy data for these patients are captured within the ITT population to day 180 (initial treatment period). The single-treated population was used only for economic modelling purposes to inform how many patients were not retreated at Day 180 (and were classified as resolved or not resolved according to OCT status, see Table 15 and Table 16).

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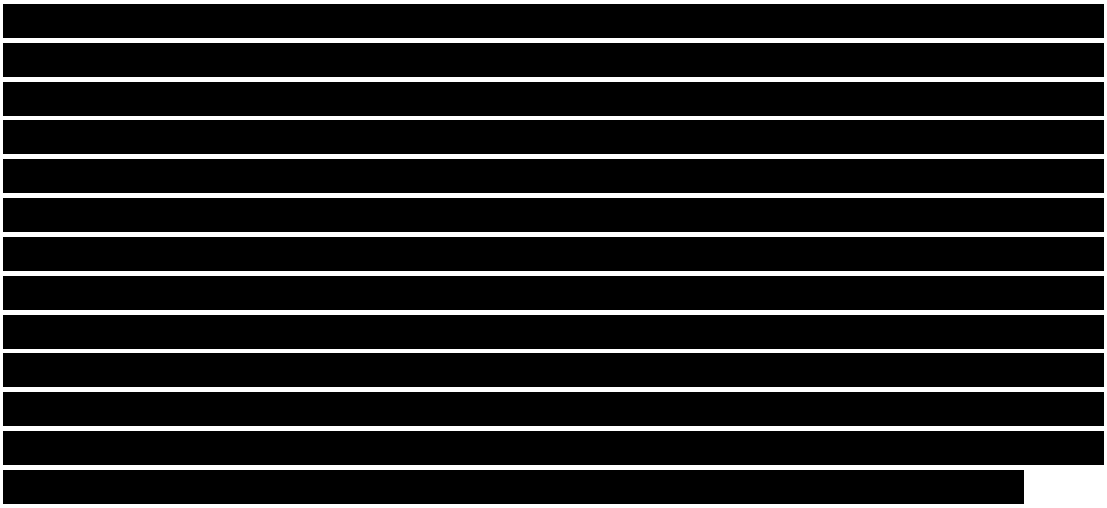

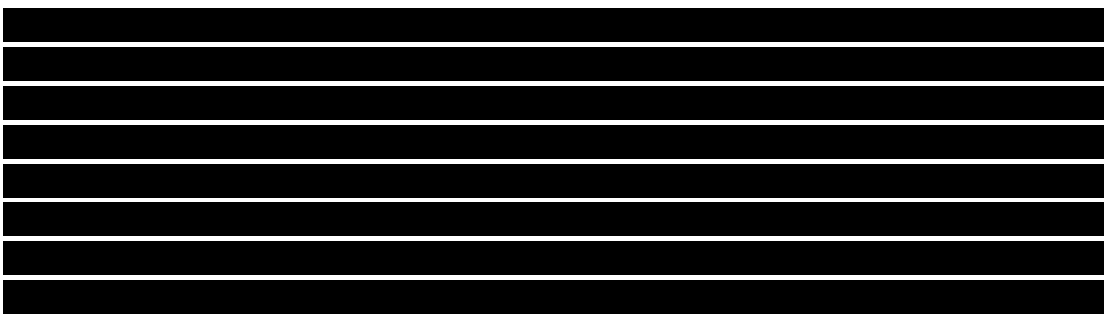

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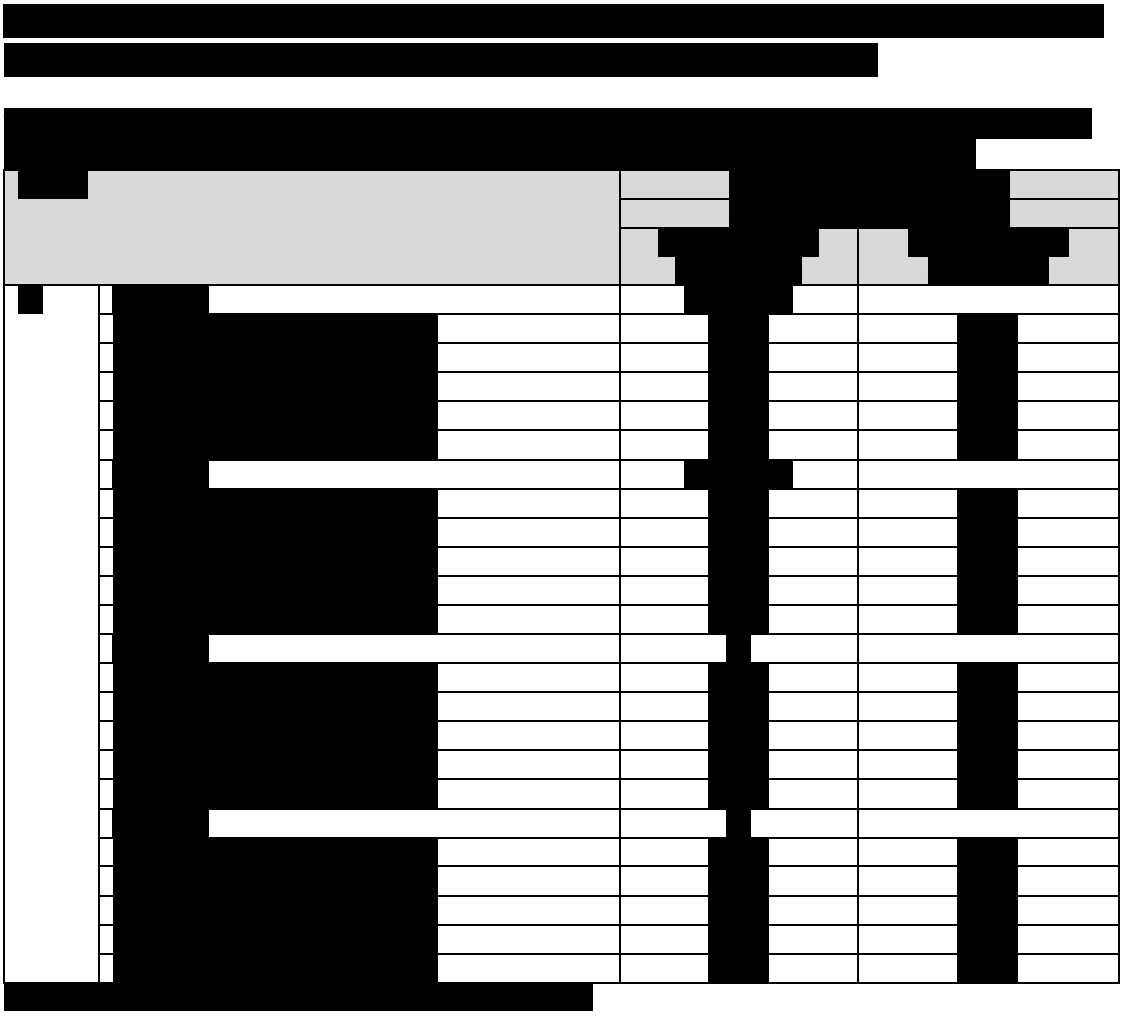

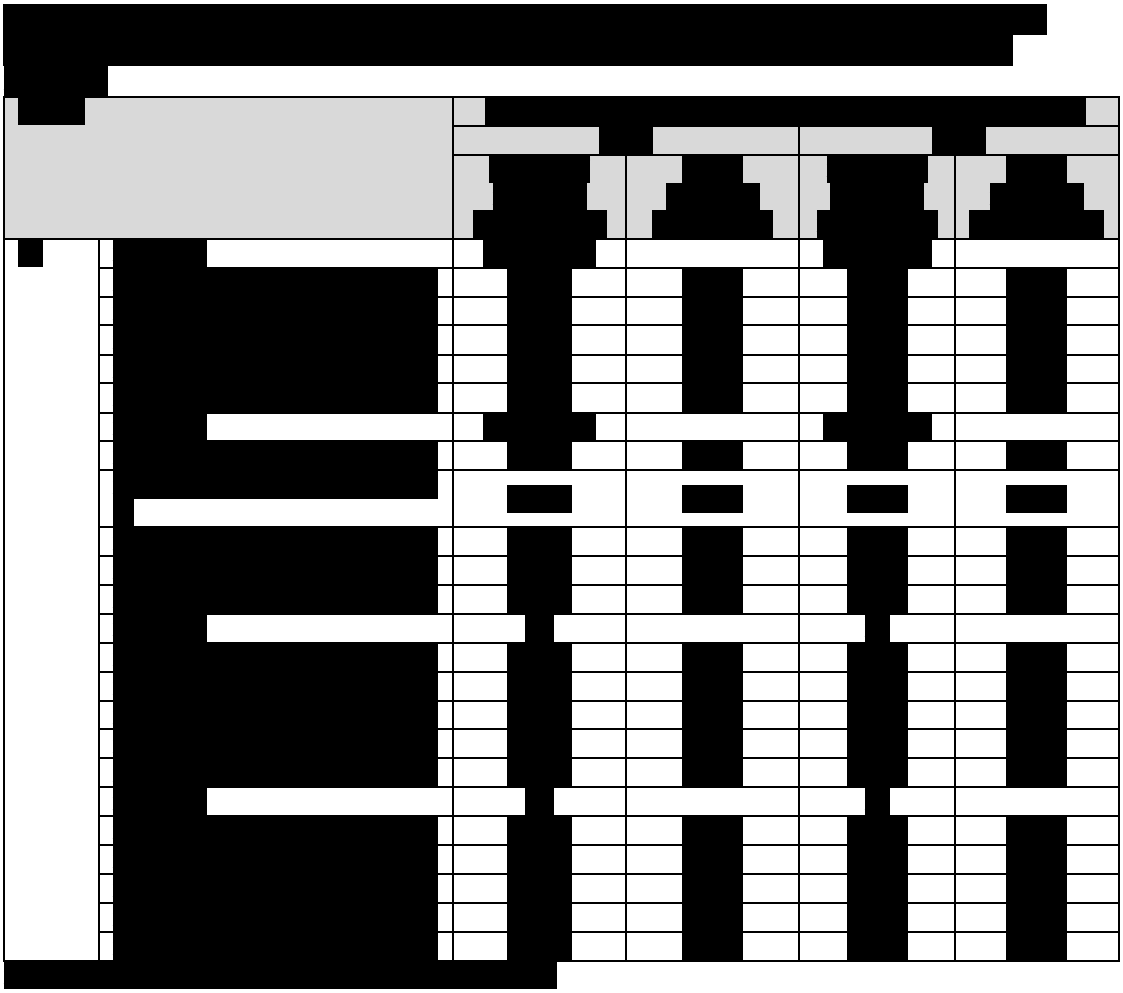

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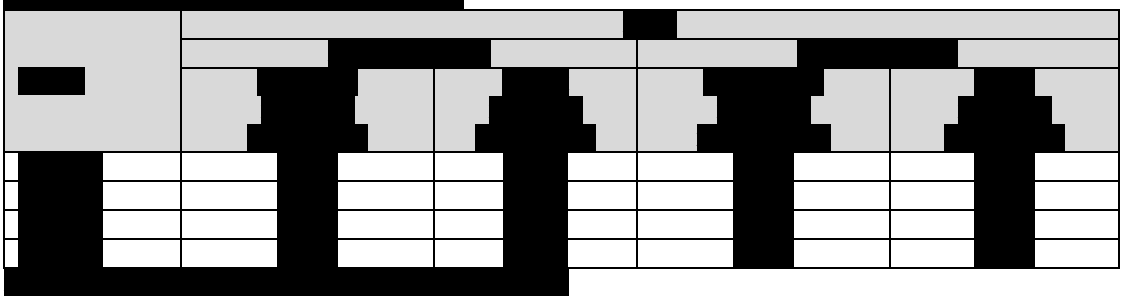

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Economic model

Months zero to six

ITT patient-level data from the GENEVA 008 and GENEVA 009 trials were pooled at baseline and each follow-up visit (one month, two months, three months and six months) for Ozurdex and observation (Sham) patients. Transition probabilities were then calculated using these data (Table 101). In Ozurdex-treated patients, transition probabilities represented the change in BCVA in the six months after the first treatment.

Months six to 12

Transition probabilities for Ozurdex-retreated patients from six to 12 months, were based on pooled patient-level data for six to 12 months from GENEVA 008 and GENEVA 009. The transition probabilities during this period represented the change in BCVA between six months, immediately prior to receiving the second Ozurdex treatment (if appropriate) and 12 months, six months after re-treatment. It should be noted that the peak effect of Ozurdex is generally observed at month 2-3 post implant. At month six, the treatment response is lower. The model captures the treatment peak benefit in the initial treatment phase (six months) by utilising different cycle lengths. However, a fixed six-month cycle length is used for the re-treatment phase and this may under estimate the benefit of Ozurdex.

Patients in the Ozurdex arm who do not receive retreatment (at six months) are assigned transition probabilities weighted by two factors:

- The proportion of patients in GENEVA 008 and GENEVA 009 who did not receive a second Ozurdex treatment because their condition had resolved Such patients were assumed to have stable visual acuity.

- The proportion of patients in GENEVA 008 and GENEVA 009 who did not receive a second Ozurdex treatment but had not resolved. Such patients were assumed to receive the same transition matrices as observation patients, the estimation of which is described below. [d]

[d] Observation patients receive the product matrix of the month three to month six transition matrix estimated from the sham arm of GENEVA 008 and GENEVA 009 clinical trials.

The condition of patients who did not receive retreatment at day 180 in the GENEVA studies was classified as resolved or unresolved according to retinal thickness (measured by optical coherence tomography [OCT]). Retinal thickness by OCT in patients considered resolved was < 250 µm and in those considered not resolved was > 250 µm.

In the absence of trial data beyond six months for observation patients, outcomes and transition probabilities for six to 12 months were based on the last two available BCVA assessments for all Sham patients (visits at three and six months) in the GENEVA 008 and GENEVA 009 clinical trials.

To account for the difference in cycle lengths, the transition probabilities in the observation arm for the three to six month period were applied twice. This transformation was performed by taking the product matrix of the three to six-month transition probabilities.

Beyond Year 1

Small changes in BCVA continue beyond year one. Transition probabilities beyond year one are based on the last set of available observed data.

- Six to 12 months for Ozurdex retreated patients
- A weighted average transition probability as described previously for patients in the Ozurdex arm not receiving retreatment
- Three to six-month transition probabilities applied twice per six-month cycle for observation

Transition probabilities were applied from years 1 to 2.5 (BRVO) and years 1 to 3 (CRVO) (see Extrapolating visual acuity). From 2.5 years (BRVO) or 3 years (CRVO) onwards it was assumed that there would be no further change in BCVA resulting from the initial event.

5.6 Meta-analysis

5.6.1 Description of meta-analysis.

N/A

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Meta-analysis of the GENEVA studies was not considered appropriate as an integrated summary of 008 and 009 was pre-planned and data were pooled to provide more statistical power for subgroup analyses.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

N/A

5.7 Indirect and mixed treatment comparisons

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

N/A, indirect and mixed treatment comparisons were not appropriate; see Section 9.4.

The master literature search described in Section 5.1 and Section 9.2 was designed to identify Ozurdex clinical trials and also any eligible studies investigating the use of triamcinolone (Kenalog formulation or equivalent) or bevacizumab in the treatment of ME following RVO. The systematic review identified a Phase III randomised study comparing dexamethasone with Sham (Haller et al., 2010) (i.e. the GENEVA study) (25). No relevant RCT evidence was identified for triamcinolone (Kenalog formulation or equivalent) or bevacizumab (See Figure 1 of Section 5.1).

The only triamcinolone studies (SCORE) (41, 60) identified via the systematic search were excluded on the basis that they use an alternative formulation of triamcinolone (Trivaris) that is not available in Europe (i.e. not Kenalog or equivalent, as stipulated in the NICE scope) and were not deemed appropriate for an indirect comparison. The available formulation of triamcinolone (Kenalog) is a crystalline suspension developed for intra-articular use. The implications of injecting the Kenalog formulation into the vitreous have not been well studied and intra-ocular injection of this formulation is specifically contra-indicated in the Kenalog SPC (61).

Furthermore, no indirect comparison with Ozurdex could be made in BRVO patients using the available literature for the ophthalmic preparation of triamcinolone (Trivaris). The only trial identified (SCORE) (41) uses standard care (which included grid photocoagulation) as a comparator rather than simply observation. The conditions of this trial therefore do not match those used in the GENEVA studies for patients with BRVO who only received a Sham procedure.

Based upon the literature search conducted (see Section 5.1, 9.2, and 9.4), no RCTs were identified which evaluated bevacizumab in RVO, therefore no robust indirect comparison can be conducted between bevacizumab and Ozurdex.

According to the literature search conducted, robust indirect comparison between Ozurdex and triamcinolone (Kenalog formulation or equivalent) or bevacizumab were not possible due to a lack of appropriate clinical data.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

N/A

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

N/A

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

N/A

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

N/A

5.7.6 Please present the results of the analysis.

N/A

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

N/A

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

N/A

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

N/A

5.8 Non-RCT evidence

N/A, no non-RCT evidence was identified.

5.9 Adverse events

Summary

- In two Phase III masked, randomised, sham-controlled GENEVA studies Ozurdex demonstrated an acceptable safety profile and was well tolerated in patients with ME associated with RVO.
- Throughout the studies the adverse event (AE) profile was similar between Ozurdex and Sham with the exception of:
    - Expected increases in IOP with Ozurdex during the initial treatment period.
    - Ocular hypertension (4.0% and 5.6% - Pooled analysis of all patients and patients with BRVO, respectively) and conjunctival hyperaemia (6.3%) in patients with BRVO treated with Ozurdex - associated with the intravitreal injection of a steroid during the initial treatment period.
    - An expected higher incidence of cataracts (11.4%) and subcapsular cataracts (12.9%) with Ozurdex/Ozurdex versus Sham/Ozurdex.
- Very few patients (≤ 1.2%) discontinued the GENEVA studies due to AEs.
- During the GENEVA studies IOP ≥ 25 mm Hg or 35 mm Hg, and IOP increases ≥ 10 mm Hg, peaked at day 60/day 240 after Ozurdex treatment but declined to near baseline levels within 6 months of the injection.
- Increases in IOP were predictable, transient and mainly required no treatment or were managed successfully with standard IOP-lowering medications - very few patients required surgical intervention (ITT population: 0.9%; retreated population: 0.7%)
- The incidences of retinal tears (≤ 2.4%), retinal detachment (≤ 0.6%) or neovascularisation (≤ 3.7%) and serious AEs (≤ 10.7%) were low and similar between treatment groups.
- The incidence of anticipated mild inflammatory responses, such as the presence of anterior chamber cells, was very low (≤ 2%) in the GENEVA studies.

5.9.1 Trials designed to primarily assess safety

None; see Section 9.8

5.9.2 Safety results from other relevant studies

The GENEVA 008 and 009 studies were designed not only to assess efficacy outcomes but also to evaluate the safety profile of Ozurdex in patients with ME due to BRVO or CRVO.

Ozurdex treatment was compared with Sham (observation) during the 12-month studies. In order to maintain treatment masking, patients assigned to the Sham group had a needless applicator pressed against the conjunctiva. It was expected that AEs relating to the method of administration, such as ocular inflammatory responses, would therefore differ between treatment groups. Patients assessed during the first six months of the studies (initial treatment period) were defined as the “ITT safety population” and included patients treated with Ozurdex or Sham respectively. Patients assessed over the entire 12-month study period (initial treatment period and OL extension) who were eligible for a further injection of Ozurdex at day 180 were defined as the “re-treated population”. The re-treated population included patients treated with Ozurdex/Ozurdex and Sham/Ozurdex. Patients that were not eligible for re-treatment (‘single-treated’ population) are not considered within this submission; these patients did not receive an injection of Ozurdex at day 180 and are captured within the safety population for the initial treatment period only. The UK licensed dose of DEX-PS-DDS is 700 µg (Ozurdex), therefore DEX 350 µg is not considered within the subsequent sections.

GENEVA studies – Initial treatment period (ITT safety population -180 days)

Executive Summary - ITT safety population

- During the initial treatment period the AE profile was similar between Ozurdex and Sham with the exception of:
    - Expected transient increases in IOP with Ozurdex - associated with the intravitreal injection of a steroid
    - Ocular hypertension (4.0% and 5.6% - Pooled analysis of all patients and patients with BRVO, respectively) and conjunctival hyperaemia (6.3%) in patients with BRVO treated with Ozurdex - associated with the intravitreal injection of a steroid
- The incidence of cataract AEs was similar between treatment groups during the initial treatment period (≤ 7.4%).
- Very few patients (≤ 1.9%) discontinued the GENEVA studies during the initial treatment period due to AEs.
- The incidences of retinal tears (≤ 0.5%), retinal detachment (0.2%) or neovascularisation (≤ 2.6%) and serious AEs (≤ 5.9%) were low and similar between treatment groups.
- Increases in IOP were transient and mainly required no treatment or were managed successfully with standard IOP-lowering medications - very few patients required surgical intervention (0.9%).
- IOP ≥ 25 mm Hg or 35 mm Hg, and IOP increases ≥ 10 mm Hg, peaked at day 60 after Ozurdex treatment but declined to near baseline levels within 6 months of the injection.
- The incidence of anticipated mild inflammatory responses, such as the presence of anterior chamber cells, was lower than expected after intravitreal injection (< 2% of patients).
- Ozurdex was well tolerated with an acceptable safety profile after 6 months.

The ITT safety population for the initial treatment period (180 days) was composed of patients who were randomised and received treatment (GENEVA 008, Ozurdex: n = 196 and Sham: n = 202; GENEVA 009, Ozurdex: n = 225 and Sham: n = 221; Pooled, Ozurdex: n = 421 and Sham: n = 423). This submission focuses only on the UK licensed dose of DEX-PS-DDS (700 µg, Ozurdex), therefore data for DEX 350 µg is not shown. There were no significant differences between treatment groups in demographic or baseline characteristics.

The ocular and systemic pharmacokinetics of DEX following intravitreal implant of DEX-PS-DDS have been assessed in primates (62). Following implantation, a high release of dexamethasone occurs over 2 months, with continued gradual release

occurring for up to six months in total (62). Plasma concentrations taken from a proportion of patients in the initial treatment period of the GENEVA studies further demonstrated that the majority of plasma dexamethasone concentrations were below the lower limit of quantification (LLOQ= 50 pg/mL) (13, 19, 20). The DEX-PS-DDS allows the targeted delivery of DEX to the posterior segment of the eye, whilst the plasma concentration of DEX remains low (62). Due to this targeted approach, the potential for systemic adverse events (AEs) is minimal (62); therefore, this submission considers ocular AEs only.

Common ocular adverse events in the study eye in any treatment group (ITT safety population - 180 days) (19, 20, 63)

Pooled analysis of the GENEVA studies demonstrated that the overall incidence of ocular AEs in the study eye was statistically significantly higher in patients treated with Ozurdex (62.9%) versus Sham (42.8%) ($P < 0.001$). The Sham procedure was needleless; therefore it was expected that some AEs reported in the studies may have been associated with the mechanical process of an intravitreal injection, rather than the active ingredient (DEX). Adverse events showing significant between-group differences are provided in Table 72.

Individual and pooled data from the GENEVA studies demonstrate that the most frequently occurring ocular AE in the study eye with Ozurdex was an increase in IOP, followed by conjunctival haemorrhage; however there was no significant difference between groups for conjunctival haemorrhage (pooled analysis: 20.2% versus 14.9%, Ozurdex versus Sham, respectively). Increased IOP was the only AE with a statistically significantly higher incidence with Ozurdex versus Sham in all analyses (individual and pooled) ($P < 0.001$). Intravitreal injections of steroids, such as DEX, are well-recognised to induce elevations in IOP with different steroids exhibiting a varying propensity to induce this effect. Therefore increases in IOP were expected and either did not require treatment or were generally successfully managed with topical IOP lowering medications (19, 20). In GENEVA 009 and the pooled analysis, ocular hypertension occurred significantly more frequently with Ozurdex versus Sham ($P \leq 0.007$). In the pooled analysis, eye pain occurred significantly more frequently with Ozurdex versus Sham ($P = 0.023$). The incidence of anterior chamber cells in the study eye was significantly higher with Ozurdex versus Sham ($P = 0.031$), although the incidence in the GENEVA studies was very low and was reported by < 2% of patients. No cases of endophthalmitis (an inflammatory condition commonly observed after intraocular procedures) were reported in the GENEVA studies.

Table 72: Common ocular adverse events with significant between-group differences (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Investigations						
Intraocular pressures increased†	46 (23.5%)	2 (1.0%)	60 (26.7%)	3 (1.4%)	106 (25.2%)	5 (1.2%)
Eye Disorders						
Anterior chamber cell	< 2%	< 2%	< 2%	< 2%	5 (1.2%)§§	0 (0.0%)
Eye pain	13 (6.6%)	6 (3.0%)	18 (8.0%)	10 (4.5%)	31 (7.4%)¶	16 (3.8%)
Ocular hypertension	7 (3.6%)	2 (1.0%)	10 (4.4%)‡	1 (0.5%)	17 (4.0%)††	3 (0.7%)
Retinal neovascularisation	< 2%	< 2%	0 (0.0%)§	8 (3.6%)	3 (0.7%)‡‡	11 (2.6%)

† (P < 0.001 all analyses); ‡ (P = 0.007); § (P = 0.003); ¶ (P = 0.023); †† (P = 0.001); ‡‡ (P = 0.032); §§ (P = 0.031)

Pooled analysis of the GENEVA studies demonstrated that the overall incidence of ocular AEs (study eye) was statistically significantly higher in patients with BRVO or CRVO treated with Ozurdex (60.4% and 68.4%, respectively) versus Sham (39.1% and 49.7%, respectively) (P ≤ 0.001). Due to the nature of the disease, patients with CRVO are more likely to develop ocular AEs than patients with BRVO. Adverse events showing significant between-group differences in patients with BRVO and CRVO are provided in Table 73 and Table 74, respectively).

The most frequently reported ocular AE (study eye) in patients with BRVO and CRVO reflected those reported in the entire RVO population (an increase in IOP, followed by conjunctival haemorrhage). The incidence of increased IOP and ocular hypertension in patients with BRVO were the only events which were significantly higher with Ozurdex group versus Sham (P < 0.001). The incidence of retinal exudates in patients with BRVO was statistically significantly less with Ozurdex versus Sham (P = 0.015). In GENEVA 009 a significantly lower incidence of retinal neovascularisation occurred in patients with BRVO treated with Ozurdex versus Sham (P = 0.023). In patients with CRVO the incidence of increased IOP in patients with CRVO was the only event which was significantly higher with Ozurdex versus Sham (P < 0.001).

Table 73: Common ocular adverse events with significant between-group differences in patients with BRVO (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n =137)	Sham (n = 130)	Ozurdex (n =151)	Sham (n = 146)	Ozurdex (n = 288)	Sham (n = 276)
Investigations						
Intraocular pressures increased	32 (23.4%)†	2 (1.0%)	34 (22.5%)†	1 (0.7%)	66 (22.9%)†	3 (1.1%)
Eye Disorders						
Ocular hypertension	7 (5.1%)§	0 (0%)	9 (6.0%)¶	1 (0.7%)	16 (5.6%)†	1 (0.4%)
Conjunctival hyperaemia	7 (5.1%)‡‡	0 (0%)	11 (7.3%)	8 (5.5%)	18 (6.3%)†	8 (2.9%)
Retinal exudates	3 (2.2%)	< 2%	0 (0%)	10 (6.8%)†	3 (1.0%)	12 (4.3%)‡
Retinal neovascularisation	< 2%	3 (2.3%)	0 (0%)††	5 (3.4%)	2 (0.7%)	8 (2.9%)

† (P < 0.001); ‡ (P = 0.015); § (P = 0.019); ¶ P = 0.031); †† (P = 0.023); ‡‡ (P = 0.022)

Table 74: Common ocular adverse events with significant between-group differences in patients with CRVO in any treatment group (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 59)	Sham (n = 72)	Ozurdex (n = 74)	Sham (n = 75)	Ozurdex (n = 133)	Sham (n = 147)
Investigations						
Intraocular pressures increased	14 (23.7%)†	0 (0%)	26 (35.1%)†	2 (2.7%)	40 (30.1%)†	2 (1.4%)

†(P < 0.001)

Ocular adverse events in the non-study eye (ITT safety population - 180 days) (19, 20)

Individual data from the GENEVA studies demonstrated that there were no statistically significant between group differences with regards to the overall incidence of ocular AEs in the non-study eye.

Common treatment-related ocular adverse events in the study eye in any treatment group (ITT safety population - 180 days) (19, 20, 63)

Pooled analysis of the GENEVA studies demonstrated that the incidence of overall treatment-related ocular AEs was statistically significantly higher in patients treated with Ozurdex (47.3%) versus Sham (17.5%) (P < 0.001). Adverse events showing significant between-group differences are provided in Table 75.

The most frequently reported and statistically significant treatment-related AEs followed the same trend as previously described for common ocular AEs. Visual disturbance was the only additional treatment-related ocular AE with a statistically significant higher incidence with Ozurdex versus Sham (P = 0.031) and was reported by < 2% of patients.

It is of note that an increase in the incidence of cataract AEs (including cortical, nuclear and subcapsular) with Ozurdex versus Sham was expected, due to the documented impact of corticosteroids on the induction of cataracts. Nevertheless,

pooled analysis of the GENEVA studies demonstrated that the difference in cataract AEs was not statistically significant between Ozurdex (7.4%) and Sham (4.5%) during the ITT phase of the study.

Table 75: Common treatment-related ocular adverse events in the study eye with significant between-group differences (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Investigations						
Intraocular pressures increased†	45 (23.0%)	1 (0.5%)	56 (24.9%)	1 (0.5%)	101 (24.0%)	2 (0.5%)
Eye Disorders						
Ocular hypertension	6 (3.1%)	1 (0.5%)	9 (4.0%)‡	1 (0.5%)	15 (3.6%)§	2 (0.5%)
Visual disturbance	< 2%	< 2%	<2%	<2%	5 (1.2%)¶	0 (0%)

† (P < 0.001 all analyses); ‡ (P = 0.020); § (P = 0.001); ¶ (P = 0.031)

Pooled analysis of the GENEVA studies demonstrated that the overall incidence of treatment-related ocular AEs (study eye) was statistically significantly higher in patients with BRVO or CRVO treated with Ozurdex (45.8% and 50.4%, respectively) versus Sham (14.1% and 23.8%, respectively) (P < 0.001). The most frequently reported treatment-related AEs were the same as previously described for common ocular AEs in patients with BRVO or CRVO (increase in IOP, followed by conjunctival haemorrhage). Treatment-related AEs with significant between-group differences in patients with BRVO or CRVO are provided in Table 76 and Table 77, respectively. The AE of conjunctival haemorrhage was considered related to the intravitreal injection procedure, whereas increases in IOP and ocular hypertension were considered related to the corticosteroid (DEX).

Table 76: Common treatment-related ocular adverse events in the study eye with significant between-group differences in patients with BRVO (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n =137)	Sham (n = 130)	Ozurdex (n =151)	Sham (n = 146)	Ozurdex (n = 288)	Sham (n = 276)
Investigations						
Intraocular pressures increased	31 (22.6%)	1 (0.8%)	31 (20.5%)	0 (0%)	62 (21.5%)†	1 (0.4%)
Eye Disorders (either eye)						
Conjunctival hyperaemia	7 (5.1%)	0 (0%)	9 (6.0%)	4 (2.7%)	16 (5.6%)‡	4 (1.4%)
Ocular hypertension	6 (4.4%)	0 (0%)	8 (5.3%)	1 (0.7%)	14 (4.9%)†	1 (0.4%)

† (P < 0.001); ‡ (P = 0.008)

Table 77: Common treatment-related ocular adverse events in the study eye with significant between-group differences in patients with CRVO (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 59)	Sham (n = 72)	Ozurdex (n = 74)	Sham (n = 75)	Ozurdex (n = 133)	Sham (n = 147)
Investigations						
Intraocular pressures increased	14 (23.7%)	0 (0%)	25 (33.8%)	1 (1.3%)	39 (29.3%)†	1 (0.7%)

† (P < 0.001)

Deaths (ITT safety population - 180 days) (19, 20, 63)

Individual and pooled data from the GENEVA studies demonstrated that one patient treated with Ozurdex died during the initial treatment period (GENEVA 009) (not considered related to the study treatment). No deaths occurred in the Sham group.

Other serious adverse events (ITT safety population - 180 days) (19, 20, 63)

Pooled analysis from the GENEVA studies demonstrated that the overall incidence of serious AEs (SAEs) during the initial treatment period (180 days) was similar between the Ozurdex (5.0%) and Sham (5.9%) treatment groups. The rates of serious ocular AEs and serious non-ocular AEs were similar across all treatment groups. None of the SAEs were considered treatment-related, with the exception of increased IOP (one patient in GENEVA 008) and ocular hypertension in the study eye (one patient in GENEVA 009). However, the difference in the incidence of these treatment-related events was not statistically significant versus Sham (Table 78).

Table 78: Serious adverse events (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Overall	10 (5.1%)	13 (6.4%)	11 (4.9%)	12 (5.4%)	21 (5.0%)	25 (5.9%)
Cardiac disorders	3 (1.5%)	2 (1.0%)	2 (0.9%)	2 (0.9%)	5 (1.2%)	4 (0.9%)
Eye disorders†	0 (0%)	1 (0.5%)	1 (0.4%)	0 (0%)	1 (0.2%)	1 (0.2%)
Ocular hypertension	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)	0 (0.0%)
Glaucoma	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0.0%)	1 (0.2%)
Gastrointestinal	2 (1.0%)	0 (0%)	1 (0.4%)	0 (0%)	3 (0.7%)	0 (0.0%)
General disorders/ administration site conditions	0 (0%)	1 (0.5%)	1 (0.4%)	1 (0.5%)	1 (0.2%)	2 (0.5%)
Hepatobiliary disorders	0 (0%)	0 (0%)	1 (0.4%)	1 (0.5%)	1 (0.2%)	1 (0.2%)
Infections and infestations	0 (0%)	1 (0.5%)	0 (0%)	4 (1.8%)	0 (0.0%)	5 (1.2%)
Injury, poisoning and procedural complications	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Investigations	1 (0.5%)	1 (0.5%)	1 (0.4%)	0 (0%)	2 (0.5%)	1 (0.2%)
IOP increased†	1 (0.5%)	0 (0%)	1 (0.4%)	0 (0%)	2 (0.5%)	0 (0.0%)
BP increased	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (0.5%)	1 (0.4%)	2 (0.9%)	1 (0.2%)	3 (0.7%)
Neoplasms benign, malignant, unspecified	1 (0.5%)	2 (1.0%)	1 (0.4%)	1 (0.5%)	2 (0.5%)	3 (0.7%)
Nervous system disorders	2 (1.0%)	4 (2.0%)	2 (0.9%)	2 (0.9%)	4 (1.0%)	6 (1.4%)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Psychiatric disorders	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0.0%)
Renal and urinary disorders	0 (0%)	0 (0%)	1 (0.4%)	1 (0.5%)	1 (0.2%)	1 (0.2%)
Reproductive system and breast disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.5%)	1 (0.5%)	1 (0.4%)	2 (0.9%)	2 (0.5%)	3 (0.7%)
Vascular disorders	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)	0 (0.0%)

†Study eye; BP, Blood pressure; IOP, Intraocular pressure; RVO, retinal vein occlusion

Discontinuations due to adverse events (ITT safety population - 180 days) (19, 20, 63)

Pooled analysis of the GENEVA studies demonstrated that few patients discontinued the trials due to AEs during the initial treatment period (180 days). Due to the method of administration (i.e. a single injection of Ozurdex at the beginning of the studies), patients did not discontinue treatment. Adverse events leading to discontinuation from the studies were reported for 1.7% (7/421) of patients treated with Ozurdex versus 1.9% (8/423) of patients treated with Sham. Of these patients, three withdrew from the Ozurdex arm and three from the Sham group in GENEVA 008, four withdrew from the Ozurdex arm and five from the Sham group in GENEVA 009. None of the events were considered treatment-related. It is of note that no patients treated with Ozurdex discontinued the studies due to retinal and/or iris neovascularisation, whereas these events, associated with the natural history of untreated disease, led to the discontinuation of three patients treated with Sham (one patient in GENEVA 008 and two patients in GENEVA 009).

Intraocular pressure in the study eye (ITT safety population - 180 days) (19, 20, 63)

Intravitreal injections of corticosteroids such as DEX are known to induce elevations in IOP to differing degrees, therefore this was an expected AE in the GENEVA studies (19, 20). It is of note that in the majority of patients experiencing increases in IOP either did not require treatment or were generally successfully managed with topical IOP lowering medications (19, 20). Very few patients (n = 4) required procedures for elevated IOP (Table 81) (19, 20).

Individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with IOP ≥ 25 mm Hg in the study eye was statistically significantly greater with Ozurdex versus Sham at days 7, 30, 60, and 90 ($P \leq 0.029$) (Table 79 and Figure 13). Pooled analysis demonstrated that the proportion of patients with IOP ≥ 35 mm Hg in the study eye was significantly greater with Ozurdex versus Sham at days 30 and 60 (Table 79 and Figure 13). In GENEVA 009 the proportion of patients with IOP ≥ 35 mm Hg in the study eye was only significantly greater at day 60 ($P = 0.004$); no significant differences were reported for this outcome in GENEVA 0008 (Table 79). Individual and pooled data demonstrated that there were no significant differences in the proportion of patients with IOP ≥ 25 mm Hg or IOP ≥ 35 mm Hg at day 180 between treatment groups (Table 79).

Table 79: Patients with IOP ≥ 25 or ≥ 35 mm Hg in the study eye (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Baseline						
≥ 25 mm Hg	0 (0.0%)	0 (0.0%)	1 (0.4%)‡‡	0 (0.0%)	1 (0.2%)‡‡	0 (0.0%)
≥ 35 mm Hg	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 1						
≥ 25 mm Hg	1 (0.5%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	3 (0.7%)	0 (0.0%)
≥ 35 mm Hg	1 (0.5%)‡‡	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Day 7						
≥ 25 mm Hg	5 (2.6%)†	0 (0.0%)	10 (4.5%)§	0 (0.0%)	15 (3.6%)‡	0 (0.0%)
≥ 35 mm Hg	1 (0.5%)‡‡	0 (0.0%)	2 (0.9%)‡‡	0 (0.0%)	3 (0.7%)‡‡	0 (0.0%)
Day 30						
≥ 25 mm Hg	20 (10.5%)‡	1 (0.5%)	27 (12.1%)‡	0 (0.0%)	47 (11.4%)‡	1 (0.2%)
≥ 35 mm Hg	2 (1.1%)	0 (0.0%)	5 (2.2%)	0 (0.0%)	7 (1.7%)††	0 (0.0%)
Day 60						
≥ 25 mm Hg	29 (15.4%)‡	1 (0.5%)	35 (16.0%)‡	0 (0.0%)	64 (15.7%)‡	1 (0.2%)
≥ 35 mm Hg	4 (2.1%)	0 (0.0%)	9 (4.1%)¶	0 (0.0%)	13 (3.2%)‡	0 (0.0%)
Day 90						
≥ 25 mm Hg	13 (6.8%)‡	0 (0.0%)	12 (5.5%)‡	0 (0.0%)	25 (6.1%)‡	0 (0.0%)
≥ 35 mm Hg	1 (0.5%)‡‡	0 (0.0%)	2 (0.9%)‡‡	0 (0.0%)	3 (0.7%)‡‡	0 (0.0%)
Day 180						
≥ 25 mm Hg	1 (0.5%)‡‡	1 (0.5%)	4 (1.9%)‡‡	0 (0.0%)	5 (1.2%)‡‡	1 (0.2%)
≥ 35 mm Hg	0 (0.0%)	0 (0.0%)	1 (0.5%)‡‡	0 (0.0%)	1 (0.2%)‡‡	0 (0.0%)
Any visit§§						
≥ 25 mm Hg	52 (26.5%)‡	3 (1.5%)	59 (26.2%)‡	0 (0.0%)	111 (26.4%)‡	3 (0.7%)
≥ 35 mm Hg	9 (4.6%)§	0 (0.0%)	16 (7.1%)‡	0 (0.0%)	25 (5.9%)‡	0 (0.0%)

Note: Percentages are calculated based on number of patients with available data for each visit; † (P = 0.029); ‡ (P < 0.001); § (P = 0.002); ¶ (P = 0.004); †† (P = 0.007); ‡‡Pairwise comparisons not done because the among-group comparison was not statistically significant; §§ Patients with IOP ≥ 25 mm Hg or ≥ 35 mm Hg at any post-baseline visit during the initial treatment period (180 days)

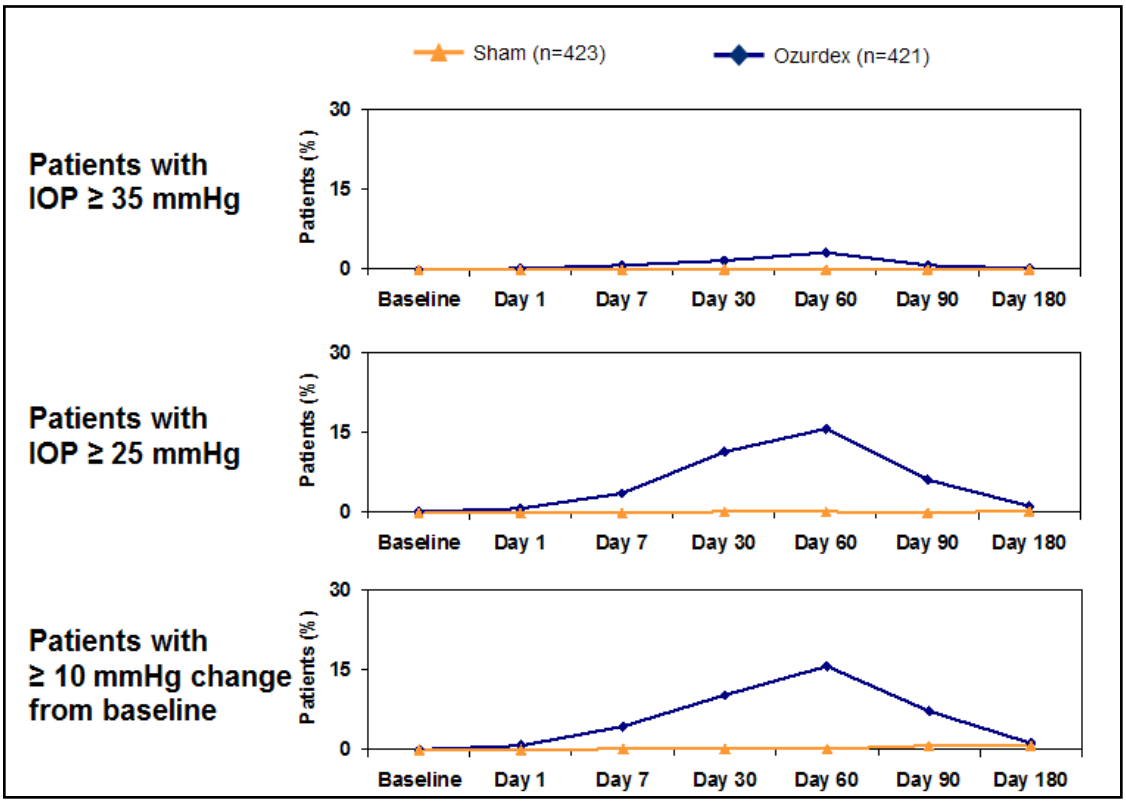
Individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with a change from baseline IOP ≥ 10 mm Hg in the study eye was statistically significantly greater with Ozurdex versus Sham at days 30, 60, and 90 (P ≤ 0.003), and additionally at day 7 in GENEVA 009 and the pooled analysis (P < 0.001) (Table 80 and Figure 13). Individual and pooled data demonstrated that there were no significant differences in the proportion of patients with IOP ≥ 10 mm Hg at day 180 between treatment groups (Table 80 and Figure 13).

Table 80: Change from baseline IOP ≥ 10 mm Hg (- 180 days)

Visit	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Day 1	2 (1.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	3 (0.7%)	0 (0.0%)
Day 7	7 (3.6%)§	1 (0.5%)	11 (4.9%)†	0 (0.0%)	18 (4.3%)†	1 (0.2%)
Day 30	18 (9.5%)†	1 (0.5%)	24 (10.8%)†	0 (0.0%)	42 (10.2%)†	1 (0.2%)
Day 60	28 (14.9%)†	1 (0.5%)	36 (16.4%)†	0 (0.0%)	64 (15.7%)†	1 (0.2%)
Day 90	13 (6.8%)‡	2 (1.0%)	17 (7.7%)†	1 (0.5%)	30 (7.3%)†	3 (0.7%)
Day 180	2 (1.1%)§	1 (0.5%)	3 (1.4%)§	2 (1.0%)	5 (1.2%)§	3 (0.8%)
Any Visit¶	50 (25.5%)†	3 (1.5%)	62 (27.6%)†	3 (1.4%)	112 (26.6%)†	6 (1.4%)

Note percentages are calculated based on number of patients with available data for each visit; † (P < 0.001); ‡ (P = 0.003); § Pairwise comparisons not done because the among-group comparison was not statistically significant; ¶ Patients with IOP increase from baseline ≥ 10 mm Hg at any post-baseline visit during the initial treatment period (180 days)

Figure 13: Changes in IOP (-180 days)



Concomitant medications and concurrent procedures for management of IOP elevation (ITT safety population - 180 days) (63)

Individual and pooled data from the GENEVA studies demonstrated that, as expected[e], there was a greater use of IOP-lowering medications in patients who received Ozurdex versus Sham.

[e] Due to the known association of intravitreal steroids with elevations of IOP

In GENEVA 009, concomitant ocular medications in the study eye were reported for 46.5% (105/226) of patients in the Ozurdex group and 22.3% (50/224) of patients in the Sham group. The most frequently reported drug classes (> 10% in any treatment group) were: ophthalmic beta blocking agents (Ozurdex: 25.7% [58/226]; Sham: 2.7% [6/224]); sympathomimetics in glaucoma therapy (Ozurdex: 12.8% [29/226]; Sham: 1.3% [3/224]); ophthalmic prostaglandin analogues (Ozurdex: 9.7% [22/226], Sham: 1.3% [3/224]); other ophthalmologicals (Ozurdex: 9.7% [22/226]; Sham: 9.8% [22/224]).

In GENEVA 008, concomitant ocular medications in the study eye were reported for 40.8% (82/201) of patients in the Ozurdex group and 19.8% (40/202) of patients in the Sham. The most frequently reported drug classes (more than 10% in any treatment group) were: ophthalmic beta blocking agents (Ozurdex: 19.4% [39/201]; Sham: 3.5% [7/202]); sympathomimetics in glaucoma therapy (Ozurdex: 10.4% [21/201]; Sham: 0.5% [1/202]); ophthalmic prostaglandin analogues (Ozurdex: 7.5% [15/201]; Sham: 1.5% [3/202]).

Individual and pooled data from the GENEVA studies demonstrated that four concurrent procedures were performed in the study eye for high ocular pressure during the initial treatment period (180 days) (0.95%; 4/421) (Table 81). Additionally in GENEVA 009, one patient in the Sham group underwent an iridotomy with laser for narrow angle anterior chamber and ocular hypertension.

Table 81: Concurrent procedures in the study eye for management of IOP elevation (- 180 days)

Study	Procedure Description	Reason for Procedure	Outcome	Adverse Event Leading to Procedure
GENEVA 008 (n = 1)	Trabeculoplasty followed by a valve procedure	Neovascular glaucoma (CRVO)	IOP controlled	IOP increased
GENEVA 009 (n = 1)	Pachymetry	Abnormal corneal thickness	no action required	IOP increased
GENEVA 009 (n = 1)	Deep sclerectomy (glaucoma procedure)	Elevated IOP	IOP controlled	Ocular hypertension
GENEVA 009 (n = 1)	Cyclocryotherapy	Elevated IOP	IOP controlled	IOP increased

Retinal detachments (ITT safety population - 180 days) (19, 20, 63)

Individual and pooled data from the GENEVA studies demonstrated that retinal detachments in the study eye occurred in one patient (0.2%) treated with Ozurdex (GENEVA 009) and one patient (0.2%) treated with Sham (GENEVA 008). No retinal detachments were reported in the non-study eye. Retinal detachments were considered applicator related in one patient treated with Ozurdex (GENEVA 009).

Retinal tears (ITT safety population - 180 days) (19, 20, 63)

Individual and pooled data from the GENEVA studies demonstrated that retinal tears in the study eye were evident in nine patients at baseline and continued to be reported during the studies (Ozurdex: two patients in GENEVA 008, one patient in GENEVA 009; Sham: two patients in GENEVA 008, four patients in GENEVA 009). Three patients had retinal tears in the study eye reported post-baseline: two patients (0.5%) treated with Ozurdex and one patient (0.2%) in the Sham group. These retinal tears were thought to be related to the applicator/insertion in both patients treated with Ozurdex and one patient treated with Sham (GENEVA 008). None of the tears were considered serious or progressed to detachments.

Neovascularisation (ITT safety population - 180 days) (19, 20, 63)

Individual and pooled data from the GENEVA studies demonstrated that iris neovascularisation[f] in the study eye was observed in two patients (0.9%) treated with Ozurdex (GENEVA 009) and six patients (1.4%) in the Sham group (three patients in each of the GENEVA studies). Retinal neovascularisation was observed for seven patients (1.7%) treated with Ozurdex (three patients in GENEVA 008 and four patients in GENEVA 009) and eight patients (1.9%) in the Sham group (three patients in GENEVA 008, five patients in GENEVA 009). Concurrent surgical procedures for the treatment of rubeosis or retinal neovascularisation were more common with Sham (six patients; three patients in each GENEVA study) versus Ozurdex (one patient in GENEVA 009).

Cataract adverse events (ITT safety population - 180 days) (19, 20, 63, 64)

Pooled analysis of baseline data from the GENEVA studies demonstrated that over 50% of patients entered the trials with a history of cataracts. Cataract AEs (including cortical, nuclear, subcapsular) were reported in the study eye for 7.4% (31/421) of patients with Ozurdex and 4.5% (19/423) with Sham. In over 30% (21/67) of patients, cataract AEs were bilateral[g]. Cataract AEs are shown in detail in Table 82.

[f] Determined by post-baseline ocular examination
[g] Study eye and the non study eye

Table 82: Cataract adverse events in the study eye (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 196)	Sham (n = 202)	Ozurdex (n = 225)	Sham (n = 221)	Ozurdex (n = 421)	Sham (n = 423)
Baseline	n = 201	n = 202	n = 226	n = 224	n = 427	n = 426
Cataract	107 (53.2%)	104 (51.5%)	137(60.6%)	127 (56.7%)	244 (57.1%)	231 (54.2%)
Cataract subcapsular	0 (0.0%)	12 (5.9%)	5 (2.2%)	3 (1.4%)	5 (1.2%)	3 (0.7%)
Cataract nuclear	21 (10.4%)	23 (11.4%)	22 (9.7%)	21 (9.6%)	43 (10.1%)	44 (10.3%)
Cataract cortical	6 (3.0%)	12 (5.9%)	10 (4.4%)	8 (3.7%)	16 (3.7%)	17 (4.0%)
IT period	n =196	n =202	n = 225	n = 221	n = 421	n = 423
Cataract	4 (2.0%)	2 (1.0%)	11 (4.9%)	4 (1.8%)	15 (3.6%)	6 (1.4%)
Cataract subcapsular	4 (2.0%)	0 (0%)	3 (1.3%)	3 (1.4%)	7 (1.7%)	3 (0.7%)
Cataract nuclear	2 (1.0 %)	0 (0%)	4 (1.8%)	5 (2.3%)	6 (1.4%)	5 (1.2%)
Cataract cortical	3 (1.5%)	2 (1.0%)	2 (0.9%)	6 (2.7%)	5 (1.2%)	8 (1.9%)

Abbreviations: IT, initial treatment

Cataract AEs (including cataract, cortical, nuclear, and subcapsular) were reported in the study eye for 7.6% (22/288) of patients with BRVO and 8.3% (11/133) of patients with CRVO treated with Ozurdex, and 5.4% (15/276) of patients with BRVO and 4.8% (7/147) of patients with CRVO treated with Sham. Cataract AEs are shown in detail in Table 83 and Table 84 for patients with BRVO and CRVO, respectively.

Table 83: Cataract adverse events in the study eye in patients with BRVO (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n =137)	Sham (n = 130)	Ozurdex (n =151)	Sham (n = 146)	Ozurdex (n = 288)	Sham (n = 276)
Cataract	3 (2.2%)	1 (0.8%)	9 (6.0%)	3 (2.1%)	12 (4.2%)	4 (1.4%)
Cataract subcapsular	1 (0.7%)	0 (0%)	2 (1.3%)	2 (1.4%)	3 (1.0%)	2 (0.7%)
Cataract nuclear	0 (0%)	0 (0%)	3 (2.0%)	4 (2.7%)	3 (1.0%)	4 (1.4%)
Cataract cortical	2 (1.5%)	0 (0%)	2 (1.3%)	5 (3.4%)	4 (1.4%)	5 (1.8%)

Table 84: Cataract adverse events in the study eye in patients with CRVO (- 180 days)

System organ class preferred term (MedDRA, version 11.0)	GENEVA 008		GENEVA 009		Pooled	
	Ozurdex (n = 59)	Sham (n = 72)	Ozurdex (n = 74)	Sham (n = 75)	Ozurdex (n = 133)	Sham (n = 147)
Cataract	1 (1.7%)	1 (1.4%)	2 (2.7%)	1 (1.3%)	3 (2.3%)	2 (1.4%)
Cataract subcapsular	3 (5.1%)	0 (0%)	1 (1.4%)	1 (1.3%)	4 (3.0%)	1 (0.7%)
Cataract nuclear	2 (3.4%)	0 (0%)	1 (1.4%)	1 (1.3%)	3 (2.3%)	1 (0.7%)
Cataract cortical	1 (1.7%)	2 (2.8%)	0 (0%)	1 (1.3%)	1 (0.8%)	3 (2.0%)

Procedures for cataracts (ITT safety population - 180 days) (63)

Pooled analysis of the GENEVA studies demonstrated that one patient had surgery for cataracts in the study eye (Ozurdex treatment group). Two patients had surgery for cataracts in the non-study eye (both in the Sham group).

GENEVA studies – Retreated safety population (- 360 days)

Executive Summary – Re-treated safety population

- The AE profile was similar between Ozurdex/Ozurdex and Sham/Ozurdex over the 12 month study period in GENEVA with the exception of:
    - An expected higher incidence of cataracts (11.4%) and subcapsular cataracts (12.9%) with Ozurdex/Ozurdex.
    - The incidence of cataract AEs was considered low, with only three patients treated with Ozurdex/Ozurdex requiring surgery in the study eye.
- Very few patients (≤ 1.2%) discontinued the GENEVA studies due to AEs.
- Incidence of retinal tears (≤2.4%), retinal detachment (≤ 0.6%) or neovascularisation (≤ 3.7%) and serious AEs (≤ 10.7%) were low and similar between treatment groups.
- A mild inflammatory response, such as the presence of anterior chamber cells, was anticipated after intravitreal injection; however, the incidence was very low after 12 months (≤ 2%).
- IOP ≥ 25 mm Hg or 35 mm Hg, and IOP increases ≥ 10 mm Hg, peaked at day 240 after Ozurdex treatment but declined to near baseline levels within 6 months of the injection.
- Increases in IOP were predictable, transient and mainly required no treatment or were managed successfully with standard IOP-lowering medications - very few patients (0.7%) required surgical intervention.
- The 12-month studies demonstrated that Ozurdex administered as two treatments (at day 0 and day 180) was well tolerated with an acceptable safety profile.

The re-treated safety population for the 12 month study period (360 days, initial treatment period and OL extension) was composed of patients who were randomised and received initial treatment (either Ozurdex or Sham) followed by an injection of Ozurdex at day 180 (Ozurdex/Ozurdex: n = 341 and Sham/Ozurdex: n = 327). The 12 month cumulative safety results are shown for the re-treated population. This submission focus on the UK licensed dose of DEX-PS-DDS (700 µg, Ozurdex), therefore data for DEX 350 µg/Ozurdex is not shown. The single-treated population are not considered for safety within this submission; these patients did not receive a second injection of Ozurdex at day 180 and are captured within the safety population up to day 180 (initial treatment period).

There were no significant differences between treatment groups in demographic or baseline characteristics for the re-treated population.

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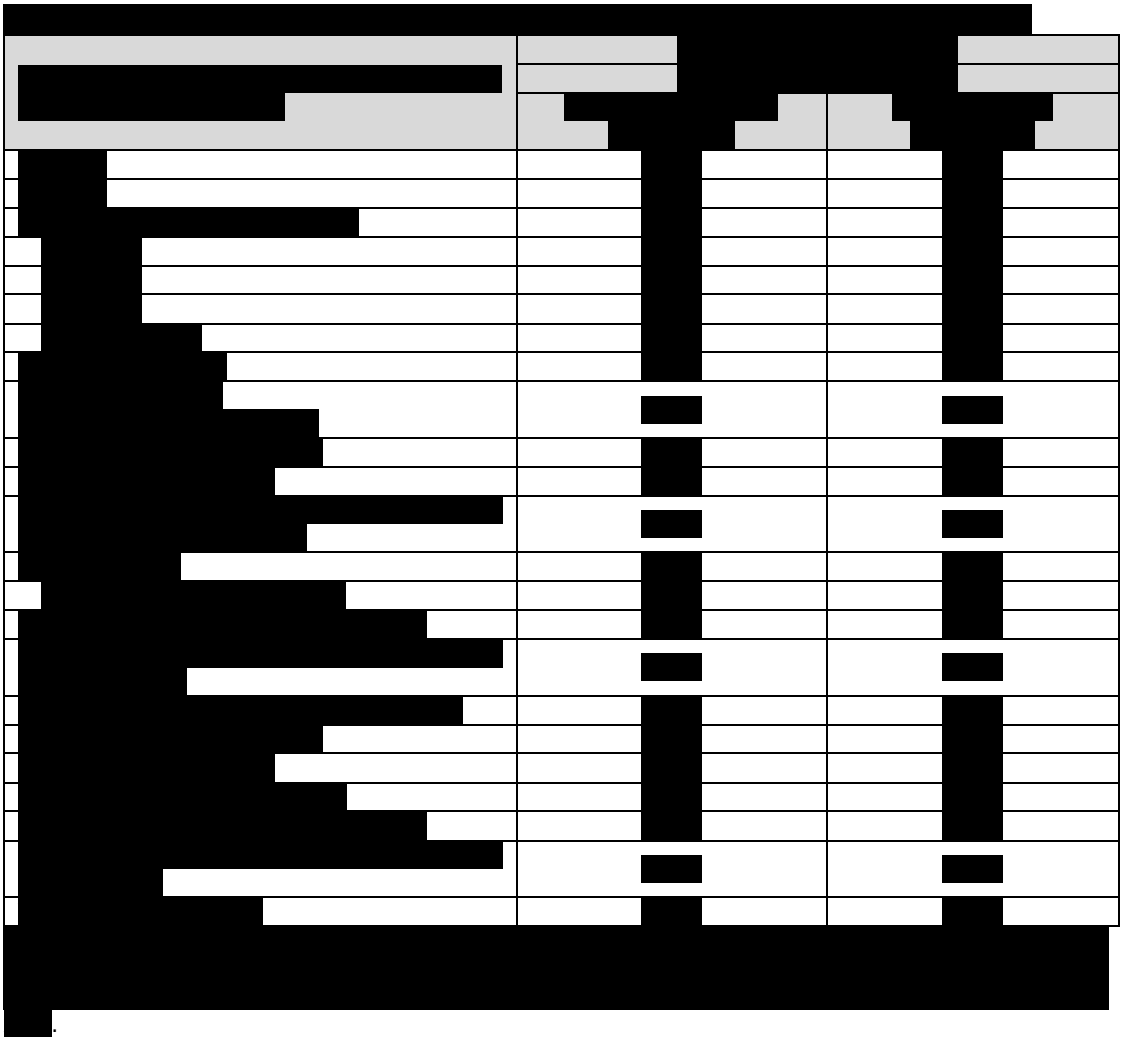

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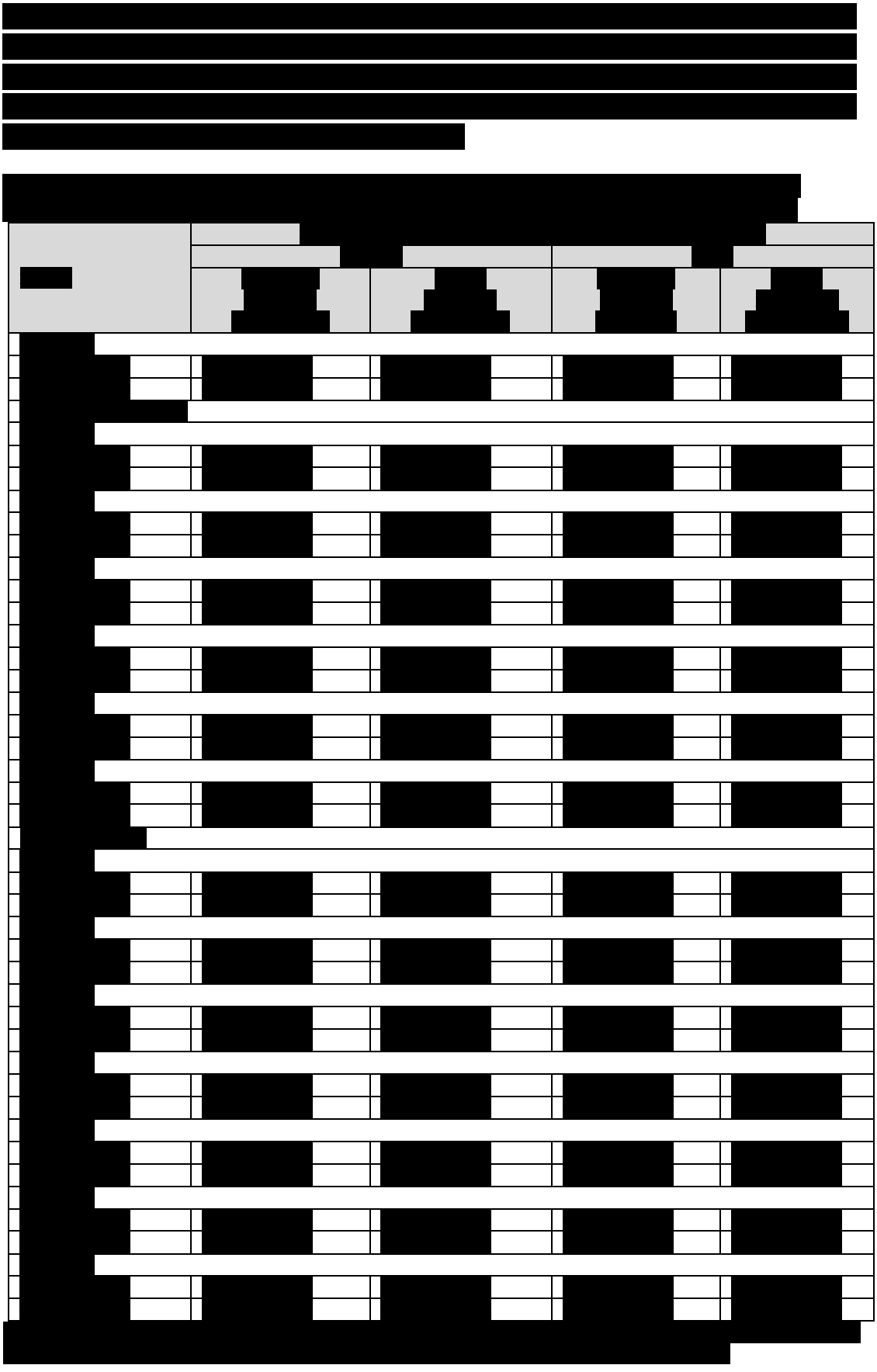

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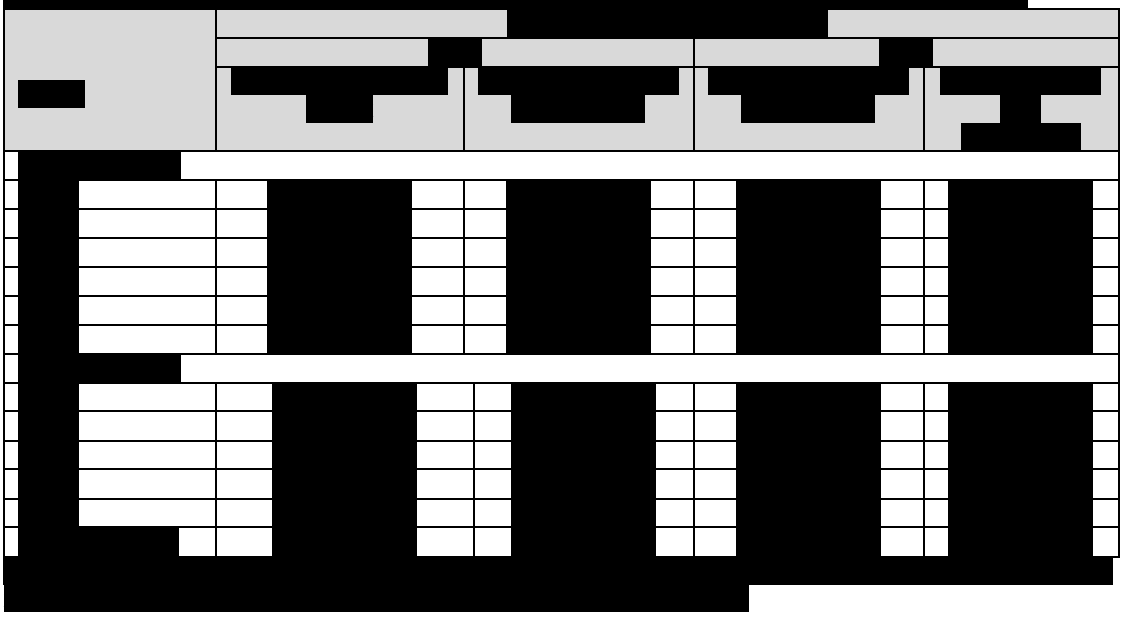

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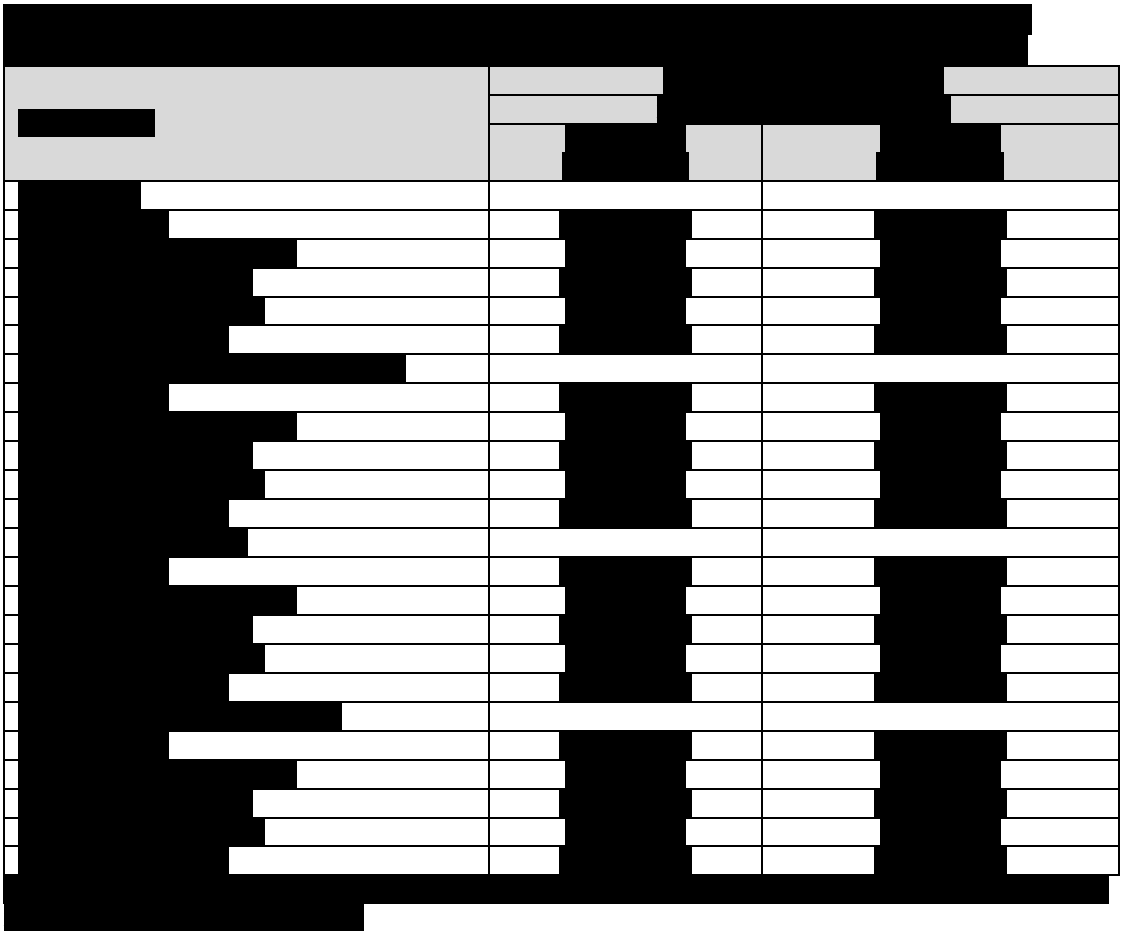

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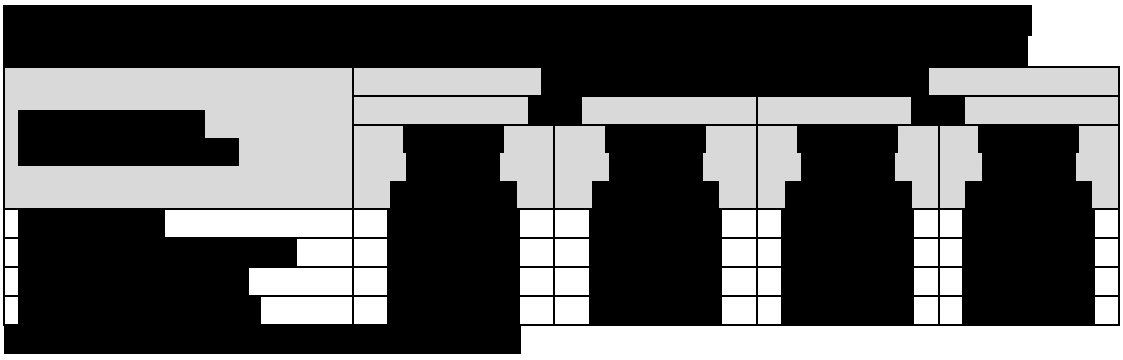

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5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The primary goal of treating BRVO and CRVO is to improve or prevent further loss of VA and reduce ME (17, 18). Despite the poor prognosis for untreated CRVO, there is no recommended treatment for ME following CRVO and no VA benefit in the use of laser therapy (1). The majority of patients with CRVO progress to become legally blind – over half of CRVO cases result in BCVA < 6/60 in the affected eye (9). Laser photocoagulation is the only recommended interventional treatment for patients with BRVO but is associated with a number of limitations. Patients with ME following BRVO > 1 year in duration and with VA of ≤ 6/60 are unlikely to benefit (3) and patients with macular haemorrhage involving the centre point are unsuitable for immediate treatment (7-9).

Ozurdex is the first and only licensed pharmacological treatment for ME following BRVO and CRVO in the UK. Ozurdex is intended for use as a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage. Ozurdex also provides a second line treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment.

Ozurdex delivers 700 µg (0.7 mg) of DEX through a solid polymer drug delivery system to the posterior segment of the eye over a period of up to six months. The innovative drug delivery system overcomes the problem of the short half life of DEX by delivering a sustained dose of DEX to target ME. In the pivotal Phase III GENEVA studies, a single treatment of Ozurdex produced significantly greater improvements in VA when compared with Sham over a variety of efficacy measures, including time to achieve a 15 letter improvement from baseline BCVA, proportion of patients achieving ≥ 15 letter improvement, proportion of patients achieving ≥ 15 letter worsening and mean change from baseline BCVA. Statistically significant differences between Ozurdex and Sham were apparent as early as day 30 after treatment. Ozurdex demonstrated similar efficacy in BRVO and CRVO subgroups.

Findings from the GENEVA studies augment natural history data relating to RVO by confirming that significant numbers of patients (particularly those with CRVO) will continue to lose VA over time if the condition remains untreated. In the GENEVA studies there was an increased likelihood of a 15 letter decrease in BCVA in patients receiving Sham when compared with Ozurdex. Similar results were observed in BRVO and CRVO subgroups. Analyses of 12 month data from the GENEVA studies demonstrated that patients receiving two injections of Ozurdex tended to have improved VA outcomes when compared with patients receiving delayed Ozurdex treatment (i.e. those patients initially allocated to Sham). Nevertheless, improvements in efficacy outcomes were still evident in those receiving their first

injection of Ozurdex at the day 180 treatment window. Such data indicate that as there no clear indicators at baseline to suggest which patients are more likely to experience spontaneous improvements, it is important to treat ME early in order to achieve maximal VA outcomes and prevent further vision loss.

In patients with persistent ME permanent retinal damage and vision loss may occur (14, 16, 29, 30) – again indicating the importance of early treating. Haemorrhages into the vitreous from neovascularisations are more likely to affect eyes with chronic ME and often result in poor final VA and a less favourable prognosis (15). As such, the longer the duration of ME, the more challenging the treatment and the poorer the outcomes expected (31). A post-hoc subgroup analysis based on the duration of ME at baseline was performed using data from the GENEVA studies. This post-hoc analysis found that the treatment response was often greater in patients with a shorter duration of ME at baseline (< 90 days) compared with a longer duration of ME (≥ 90 days). This supports evidence from randomised controlled studies (BRAVO, BVOS and SCORE) demonstrating that the longer the duration of ME the smaller the improvements in BCVA (7, 41, 66). The GENEVA studies highlight the importance of early treatment for ME in RVO in order to achieve optimal VA outcomes.

Key clinical evidence from the GENEVA studies is summarised below:

In the ITT population:

- The cumulative response rate for time to achieve ≥ 15 letters BCVA was consistently and distinctly higher with Ozurdex versus Sham with improvements apparent as early as day 30 ($P < 0.001$).
- A significantly greater proportion of patients treated with Ozurdex versus Sham achieved an improvement of ≥15 letters from baseline at days 30, 60 and 90 ($P \leq 0.039$), with the exception of day 90 in patients with CRVO.
- The window for scheduled post-implant visits varied and consequently patients assessed beyond day 180 were included in the assessment of the proportion of patients with an improvement of ≥ 15 letters BCVA from baseline. The exclusion of these patients in a post-hoc analysis resulted in a statistically significantly higher proportion of patients with an improvement of ≥ 15 letters BCVA at all time points, including day 180, with Ozurdex versus Sham ($P \leq 0.017$).
- The mean change from baseline BCVA in the number of letters read correctly was consistently significantly greater with Ozurdex versus Sham throughout the 6-month studies ($P \leq 0.016$), with the exception of day 180 in patients with CRVO.
- The beneficial effects of Ozurdex were demonstrated not only in terms of a ≥ 15 letters improvement in BCVA, but also in the prevention of ≥ 15 letters worsening throughout the 6-month studies.
- The proportion of patients with at least 1-grade improvement in general vision was statistically significant with Ozurdex versus Sham at days 30, 60 and 90 ($P \leq 0.015$). In clinical practice it is generally considered that visual performance is dictated by the better-seeing eye (34). Therefore, this level of improvement is clinically relevant as the majority of patients (97.4%) in the GENEVA studies received treatment in their worse-seeing eye.
- A longer duration of ME is associated with a poorer prognosis for improvements in VA. In the Sham group, every one month increase in the duration of ME was associated a with significantly lower likelihood of gaining ≥ 15 letters in BCVA at

day 180 (P = 0.02). This illustrates the need to address ME promptly in order to obtain the maximum benefit from treatment with regards to improvement in VA.

- In all patients with a duration of ME ≥ 90 days, a statistically significantly higher proportion achieved a ≥ 15 letters improvement in BCVA with Ozurdex versus Sham at days 30, 60 and 90 (P ≤ 0.033).
- A significantly greater proportion of patients with CRVO treated with Ozurdex versus Sham achieved a BCVA of ≥ 69 letters (Snellen fraction ≤ 20/40) at days 30 and 60 (P ≤ 0.004). This was also applicable to patients with BRVO with MH at days 30, 60 and 90 (P ≤ 0.001) and at day 60 in patients with BRVO with previous laser treatment (P = 0.023).
- Significantly fewer patients with CRVO treated with Ozurdex versus Sham lost vision to a BCVA of ≤ 38 letters (Snellen fraction ≥ 20/200) at days 30 and 60 (P < 0.028). This was also applicable to patients with BRVO with MH at day 60 (P = 0.021). A similar proportion of patients with BRVO with previous laser treatment, treated with Ozurdex versus Sham fell to a BCVA ≤ 38-letters.

In the re-treated population:

In the re-treated population, improvements in efficacy outcomes after 12-months appeared to be greater after two injections of Ozurdex (Ozurdex/Ozurdex) versus a single injection of Ozurdex (Sham/Ozurdex). However, improvements in efficacy outcomes were evident in the Sham/Ozurdex group after the injection of Ozurdex at day 180.

- The cumulative response rate for time to achieve ≥ 15 letters BCVA was consistently and distinctly higher with Ozurdex/Ozurdex versus Sham/Ozurdex throughout the 12-month studies (P ≤ 0.005).
- The proportion of patients with an improvement in BCVA of ≥ 15 letters from baseline decreased across all groups by day 360 of the OL extension, but remained higher than reported at days 90 and 180 of the initial treatment period.
- The mean change from baseline BCVA in the number of letters read correctly was statistically significantly greater with Ozurdex/Ozurdex versus Sham/Ozurdex at day 210 and 240 (with the exception of day 240 in patients with BRVO).
- The beneficial effects of Ozurdex were demonstrated not only in terms of a ≥ 15 letters improvement in BCVA, but also in the prevention of ≥ 15 letters worsening throughout the 12-month studies.
- A similar proportion of patients with CRVO, BRVO with MH and BRVO with previous laser treatment treated with Ozurdex/Ozurdex versus Sham/Ozurdex achieved a BCVA of ≥ 69 letters (Snellen fraction ≤ 20/40) at all timepoints.
- Significantly fewer patients with CRVO treated with Ozurdex/Ozurdex versus Sham/Ozurdex lost vision to a BCVA of ≤ 38 letters (Snellen fraction ≥ 20/200) at days 210, 240 and 270 (P ≤ 0.028); with significance neared at day 360 (P = 0.050). A similar proportion of patients with BRVO with MH and BRVO with previous laser treatment treated with Ozurdex/Ozurdex versus Sham/Ozurdex fell to a BCVA ≤ 38-letters at all timepoints.

Ozurdex provides clinician's with a potentially immediate treatment option in patients where the only viable management strategy has previously been delayed treatment, with associated impact on predicted outcomes, or observation. The GENEVA studies clearly demonstrate that Ozurdex reduces the risk of further vision loss whilst

increasing the chance of improvements in VA in patients with ME following BRVO or CRVO.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The GENEVA studies were robust clinical trials which utilised accepted efficacy measures – primarily BCVA assessed via the ETDRS chart (a standard testing procedure for more than 20 years) (49). Randomisation within the studies was considered appropriate. Patients were randomised using a 1:1:1 allocation ratio performed centrally (using an interactive voice response system) and stratified by the underlying cause of RVO (BRVO or CRVO). No clinically relevant differences between groups were observed for demographic and disease characteristics at baseline and no unexpected imbalances in drop-outs were reported over the course of the trial.

Patients were masked with regard to study treatment, and key efficacy variables were collected and evaluated by follow-up investigators who were also masked to the study treatment. In order to maintain masking of treatment, a needless applicator was pressed against the conjunctiva of the eye in patients assigned to the Sham group and actuated so patients were able to hear the audible click to simulate the actual procedure. Therefore, some AEs reported in the studies may have been associated with the mechanical process of an intravitreal injection, rather than the active ingredient (DEX).

Ozurdex is the only licensed pharmacological treatment for ME following BRVO or CRVO in the UK. Hence the comparator used in the GENEVA studies was a Sham procedure followed by observation. This is consistent with the standard approach (i.e. observation) for patients with ME following CRVO and patients with ME following BRVO considered not suitable for laser treatment (including patients with retinal haemorrhage affecting the macular or foveal ischaemia). According to the MHRA, healthcare professionals may regard it necessary to prescribe or advise on the use of an unlicensed medicine through the so-called ‘specials’ regime when no licensed suitable alternative is available (10). A lack of licensed pharmacological therapies has led to the off-license use of triamcinolone or bevacizumab in the treatment of ME following RVO. However, neither triamcinolone nor bevacizumab were developed, or are recommended by their manufacturers, for use as an intravitreal injection (as described in Section 2. The SPC for bevacizumab contains a special warning against intravitreal use (67). Unapproved intravitreal use has been associated with severe eye inflammation and sterile endophthalmitis (10). Triamcinolone (Kenalog) is formally contraindicated for intraocular use within its SPC (12). In the GENEVA studies, Ozurdex is used as per its SPC, reflecting the product’s intended use in clinical practice.

The main limitation of the trial methodology was that the study was powered to assess outcomes in all patients, rather than in the subgroups of patients with BRVO or CRVO. However, the identical masked, randomised, sham-controlled, three-arm, parallel-group design of the studies enabled the pre-planned pooling of data, thereby providing greater statistical power for subgroup analyses.

Patients with CRVO were not screened for perfused or ischaemic disease, although the relatively good vision (>20/200) of the patient population at baseline suggests most patients had perfused disease (25). However, the development of neovascularisation in 2.6% patients treated with Sham suggests that ischaemic disease may have been present in some patients (25). This potentially led to an underestimation of the benefits of treatment within the larger population of patients with perfused disease (25).

The GENEVA studies demonstrate that patients treated with Ozurdex are less likely to experience a 15-letter decrease in BCVA than those receiving Sham. This suggests that patients with RVO (particularly CRVO) will continue to lose VA over time if the condition is not treated. The data derived from the GENEVA studies augments the current evidence base regarding the natural history of RVO. The GENEVA studies (19-22) successfully demonstrate that in patients with ME following BRVO or CRVO, Ozurdex offers long-lasting improvements in VA from a single injection whilst being well tolerated with an acceptable safety profile.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The population described within the decision problem was “people with macular oedema caused by RVO”. This submission considers this population; specifically those patients with ME following CRVO, BRVO with MH, and BRVO previously treated with laser. Ozurdex is intended to provide a first-line pharmacological treatment option for all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with MH. Ozurdex also provides a second-line treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment.

In patients with persistent ME (> 8 months duration) (29), permanent retinal damage and vision loss may occur (14, 16, 29, 30). Haemorrhages into the vitreous from neovascularisations are more likely to affect eyes with chronic ME and often result in poor final VA and a less favourable prognosis (15). As such, the longer the duration of ME, the more challenging the treatment (31). It was therefore considered relevant (as indicated in the decision problem) to include BCVA outcomes within subgroups divided by the duration of ME (time since diagnosis).

The main comparator for the condition under review is observation (best supportive care), as there are currently no licensed pharmacological interventions for ME following BRVO or CRVO and immediate laser photocoagulation is not considered appropriate for the subgroups considered within this submission (CRVO, BRVO with MH, and BRVO previously treated with laser). In the GENEVA studies, Ozurdex is compared with a Sham procedure followed by observation, reflecting the main comparator within the decision problem.

A primary goal of treatment in BRVO or CRVO is the improvement of VA or the prevention of further vision loss (17, 18). In accordance with treatment goals in clinical practice and outcomes stated within the decision problem, the efficacy of Ozurdex in the GENEVA studies was primarily assessed via improvements in BCVA. Data derived from clinical studies for Ozurdex consider VA in the study eye. As RVO is predominantly a monocular disease at first presentation, BCVA in the affected eye is the most important measure of health-related benefit. Visual acuity in the whole person is not considered as although improvements in overall visual functioning may be greater when the treated eye is considered 'better-seeing', treatment is warranted even when the affected eye is the worse-seeing eye (WSE) (35).

In the GENEVA studies, changes in BCVA were assessed using the ETDRS chart (49).The standardised format of ETDRS chart overcomes some of the limitations posed by the Snellen chart (51). A 15-letter change in BCVA using the ETDRS method considerably exceeds the amount required to have a high degree of certainty that the observed alteration is a valid change in VA and not attributable to random chance (49, 50). The GENEVA studies considered clinically relevant outcomes such as categorical changes from baseline BCVA (including ≥ 15 letters improvement, ≥ 15 letters worsening, and ≥ 10-letters improvement), as well as mean changes to BCVA.

Contrast sensitivity (CS) is not routinely measured in UK clinical practice. Where CS is measured, the Pelli-Robson chart is most often used. However, it should be noted that although this measure has been adopted in a research setting, the Pelli-Robson chart is not widely used in clinical practice (43). It has been suggested that use of the Pelli-Robson chart is limited when an assessment of each eye individually or repeated measures of CS (e.g. in longitudinal studies) is required (44). Data from the GENEVA studies for contrast sensitivity are presented within this submission, however, the reliability /validity of CS as an outcome measure in retinal disease is open to debate (45).

In patients with ME, thickening of the macular region of the retina occurs in association with an excessive accumulation of fluid (31). Optical Coherence Tomography (OCT) may help in determining the prognosis in ME and is sensitive imaging method for detecting and quantifying macular thickening (31). In the GENEVA studies changes in retinal thickness were relevantly assessed using OCT.

Adults experiencing sight loss will experience an associated loss in Health Related Quality of Life (28) and it is known that RVO is associated with decreased patient-reported visual functioning (32). Health-related quality of life (HRQL) was considered as an outcome measure within the decision problem. The GENEVA studies assessed the impact of Ozurdex treatment upon patient-reported visual functioning using the vision-specific National Eye Institute Visual Functioning Questionnaire 25 (NEI-VFQ-25). The NEI-VFQ-25 is a shortened version of the 51-item NEI-VFQ Field Test Version and consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. In clinical practice it is generally considered that visual performance is dictated by the better-seeing eye (34). Although improvements in visual functioning may be greater when the treated eye is

'better-seeing', treatment is also warranted when the affected eye is the worse-seeing eye (35). The basis for treatment in a patient's worse-seeing eye is in part to preserve or improve VA in that eye in the event of vision loss in the better-seeing eye (35). Improving VA in the worse-seeing eye may be beneficial for a patient's vision-related functioning (35) and, therefore, HRQL. A 1-grade improvement using the NEI-VFQ-25 is considered to be the minimum level of change that can be assessed by a patient in their visual functioning as a result of vision in both eyes.

The decision problem indicates that data regarding the adverse effects of treatment should be presented within this submission. The AEs reviewed in the GENEVA studies bear particular relevance to those expected in clinical practice. Due to the nature of administration and limited systemic effects of DEX the main focus was ocular AEs. Intraocular injections are associated with the risk of an inflammatory response (68), therefore the GENEVA studies looked for evidence of such ocular AEs, such as the presence of anterior chamber cells and endophthalmitis. The association between increases in IOP and the intravitreal injection of steroids is also well-recognised; hence changes in IOP were evaluated extensively in the GENEVA studies. The formation of cataracts was also stringently explored due to the link between cataract development and steroid use (28). Adverse events potentially related to the mode of administration of intravitreal injections were also evaluated, such as retinal detachments and retinal tears.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Macular oedema (ME) is a common complication of RVO (3, 4). It is the primary cause of vision loss in patients with BRVO (5) and one of the leading causes of vision loss in patients with CRVO (6). The primary goal of treating BRVO and CRVO is to improve or prevent further loss of VA and reduce ME (17, 18). However, due to a paucity of evidence-based treatment options for RVO, there is uncertainty around the best pharmacological approach. A lack of licensed pharmacological treatment options for ME following CRVO or BRVO has led to the use of therapies not developed or indicated for the treatment of RVO (e.g. triamcinolone and bevacizumab) in clinical practice. The safety and efficacy of triamcinolone and bevacizumab as intravitreal injections has yet to be established and formulations of these therapies are not designed for ocular use (as advised by the manufacturers) (11, 12). Indeed, triamcinolone (Kenalog formulation) is actively contraindicated for intraocular use. A systematic review of the literature (as described in Section 5.7 and 9.4) demonstrated that based on the clinical evidence available robust indirect comparisons of triamcinolone (Kenalog formulation) or bevacizumab versus Ozurdex were not possible. In addition, triamcinolone nor bevacizumab were developed, or are recommended by their manufacturers, for use as an intravitreal injection (as described in Section 2). Therefore, neither triamcinolone nor bevacizumab were considered as appropriate comparators to Ozurdex. Ozurdex represents the only

licensed pharmacological intervention available for the treatment of ME following BRVO or CRVO. The evidence provided within this submission, based upon the GENEVA clinical trials, is primarily for the 700 µg dose of DEX (i.e. Ozurdex). This is consistent with the dose recommended in clinical practice and described within the SPC for Ozurdex (13).

The patient demographics in the GENEVA studies are representative of the UK population. The GENEVA studies included centres in Europe (Austria, France, Germany, Italy, Poland, Spain and the UK) and the majority of patients were Caucasian (75%). A recent systematic review by Rogers et al (2010) (69) demonstrated that the prevalence of RVO is similar between men and women. Therefore, the similar ratio of males (53.4%) to females (46.6%) in the GENEVA studies would be observed in clinical practice. BRVO is two to three times more common than CRVO (1, 70). The percentage of patients with BRVO (65.5%) was greater than observed for CRVO (34.5%) in the GENEVA studies and is therefore likely to be representative of the proportion of patients with BRVO and CRVO in England and Wales.

At present, observation is one of the main clinical approaches adopted in England and Wales for the management of patients with ME following CRVO and patients with ME following BRVO considered not suitable for laser treatment. Patients unsuitable for immediate laser treatment include those with MH in whom treatment is currently delayed for three to six months following the initial event to allow for the absorption of the majority of the haemorrhage (1). In these circumstances, typical management presently comprises observation although evidence clearly suggests that delaying intervention may reduce final VA outcomes for patients (3). The GENEVA studies compared Ozurdex with a Sham procedure followed by observation. Therefore, in the patient subgroups considered within this submission (CRVO, BRVO with MH, and BRVO with previous laser treatment) the results of the GENEVA studies are applicable to clinical practice in England and Wales.

Ozurdex offers clinicians a licensed first-line pharmacological option for use in those patients for whom immediate treatment options are limited. This includes all patients affected by ME following CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with MH. Ozurdex also provides a treatment option for patients affected by ME following BRVO who have not previously responded to laser treatment.

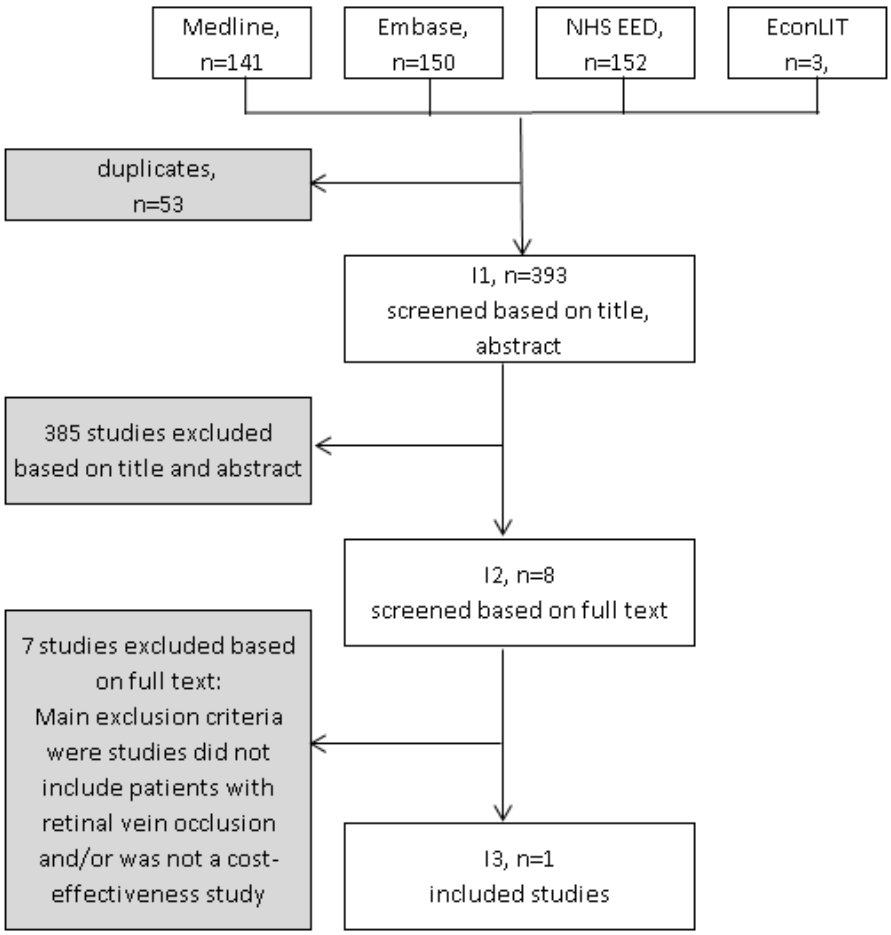
6 Cost-effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

A systematic review of the literature was carried out in order to identify existing cost-effectiveness studies in the treatment of ME secondary to RVO. Cost-effectiveness search terms were combined with terms for the disease area specified in Section 9.10. The inclusion and exclusion criteria were chosen to identify all economic evaluations assessing treatments for ME secondary to RVO. The results of these searches are reported within this section. The methods used are reported in Section 9.10.

Figure 15: Consort flow diagram for cost-effectiveness studies



393 potentially relevant publications were identified for inclusion in the systematic review of cost-effectiveness, of which 385 were excluded on the basis of title and abstract. After review of eight full text papers, a further seven were excluded. Therefore, one paper was identified as appropriate for inclusion (Figure 15).

6.1.2 Description of identified studies

Table 97: Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Brown (23)	2002	U.S.	A cost-utility model to compare the incremental cost-effectiveness of laser therapy versus observation for ME occurring secondary to BRVO	Branch Vein Occlusion Study Group enrolled 139 eligible eyes with branch retinal vein occlusion assigned randomly to either a treatment group or untreated control group. Eligible eyes had a visual acuity ranging from 20/40 to 20/200 and vision was decreased primarily due to ME associated with the branch vein occlusion. The mean follow-up for this study was 3.1 years and mean age of patients was 66 years.	0.23 (laser therapy, no treatment)	NS	$6,118

Abbreviations: ICER, incremental cost-effectiveness ratio, QALY(s), quality-adjusted life year(s), NS, not stated

The study by Brown et al., (23) set out to estimate the cost-effectiveness of laser photocoagulation vs. observation in BRVO from a US perspective and considering a lifetime horizon. Efficacy estimates were taken from the Branch Vein Occlusion Study Group (BVOS) study (n = 139). The analysis used a decision-analytic model (a decision tree and Markov model) in order to estimate costs and effects, the latter of which was measured in terms of quality-adjusted life years (QALYs). Costs included the cost of laser therapy and additional fluorescein angiography.

Patients were assigned a mean level of VA based on their mean score at the end of the BVOS trial. Patients experiencing BRVO in their WSE were not attributed any additional level of utility from improved VA in the affected eye. Other key features of the model included the use of a 3% constant risk of fellow eye occurrence (FEO), based on data presented in Hayreh et al (1994). This was only modelled for patients with the index RVO in their WSE (71). Results suggest that laser photocoagulation is a cost-effective option in the treatment of BRVO, with a base-case ICER of $6,118.

6.1.3 Quality assessment

A quality assessment was completed for the study included in the review. The completed checklist is available in Section 9.11.

6.2 De novo analysis

6.2.1 Patients

The model considered patients with ME resulting from CRVO or BRVO who in the affected eye at first entry to the model have:

- A retinal thickness of ≥ 300 µm, as measured by optical coherence tomography (OCT) and,
- A BCVA, as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) method, of between 34 and 68 letters (approximately 20/200 to 20/50 in Snellen equivalents)[h].

[h] The term BCVA refers to a person's visual acuity with their vision optically 'best corrected' by means of standardised testing and refraction with corrective lenses using a standardised visual chart. In clinical trials the standardized ETDRS VA chart is used instead of the Snellen VA chart that may be more commonly used in clinical practice or routine lay discussion of VA. The ETDRS is the gold standard used in clinical trials because the chart consists of lines each containing 5 letters, with a halving of letter sizes every third line from top to bottom. This allows statistical analyses to be performed using the ETDRS chart (whereas this is not possible with typical Snellen chart. For the ETDRS chart, a letter score is generated from 0 to 100 (representing the number of letters read correctly). A higher score represents better VA (~85 is 'normal' or average vision). A one-line change on the ETDRS chart corresponds to a 5 letter score change (improvement or worsening); a change of ≥ 15 letters is a common clinical trial benchmark for effectiveness of a treatment. Approximate Snellen equivalents to the ETDRS are presented in this report to aid intpretation of ETDRS acuities with the more commonly used in daily practice Snellen. The Snellen chart and scoring is based on correct letters read at a distance of 20 feet. VA is represented as a fraction, with the distance at which you are standing being the numerator (top part of fraction), and the normal maximum legible viewing distance as the denominator (bottom of fraction). So if, at 20 feet, you can read the letters on the row marked "20", this means you have normal vision (20/20). If at 20 feet, the smallest letters you can read are the letters on the row marked "40", this means you have VA of 20/40 (i.e. half normal VA; you can read at 20 feet what a "normal" sighted person can read at 20 feet).

These criteria represent the inclusion criteria for the Ozurdex Phase III trials GENEVA 008 and GENEVA 009. The model considered four patient populations fulfilling the criteria described above.

1. First-line treatment for all patients affected by ME following RVO (patient population referred to hereafter as "All RVO").

Clinical data for the all RVO population was derived from the GENEVA trials; the inclusion criteria for this population is described in Table 8 of Section 5.

2. First-line treatment for all patients affected by ME following CRVO (patient population referred to hereafter as "CRVO").

Clinical data for the CRVO population was derived from the GENEVA trials; the inclusion criteria for this population is described in Table 8 of Section 5.

3. Treatment for all patients affected by ME following BRVO with macular haemorrhage, who are not considered appropriate for immediate laser treatment (patient population referred to hereafter as "BRVO with macular haemorrhage").

Macular haemorrhage refers to the presence of blood in the centre of the retina, which may prevent the immediate use of laser photocoagulation treatment for ME following BRVO. Clinical guidelines from the Royal College of Ophthalmologists (RCO) (1) recommend waiting for at least three months for the macular haemorrhage to clear following BRVO, before performing laser treatment. It is clear that delaying treatment will reduce the potential benefit that a patient can experience from treatment, with evidence from a range of studies demonstrating that the longer the duration of ME the smaller the improvements in BCVA (7, 41).

[redacted]

In patients with BRVO with macular haemorrhage, Ozurdex provides an immediate treatment option. In GENEVA 008 and GENEVA 009 the presence of macular haemorrhage at baseline was assessed by use of standardised fundus photographs that were rated at a central reading centre by trained and masked assessors using a standard template. A total of 88.5% (255/288) of the Ozurdex treatment group and

94.2% (260/276) of the Sham group had “Definite” presence of macular haemorrhage at the qualification or baseline study visit (Table 9 of Section 5).

Clinical data for patients with BRVO and macular haemorrhage were derived from the GENEVA trials *a posteriori.*

Further subgroup analyses of patients with BRVO are presented for patients with ME < 90 days and patients with ME ≥ 90 days to further inform the impact of duration of ME on BCVA outcomes following treatment.

4. Treatment for all patients affected by ME following BRVO who have previously been treated with and not responded to laser treatment (patient population referred to hereafter as “BRVO with previous laser treatment”).

In this population, patients with BRVO were considered who had previously received laser photocoagulation treatment for ME yet still had persistent ME and vision loss. Of the 564 patients with BRVO in the pooled GENEVA 008 and GENEVA 009 trials, 72 (12.8%) patients had previously received laser photocoagulation treatment, based on medical history records indicating previous receipt of laser photocoagulation for ME due to BRVO in the study eye (Table 9 of Section 5).

Clinical data for patients with BRVO with previous laser treatment were derived from the GENEVA trials *a posteriori*.

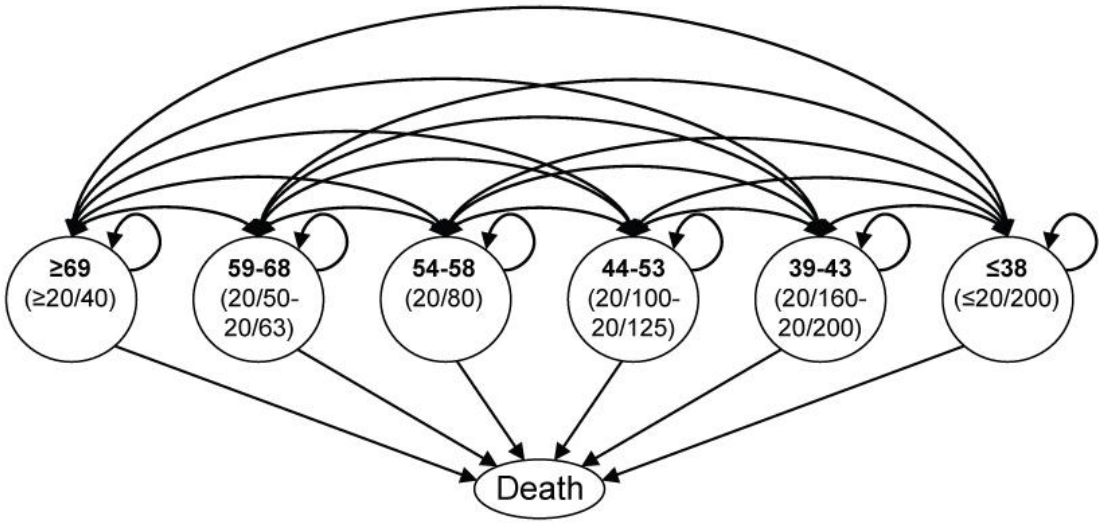
Model structure

6.2.2 Model schematic

A Markov model was developed in Microsoft® Excel. This approach was used to estimate lifetime outcomes and costs for patients with ME and vision loss following BRVO or CRVO treated with Ozurdex compared with a strategy of observation. The evaluation was conducted from the perspective of the NHS and personal and social services in England and Wales.

The model comprised six health states based on BCVA in the affected eye (described hereafter as BCVA), as measured by the ETDRS method (see Section 9.20), and the absorbing state death (Figure 16). Patients entered the model after diagnosis of ME following RVO and remained in the model until they reached 100 years of age, or death. Patients could move between health states at the start of each new cycle as a consequence of model events, i.e. a change in BCVA or death.

Figure 16: Markov model



Six numbered states represent BCVA categories, corresponding to numbers of letters as read on the ETDRS chart, with Snellen equivalent (feet) in parentheses.

The proportion of patients in each health state at the beginning of each cycle was calculated. Values were assigned to each health state to reflect both the health benefits and costs associated with spending one cycle in that state.

QALYs were calculated based on the proportion of live patients in each BCVA health state at the beginning of each cycle multiplied by the BCVA-associated utility score for that state. The proportion of patients was half-cycle adjusted by averaging the proportion predicted by the model at the start and the end of each cycle.

Costs incurred during each model cycle included the costs of treatment, treatment-related resource use, the management of treatment-related adverse events and blindness defined as vision of ≤ 38 letters (≤20/200) in the better-seeing eye (BSE). Costs and benefits occurring in future years were discounted at a rate of 3.5% per annum in line with current NICE guidance.

The overall lifetime costs and benefits of treating patients with either Ozurdex or observation were calculated by summing QALYs and costs across states and cycles.

Incremental cost-effectiveness ratios (ICERs; incremental costs per QALY gained) for Ozurdex, compared with observation were calculated as the difference in total costs divided by the difference in total QALYs over the lifetime of the model.

Clinical outcome data for Ozurdex and observation arms within the model were derived from the Phase III trials GENEVA 008 and GENEVA 009, described in Section 5. The Sham arm in these studies, in which patients were exposed to a needleless DDS applicator without trial medication, is used to provide data for the observation arm of the model.

6.2.3 Justification of model structure

The Markov approach used within this submission has been adopted in previous economic evaluations of interventions used in the treatment of conditions affecting visual acuity (23, 24). This approach provides an appropriate structure with which to model changes in visual acuity over time and the associated resource use and costs.

Whilst the management of ME following RVO is limited to approximately 2.5 years in BRVO and 3 years in CRVO (see Extrapolating visual acuity) the benefits of treatment relating to visual acuity may persist for the patient's lifetime[i]. A Markov model, which facilitates the inclusion of lifetime benefits, was therefore deemed to be the most appropriate methodology.

The lifetime time horizon used in the model assumes a maximum age of 100 years. This time horizon is in accordance with the NICE reference case, and has been used in previous economic evaluations of technologies in retinal conditions including vision loss due to BRVO (23, 24). The cohort considered by the model was assumed to have the mean age of patients at diagnosis in the GENEVA studies (base-case, 64.5 years [Section 5.3.4 Baseline characteristics[j]). This informed the application of an annual mortality risk. Due to the uncertainty surrounding long-term projections of disease progression, sensitivity analyses were conducted, in which the average age at diagnosis was varied.

The model employed a cycle length of one month for the first three months following presentation with RVO, followed by a three-month cycle in months four to six and six-monthly cycles thereafter. The use of relatively short cycles for the first six months facilitated the capture of short-term changes in BCVA following presentation with RVO and first treatment with Ozurdex. Model cycles also correspond to the timing of visits within the GENEVA trials thereby facilitating the use of patient-level data to estimate transition probabilities. Six-monthly cycles were considered appropriate thereafter as Ozurdex has been shown to produce improvements in visual acuity for up to 6 months (25, 46). In addition, Ozurdex was administered at six-monthly intervals during the GENEVA study programme.

6.2.4 Definition of health states

Health states in the model are designed to capture the observed improvements in BCVA resulting from treatment with Ozurdex and the loss in BCVA in patients following an observation strategy only. Health states based on BCVA facilitate the estimation of the cost and health benefits resulting from gains in BCVA via the application of health state-specific costs, health-related quality of life (HRQL) and excess mortality.

The six BCVA health states used in the model ranged from HS0, corresponding to best vision (BCVA ≥ 69 letters on the ETDRS chart) to HS5, corresponding to worst vision (BCVA ≤ 38 letters) (Table 98).

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[i] Unlike, for example, age-related macular degeneration, RVO can be considered an acute event in which patients can expect to achieve a new stable level of visual acuity.

[j] Expert opinion confirmed that baseline characteristics in the GENEVA studies were broadly reflective of clinical practice (see Section 6.3.5 for details)

Table 98: BCVA model health states and comparison with GENEVA 008/GENEVA 009 endpoints

BCVA Health State	HS0	HS1	HS2	HS3	HS4	HS5
ETDRS, number of letters	≥ 69	59-68	54-58	44-53	39-43	≤ 38
Snellen equivalent, feet (metres) †	≥ 20/40 (≥ 6/12)	20/50-20/63 (6/15-6/20)	20/80 (6/24)	20/100-20/125 (6/30-6/38)	20/160-20/200 (6/48-6/60)	≤ 20/200 (≤ 6/60)
Assumed ETDRS in state	75.00	63.50	56.00	48.50	41.00	33.00
Corresponding category in GENEVA 008 and GENEVA 009‡	~ ≥ 3-line gain from HS2	~ 1- or 2-line gain from HS2	no gain/ loss	~ 1- or 2-line loss from HS 2	~ ≥ 3-line loss from HS 2	~ ≥ 4-line loss

Abbreviations: BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; HS, health state.† the ETDRS chart and Snellen chart are standard methods of determining visual acuity; ‡ enrolled trial population with mean baseline BCVA of 54.

A five-letter change on the ETDRS chart corresponds to a one-line change and the minimum level of change on ETDRS that can reasonably be attributed to an intervention (as opposed to simply occurring by chance) (49, 50). Model health states were selected based on their relevance in terms of untreated natural history, functioning or legal thresholds, for example, driving restrictions common to many countries, and to corresponding empirical changes commonly reported in clinical trials using the ETDRS chart, including the GENEVA 008 and GENEVA 009 Ozurdex trials (Table 98).

Few patients with CRVO or BRVO improve without treatment to the best health state (≥ 69 letters) (72, 73). In addition, the threshold of 69 letters corresponds to approximately 20/40 feet on the Snellen chart, a common cut-off for driving restrictions in many Western countries (47). The worst health state (ETDRS ≤ 38 letters, Snellen equivalent ≤ 20/200 feet) is a common threshold for legal blindness in many countries (48). It is associated with increased direct medical costs and indirect costs when associated with BCVA in the better-seeing eye (BSE) (74) and mortality (75).

The intermediate BCVA health states and the thresholds among adjacent states were informed by the mean baseline BCVA reported in the Ozurdex Phase III trials, which was 54 letters (Section 5.3.4 Baseline characteristics). Mean baseline BCVA reported in the Ozurdex Phase III trials was included in HS2 (54-58 letters, Snellen equivalent 20/80 feet). HS1 (59-68 letters) corresponds to approximately a 1- or 2-line gain on the ETDRS chart from HS2, and HS0 (≥ 69 letters) corresponds to a 3-line or greater gain on the ETDRS chart from HS2. Similarly, HS3 (44-53 letters) corresponds to a 1- or 2-line loss on the ETDRS chart, HS4 (39-43 letters) corresponds to a 3-line loss and HS5 (≤ 38 letters) corresponds to a 4-line or greater loss on the ETDRS chart.

The distribution of patients across the six health states at baseline in GENEVA 008 and 009 for the four patient populations of interest in this evaluation are shown in Table 99. The baseline distribution assumed in the model was an average of the

baseline distributions of the BRVO and CRVO populations of interest weighted by the ratio of BRVO/CRVO (65.5%/34.5% in the base-case).

Changes in BCVA for patients in the Ozurdex or observation groups of the model were derived from the GENEVA 008 and GENEVA 009 clinical trials (Section 5), a clinical experts panel (54) and natural history data (72, 73), as described subsequently in Sections 6.3.1 and 6.3.2.

Table 99: Baseline BCVA distribution by patient group (GENEVA 008-009 pooled)

BCVA Health State, ETDRS letters (Snellen, feet)†	All RVO			CRVO			BRVO with macular haemorrhage			BRVO with previous laser treatment		
	Ozurdex	Sham	Total	Ozurdex	Sham	Total	Ozurdex	Sham	Total	Ozurdex	Sham	Total
	N=421	N=423	N=844	N=133	N=147	N=280	N=255	N=260	N=515	N=36	N=36	N=72
HS0 ≥ 69 (≥ 20/40)	0.0%	1.2%	0.6%	0%	0.7%	0.4%	0%	1.2%	0.6%	0%	0%	0%
HS1 59-68 (20/50-20/63)	40.9%	39.5%	40.2%	35.3%	37.4%	36.4%	42.0%	40.4%	41.2%	27.8%	36.1%	31.9%
HS2 54-58 (20/80)	16.9%	22.0%	19.4%	18.0%	23.8%	21.1%	16.9%	20.4%	18.6%	19.4%	25.0%	22.2%
HS3 44-53 (20/100-20/125)	23.0%	19.4%	21.2%	18.0%	15.0%	16.4%	25.1%	22.3%	23.7%	27.8%	22.2%	25.0%
HS4 39-43 (20/160)	8.3%	7.6%	7.9%	12.0%	6.1%	8.9%	6.7%	8.5%	7.6%	16.7%	11.1%	13.9%
HS5 ≤ 38 (≤ 20/200)	10.9%	10.4%	10.7%	16.5%	17.0%	16.8%	9.4%	7.3%	8.3%	8.3%	5.6%	6.9%
Mean (SD)	54.3 (9.9)	54.7 (9.9)	54.5 (9.9)	52.4 (10.6)	53.3 (10.8)	52.9 (10.7)	54.9 (9.7)	55.3 (9.4)	55.1 (9.5)	52.8 (9.9)	54.6 (9.0)	53.7 (9.5)
Range	34-68	28-80	28-80	34-68	28-69	28-69	34-68	34-80	34-80	34-68	37-67	34-68

Abbreviations: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment of Diabetic Retinopathy Study; HS, health state; macular haemorrhage, macular haemorrhage, SD, standard deviation.
† Snellen equivalent is an approximation only.

6.2.5 Context

ME is a common complication of RVO (3, 4). It is the primary cause of vision loss in patients with BRVO (5) and one of the leading causes of vision loss in patients with CRVO (6). The primary goal of treating BRVO and CRVO is to improve or prevent further loss of visual acuity and reduce ME (17, 18).

The observation arm within the model acts as a control to demonstrate how a patient's visual acuity is affected when treatment is not provided.

Patient subgroup analysis and scenario analysis are used to present cost-effectiveness results based on clinically relevant subpopulations. Base-case analyses for CRVO and BRVO populations differentiate patients on the basis of aetiology and in whom guidelines recommend different management strategies (1). These guidelines predate the availability of Ozurdex and recommend observation in CRVO patients and laser photocoagulation in BRVO patients who are suitable for treatment.

Subgroup analysis is also used to present the cost-effectiveness of Ozurdex in BRVO patients with differing durations of ME at the start of treatment (≤ 90 days; > 90 days). This analysis is included as the longer the duration of ME following BRVO, the more likely a patient is to experience a poorer final BCVA outcome. In addition, the longer the duration of ME, the more challenging the treatment (31).

6.2.6 Key features of the economic analysis

Table 100: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	The lifetime of the patient population (maximum 100 years of age)	The time horizon chosen reflects that used in previous economic evaluations of technologies in retinal conditions (23, 24). The assumed age of the cohort at baseline is based on the mean age of patients at diagnosis in the GENEVA studies (base-case, 64.5 years, confirmed by expert opinion (see Section 6.3.5). This informs the application of an annual mortality risk. A lifetime horizon was considered appropriate as it incorporates all benefits and costs associated with treatment. However, due to the uncertainty surrounding long-term projections of disease progression, sensitivity analyses were conducted, in which the average age at diagnosis was varied.	NICE methods guide
Cycle length	Cycle length of one month for the first three months following	The use of relatively short cycles for the first six months facilitated the capture of short-	GENEVA 008 and 009 (19-22,

Factor	Chosen values	Justification	Reference
	presentation with RVO, followed by a three-month cycle in months four to six and six-monthly cycles thereafter.	term changes in BCVA following presentation with RVO and first treatment with Ozurdex. Model cycles also correspond to the timing of visits within the trials, facilitating the use of patient-level data to estimate transition probabilities. Six-monthly cycles were considered appropriate thereafter as Ozurdex has been shown to produce improvements in visual acuity for up to 6 months (25, 46). In addition, Ozurdex was administered at 6-monthly intervals during the GENEVA study programme.	25, 46)

Half-cycle correction	Half-cycle correction was applied to health state utilities and annual costs. This was done by applying utilities and costs to the average of the number of patients at the start and end of each cycle. As treatment costs were assumed to occur at the start of a model cycle, half-cycle correction was not applied to treatment costs.	Half-cycle correction to health state utilities and annual costs effectively accounts for those patients that leave the given state in each cycle, who are assumed to accrue only half a cycle's utility and cost. [k]	(76)
Were health effects measured in QALYs; if not, what was used?	Yes	Specified in the decision problem (final scope).	NICE methods guide
Discount of 3.5% for utilities and costs	Costs and benefits occurring in future years were discounted at a rate of 3.5% per annum.	Approach recommended by NICE	NICE methods guide
Perspective (NHS/PSS)	NHS/PSS	Specified in the decision problem (final scope).	NICE methods guide

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

[k] For example, if 10 patients began a cycle and eight finished the cycle, with two having moved to another state, the average number of patients in that state during the full cycle would be nine. This is the equivalent of eight patients accruing utility and cost for a full cycle and two for only half a cycle each, equating to nine full cycles in total.

Technology

6.2.7 Intervention and comparator

Patients entering the model receive Ozurdex or observation.

Ozurdex is the only pharmacological treatment licensed for use in ME following RVO. Ozurdex use in the model reflects the licensed indication and dose as specified within the SPC (13).

The current standard of care for patients with ME following RVO is poorly defined, and no therapeutic interventions are currently recommended in both CRVO and BRVO.

In CRVO there is no proven treatment for ME and no visual acuity benefit in the use of laser therapy (1). Therefore, observation is the current management strategy in clinical practice.

Prior to the availability of Ozurdex, laser photocoagulation was the only recommended interventional treatment for patients with BRVO. However, immediate laser photocoagulation may not be appropriate for patients with macular haemorrhage involving the centre point (7-9). In this circumstance, typical management presently comprises observation.

There are a number of unlicensed therapies highlighted in the final NICE scope for this appraisal, which are not included in this analysis. These therapies include intravitreal triamcinolone acetonide (IVTA; 'Kenalog' formulation or equivalent) and bevacizumab.

The rationale for the use of IVTA to treat macular oedema is that corticosteroids reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF (1). The Summary of Product Characteristics (SPC) for Kenalog® explicitly states that Kenalog is contraindicated for intraocular injection. The SPC further states a special warning that adequate studies to demonstrate the safety of Kenalog use by intraocular (intravitreal) injections have not been performed (61). A systematic review undertaken to identify RCTs of Kenalog or its equivalent, did not identify any relevant RCT data in this indication, ME following RVO (See Figure 1 of Section 5.1 and Section 5.7). The only triamcinolone studies (SCORE) (41, 60) identified were not deemed appropriate as they use an alternative formulation of triamcinolone (Trivaris) that is not available in Europe. The formulations of Trivaris and Kenalog differ. Kenalog, the formulation commercially available in the UK, is a crystalline suspension developed for intra-articular use. The implications of injecting the Kenalog formulation into the vitreous have not been well studied (61). Therefore, there were no RCT data to facilitate an indirect comparison of Kenalog, or its equivalent, and Ozurdex.

The SPC for bevacizumab also contains a special warning against intravitreal use. This warning states that adverse reactions have been reported from unapproved intravitreal use. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, increased intraocular pressure, intraocular

haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these appeared as serious adverse reactions (67). A systematic review of RCTs of bevacizumab was undertaken but did not identify RCT data in this indication, ME following RVO (See Figure 1 of Section 5.1 and Section 5.7). It was therefore not possible to perform an indirect comparison of bevacizumab versus Ozurdex.

The Sham arm in the GENEVA studies is used as a proxy for observation in clinical practice for the purposes of modelling. Predicted model outcomes were compared against long-term natural history data during development of the economic model to validate the approach taken to modelling the long-term effects of retinal vein occlusion on visual acuity (7, 8, 77).

6.2.8 Treatment continuation rule

A treatment continuation rule has not been assumed in the economic model.

6.3 Clinical parameters and variables

6.3.1 Implementation of clinical data in the model

Patient population included in the model

The patient population used for the analysis includes patients with ME and vision loss following CRVO or BRVO receiving Ozurdex treatment or observation (Sham) from the pooled GENEVA 008 and GENEVA 009 trials. A total of 1,267 patients were randomized to receive Ozurdex (427 patients), DEX 350 µg (414 patients) or Observation (426 patients). The effects of DEX 350 µg were generally similar to, albeit somewhat less efficacious than, those of Ozurdex. This analysis includes the data for Ozurdex only, which is the dose form approved by the European Medicines Agency (EMA) (700 µg). The patient population considered in the model therefore includes 427 patients who were randomized to Ozurdex and 426 patients who were randomized to the Observation arm.

Patients receiving Ozurdex treatment

Of the 427 patients randomized to receive Ozurdex, four patients did not receive study treatment and two patients randomized to Ozurdex received DEX 350 µg (one patient) and Sham (one patient). This analysis therefore includes 421 patients who received Ozurdex treatment.

Patients received masked treatment on day 0 and were monitored from initial treatment to day 180. At day 180, patients were eligible to receive an open-label (OL) treatment with Ozurdex. Eligibility for retreatment was defined as BCVA < 84 letters (approximately 20/20 Snellen equivalent) or retinal thickness by OCT > 250 µm in the central 1 mm macular subfield, and in the investigator's opinion, the procedure would not put the patient at significant risk.

Of the 421 Ozurdex patients, 20 patients received initial treatment but discontinued before day 180. A further 60 patients entered the OL phase but were not eligible for re-treatment. Therefore, 80 patients received a single injection of Ozurdex.

The remaining 341 patients who received Ozurdex at the first injection, completed the initial treatment period to day 180 and received a second injection of Ozurdex. For both the initial treatment and OL phases, the last observation carried forward method was used.

Patients receiving Observation

Of the 426 patients randomized to the Observation arm, four patients did not receive a sham injection. However, one patient mis-randomised to the Ozurdex arm (randomised to Ozurdex but actually received Sham) was included in the observation group for the model. The analysis therefore includes 423 patients who received Observation treatment.

Patients received masked treatment on day 0, and were monitored from initial treatment to day 180. At day 180, patients were eligible to receive an OL treatment. Again eligibility criteria for treatment with Ozurdex were BCVA < 84 letters (approximately 20/20 Snellen equivalent) or retinal thickness by OCT > 250 µm in the central 1 mm macular subfield, and in the investigator's opinion, the procedure would not put the patient at significant risk.

Of the 423 Observation patients, 24 patients received sham injection but discontinued before day 180. Of the remaining 399 patients who entered the OL phase, 72 patients were not eligible to receive an Ozurdex injection. Therefore, 327 patients (326 randomised patients and the 1 mis-randomised patient), received an Ozurdex injection at OL day 180.

This population is hereafter referred to as the modified intent-to-to-treat (mITT) population. Pooled patient-level data from GENEVA 008 and GENEVA 009 were used to calculate transition probabilities for the model.

Data used

Based on the mITT population used in the model, an injection of Ozurdex at the commencement of the OL period was administered to 81% (341/421) and 77% (327/423) patients in the Ozurdex and Sham groups, respectively (Figure 4).

BCVA was assessed in all patients (Ozurdex and Sham) at one, two, three, and six months in the masked, randomised controlled period. BCVA was also assessed at seven, eight, nine and 12 months in Ozurdex-treated patients during the OL safety follow-up.

Transition probabilities were based on patient-level data pooled from GENEVA 008 and 009 studies: from baseline to month 12 in Ozurdex-treated patients and from baseline to six months in the observation (Sham) group.

Extrapolation of outcomes from the GENEVA studies was required in order to estimate changes in BCVA from six to 12 months in the observation (Sham) group and long-term BCVA changes (beyond 12 months to 2.5 and 3 years respectively, for BRVO and CRVO) in the Ozurdex and observation (Sham) treatment arms.

When extrapolating visual acuity, Brown et al (2002) (23) assumed stabilisation in BCVA from year three in the previous economic evaluation of laser therapy in patients with RVO. The assumptions regarding time to stabilisation in this analysis adopt comparable time horizons and were based on the opinions of ophthalmologists at three advisory board meetings (see Table 102), who suggested that patients with BRVO are typically discharged at 2.5 years and patients with CRVO at three years. Results of a survey of four UK ophthalmologists (78), designed to collect estimates of clinical resource use over time, also reported no routine hospital visits beyond three years.

In the absence of observed data from month six in the observation (Sham) group and month 12 in the Ozurdex-treated group, the last available set of transition probabilities was reapplied until stabilisation of visual acuity as follows:

- Using data from months six to 12 for Ozurdex retreated patients
- Using data from months three to six derived from the Sham (observation arm) for:
    - Observation patients (Sham)
    - Ozurdex patients who did not receive a further Ozurdex treatment at the start of a model cycle but whose OCT met the retreatment criteria (OCT > 250 µm) and were therefore considered as unresolved.

  As these data facilitated the estimation of three-month transition probabilities, transition probabilities were applied twice per six-month period (using a transition matrix that is the product of the month three to month six transition matrix with itself).
- An identity matrix was applied to Ozurdex patients who were not retreated and had resolved macular oedema (OCT ≤ 250 µm) at the start of any model cycle; effectively maintaining them in the BCVA healthstate reached.

The calculation of transition probabilities and the extrapolation thereof is discussed in Section 6.3.2.

Adverse events

Ozurdex-related adverse events captured in the model included intraocular pressure (IOP), cataracts and retinal tears or detachments. These were the main adverse events observed in the GENEVA 008 and GENEVA 009 Ozurdex trials and which, as advised by the clinical expert panel, would be those that could require additional treatment.

Further information regarding the incidence of adverse events, how they were treated and the costs associated with their treatment is provided in Section 6.5.7.

6.3.2 Transition probabilities

The availability of trial data for 12 months for Ozurdex, six months for observation, and the lifetime modelling approach meant that it was necessary to apply different assumptions in the calculation of transition probabilities in different time-periods of the model.

The data and assumptions used in each time-period are described below and summarised in Table 101. Transition probabilities are presented in Appendix 9.22 and the sample size used for calculations is detailed in Table 99.

Months zero to six

Patient-level data from the GENEVA 008 and GENEVA 009 trials were pooled at baseline and each follow-up visit (one month, two months, three months and six months) for Ozurdex and observation (Sham) patients. Transition probabilities were then calculated using these data (Table 101). In Ozurdex-treated patients, transition probabilities represented the change in BCVA within the six months after the first treatment.

Months six to 12

Transition probabilities for Ozurdex-retreated patients from month 6 to 12 were based on pooled patient-level data for months 6 to 12 from GENEVA 008 and GENEVA 009. The transition probabilities during this period represented the change in BCVA between month 6, immediately prior to receiving the second Ozurdex treatment (if appropriate) and month 12, six months after re-treatment. As the peak effect of Ozurdex is generally observed at months two to three post implant, at month six the treatment response is lower. The model captures the treatment peak benefit in the initial treatment phase (six months) by utilising different cycle lengths. However, a fixed six-month cycle length is used for the re-treatment phase and this may under estimate the benefit of Ozurdex.

Patients in the Ozurdex arm who do not receive retreatment (at six months) are assigned transition probabilities weighted by two factors:

- The proportion of patients in GENEVA 008 and GENEVA 009 who did not receive a second Ozurdex treatment because their condition had resolved. Such patients were assumed to have stable visual acuity.

- The proportion of patients in GENEVA 008 and GENEVA 009 who did not receive a second Ozurdex treatment but had not resolved. Such patients were assumed to receive the same transition matrices as observation patients, the estimation of which is described below. [l]

[l] Observation patients receive the product matrix of the month three to month six transition matrix estimated from the sham arm of GENEVA 008 and GENEVA 009 clinical trials.

Stabilisation of visual acuity for those not retreated was defined as, for those patients not being retreated at day 180, having a retinal thickness of ≤ 250 µm, as measured by optical coherence tomography (OCT).

In the absence of trial data beyond six months for observation patients, outcomes and transition probabilities from month 6 to month 12 were based on the last two available BCVA assessments for all Sham patients (visits at three and six months) in the GENEVA 008 and GENEVA 009 clinical trials.

As these data provided a three-month transition probability and the model uses six-month cycles from month six, the transition probabilities derived from the month 3 and month 6 visits for the Sham group were applied twice. This transformation was performed using a transition matrix that is the product of the month three to month six transition matrix with itself.

Beyond Year 1

Transition probabilities beyond year one were based on the last set of available observed data in the GENEVA 008 and GENEVA 009 clinical trials.

- Month 6 to month 12 from the Ozurdex arm for Ozurdex retreated patients
- A weighted average transition probability as described previously for patients in the Ozurdex arm not receiving retreatment (see Ozurdex patients not retreated)
- Three to six-month transition probabilities from the Sham arm applied twice per six-month cycle for observation

Transition probabilities were applied from years 1 to 2.5 (BRVO) and years 1 to 3 (CRVO). From 2.5 years (BRVO) or 3 years (CRVO) onwards it was assumed that there would be no further change in BCVA from that achieved at the point of stabilisation (years 2.5 and 3 for BRVO and CRVO respectively) (see Extrapolating visual acuity).

Table 101: Source of patient outcomes to calculate model transition probabilities

Timeframe	Cycle length	Ozurdex		Observation	Reference
		Retreated	Not retreated		
0–6 mths	1 mth from 0–3 mth; 3 mths from 3–6 mths	Observed data for TPs: 0–1 mth 1–2 mths 2–3 mths 3–6 mths	N/A	Observed data for TPs: 0–1 mth 1–2 mths 2–3 mths 3–6 mths	GENEVA 008, GENEVA 009: Pooled PLD
6–12 mths	6 mths	Observed data for TPs: 6–12 mths	TP is the weighted average of: the identity matrix (no change) in patients assumed to have achieved stabilisation, and observation TPs from 3–6 mths (applied twice) in patients whose visual acuity was deemed not to have stabilised	As per TPs from 3–6 mths (applied twice)	GENEVA 008, GENEVA 009: Pooled PLD
12 mths–2.5 or 3 yrs (BRVO or CRVO)	6 mths	As per TPs from 6-12 mths	TP is the weighted average of: the identity matrix (no change) in patients assumed to have achieved stabilisation, and observation TPs from 3–6 mths (applied twice) in patients whose visual acuity was deemed not to have stabilised	As per TPs from 3–6 mths	GENEVA 008, GENEVA 009: Pooled PLD
All years beyond year 1	6 mths	Transition to Death state			English and Welsh life tables (79)
All years	6 mths	Fellow eye occurrence			Weibull regression based on data from Hayreh (71)
>2.5 or 3 yrs† (BRVO or CRVO)	6 mths	BCVA stability assumed			Clinical expert opinion (80), Brown et al (23)

BCVA, Best-Corrected Visual Acuity; PLD, patient level data; mth, month; TP, transition probability; yr, year. † a patient can also transition to the Death state as for the 12 mth–3 yr period.

6.3.3 Variation of transition probabilities over time

It was assumed that there would be no further change in BCVA due to ME and RVO from 2.5 years (BRVO) or 3 years (CRVO) onwards as the patient's vision stabilises (see Extrapolating visual acuity). Thereafter, the patient remains in the same BCVA state until the age of 100 or until death unless WSE patients experience a retinal vein occlusion in their BSE.

Outcomes for patients experiencing a fellow eye occurrence of RVO (FEO) were based on the initial RVO until the point at which they suffer their second RVO in their fellow eye (as described in more detail in Section 6.3.7 (fellow eye occurrence)). From this point, outcomes were then modelled for the second RVO, with patients achieving vision stability after the occurrence of the second event after 2.5 and 3 years in BRVO and CRVO, respectively.

6.3.4 Linking intermediate outcome measures to final outcomes

N/A

6.3.5 Clinical experts

Table 102: Advisory boards and other use of expert opinion

	Advisory Boards and expert opinion			
Details	New York, September 30th 2009 ("New York Clinical Expert Panel") (54)	Edinburgh, November 12th 2009	Edinburgh, May 12th 2010	Estimations of routine clinical resource use
Criteria for selection	Ophthalmologists from four countries[m] participated with expertise in RVO and/or economic modelling	Ophthalmologists practising in Scotland	Ophthalmologists practising in Scotland	Ophthalmologists practising in the UK
Number approached	7	8	6	4
Number participating	5	5	2	4
Conflict of interest	Experts were paid by Allergan for their attendance at the one-day adboard	Experts were paid by Allergan for their attendance at the one-day adboard	Experts were paid by Allergan for 3 hours' preparation and their attendance at the one-day adboard	Experts were paid by for an hour of their time.

[m] UK; Austria; Canada; U.S

	Advisory Boards and expert opinion			
Information provided	Experts received a PowerPoint presentation of the clinical evidence from the GENEVA clinical trials and were presented key clinical questions to fill data gaps for the economic model	Experts received a PowerPoint presentation of the clinical evidence from the GENEVA clinical trials	Experts received the clinical sections of the SMC submission prior to the meeting for review and were presented the economic model on the day of the advisory board meeting.	Experts received the questionnaire detailed in Section 9.13
Method of elicitation	Open discussion facilitated with a PowerPoint of questions	Open discussion facilitated with a PowerPoint of questions	Open discussion facilitated with a PowerPoint of questions	
Questions	Questions were asked regarding the extrapolation of clinical outcomes beyond the study data, re-treatment rates, timepoints for stabilization of VA in RVO, resource use assumptions, cost of vision loss,	Questions broadly included the generalisability of clinical trial data to the Scottish populace, natural history of RVO, identification of comparators, resource use, retreatment criteria and relevant subgroups.	Questions were asked regarding the clinical validity of model assumptions, BSE:WSE split, medical resource use for Ozurdex and, in the absence of clinical data, the mean time to stabilisation of visual acuity after the occurrence of ME following RVO.	
Attaining consensus	Consensus was attained via discussion.	Consensus was attained via discussion.	Consensus was attained via discussion.	N/A

Summary of selected values

6.3.6 Summary list of variables used

Model parameters, references, ranges used in deterministic sensitivity analysis and information used in PSA are presented in Table 153 of the Appendix.

6.3.7 Extrapolation of trial outcomes

Extrapolation of transition probabilities

The extrapolation of transition probabilities beyond the duration of the GENEVA clinical trials is discussed in Section 6.3 and summarised in Table 101. Clinical expert opinion was sought regarding the clinical validity of these assumptions (Section 6.3.5). The input of two external academic health economists was sought to evaluate the methodological approach to extrapolation.

Fellow eye occurrence (FEO)

In patients who have experienced RVO, there is a risk of developing a subsequent RVO in the fellow eye. The impact of an RVO in the fellow eye has previously been modelled by Brown et al (23) for the use of laser therapy in RVO and also by Gupta et al (81) in epiretinal membrane surgery.

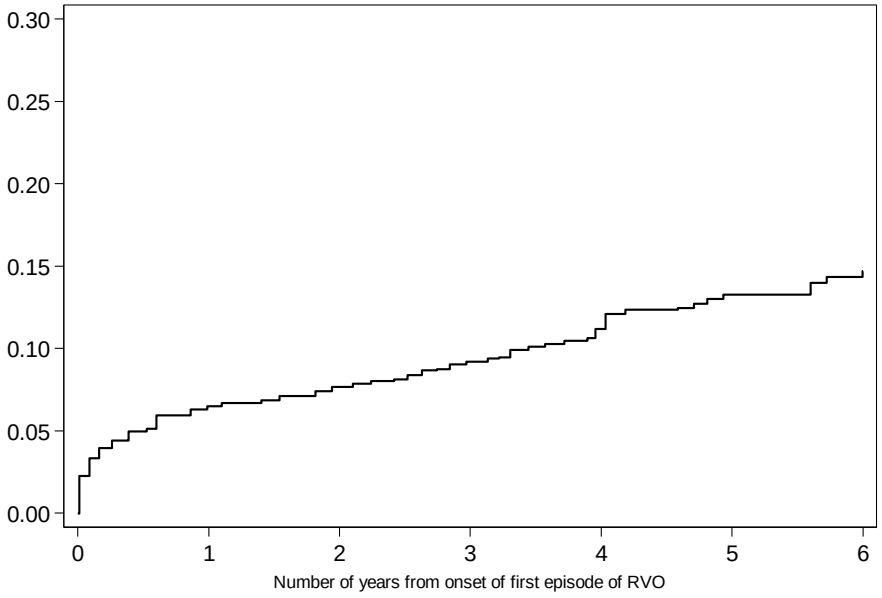
By modelling the incidence of a second RVO in a patient's BSE, the model is able to incorporate the impact of deterioration in the BSE, when the WSE has already been affected by an RVO. The model did not consider FEO in the WSE or subsequent occurrence in the same eye for pragmatic reasons, although both these events are possible. The cumulative probability of developing a second episode of the same or a different type of RVO in the same eye has been estimated to be 2.5% within four years (71). The exclusion of FEO in the WSE or subsequent occurrence in the same eye is a limitation of the analysis. The implications of this limitation are discussed in Section 6.9.

As in the evaluation by Brown et al (23), the incidence of FEO was based on data from Hayreh et al (71). This study, designed to assess the recurrence of RVO in 1,108 patients (1,229 eyes) with various types of RVO, reported a cumulative incidence of RVO in the fellow eye of 11.9% within 4 years. Data in this analysis did not allow differential analyses for BSE and WSE patients or for patients with CRVO developing BRVO or vice versa. The probability of FEO in this analysis is therefore assumed to be independent of BSE/WSE diagnosis and CRVO/BRVO status at baseline.

Based on the Kaplan-Meier analysis presented by Hayreh et al, it was apparent that the instantaneous risk of fellow eye involvement declines over time (71). In order to model the time-dependent occurrence of fellow eye involvement, parametric survival analysis was used to determine the probability of FEO for each model cycle for the duration of the model.

A published technique was used (82) in order to reproduce the data points presented by Hayreh and colleagues. Based on the extracted data points, the incremental number of FEOs between each time point was estimated. These values formed the basis of a pseudo patient-level dataset of 1,108 patients. The results of this process are presented in Figure 17.

Figure 17: Estimated Kaplan-Meier failure



[redacted]

[redacted]

Figure 18: Cox-Snell residuals for various functional forms

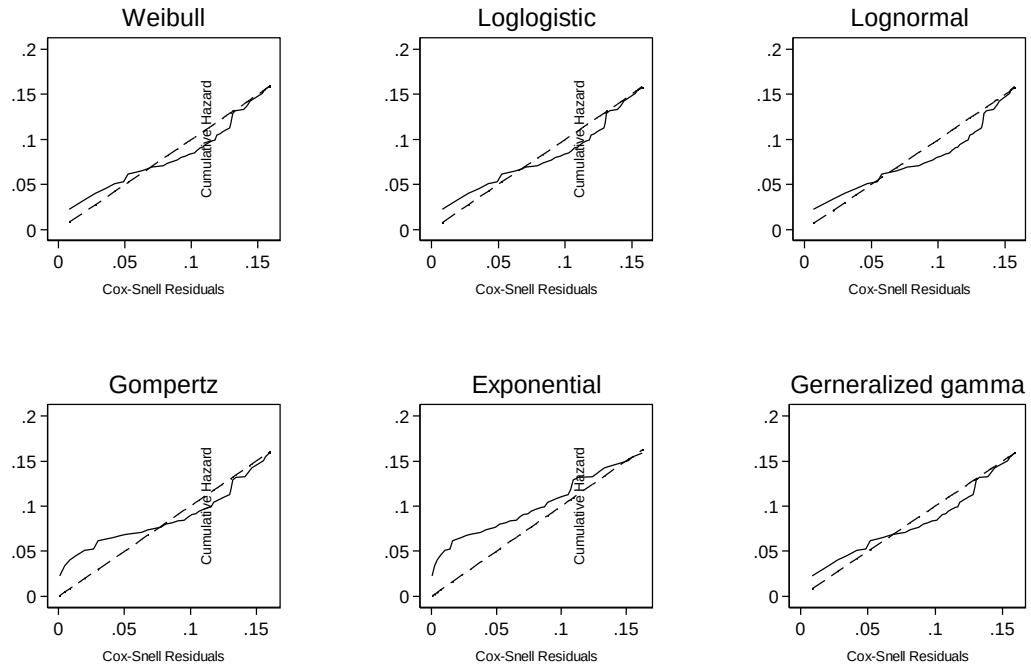


Table 104: Model fit for various functional forms

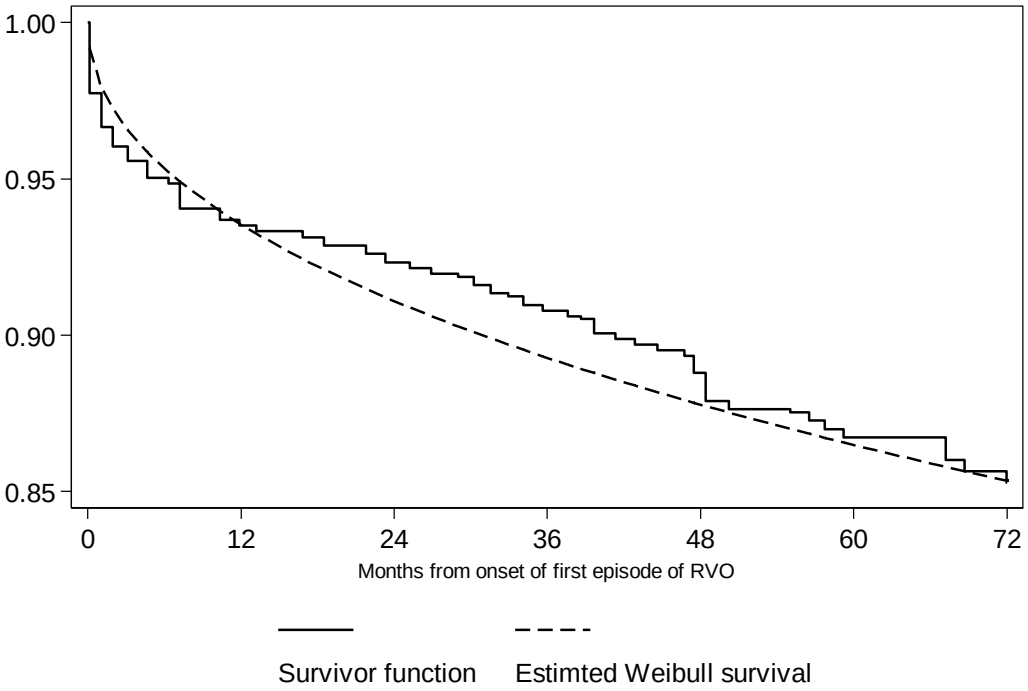
Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	1108	-808.844	-808.844	1	1619.688	1624.698
gompertz	1108	.	-792.4002	2	1588.800	1598.821
lognormal	1108	.	-752.4465	2	1508.893	1518.914
loglogistic	1108	.	-751.3174	2	1506.635	1516.655
weibull	1108	-750.6872	-750.6872	2	**1505.374**	1515.395
generalized gamma	1108	.	-750.1047	3	1506.209	1521.24

Abbreviations: Obs, observations; ll, log likelihood; df, degrees of freedom, AIC, Akaike information criterion; BIC Bayesian information criterion.

Figure 19 plots the estimated survivor against the estimated Kaplan-Meier survivor function. Results show evidence of a declining hazard of FEO over time. The results from the Weibull regression were used to estimate the probability of FEO during each Markov cycle[n]. Note it is assumed that 100% of RVOs in the fellow eye presented by Hayreh and Colleagues represent instances of ME secondary to RVO. This is justified on the basis that Hayreh and colleagues studied only patients presenting in the authors' Ocular Vascular Clinic (71). Given this fact, it was felt reasonable to assume that the study cohort would comprise symptomatic patients only. This assumption is explored in sensitivity analysis (Table 115).

[n] The transition probability tp for cycle length u at time t is given as $tp(t_u) = 1 - \exp\{\lambda(t-u)^{\gamma} - \lambda t^{\gamma}\}$ (83), where λ is the exponential of the "_cons" terms and γ is the "p" term from Table 1.

Figure 19: Parametric Weibull survival vs. estimated Kaplan-Meier survival



For example, based on this analysis 6.5% of patients with an RVO in their WSE would develop a second RVO in their BSE by the end of their first year. For these patients, the costs and QALYs in their first year are assumed to be that applicable for a WSE. At the end of the first year, these patients are assumed to begin treatment as a patient with an RVO in their BSE.

It is assumed that the distribution of FEO will be 65.5% BRVO and 34.5% CRVO; the split observed in the GENEVA studies at baseline (Table 9 of Section 5). It is important to note that reported ICERs reflect the initial event (BRVO or CRVO) irrespective of whether patients subsequently experience an FEO of a different aetiology. For example, the ICER reported for CRVO patients will reflect their initial event, even if they subsequently experience a BRVO in their fellow eye. In the absence of mortality, the 10-year cumulative probability of either a CRVO or BRVO patient at baseline experiencing a subsequent CRVO is 6.3%. Similarly, the 10-year cumulative probability of either a CRVO or BRVO patient at baseline experiencing a subsequent BRVO is 12.1%.

As previously highlighted, the effects of subsequent RVO in the same eye and fellow eye recurrence in the WSE have not been modelled, and may be viewed as a limitation of the analysis. A further limitation of the analysis is that patients were exposed to the risk of FEO assuming that they had entered the model on day one of the initial RVO whereas in clinical practice patients may present for treatment at a later date.

6.3.8 Summary of assumptions used

Table 105: Key model assumptions

Structural component	Chosen base-case assumption	Rationale	Validation / test in sensitivity analysis
% BSE:WSE	90:10	The BSE:WSE split in GENEVA 008 and 009 was not considered representative of the patient population in clinical practice. Patients with a non-study eye ≤34 letters were excluded from these studies. This resulted in a smaller proportion of BSE patients than would be expected in clinical practice. This % split was recommended by the New York Clinical Expert Panel as being representative of pts seen in clinical practice (54).	A pooled analysis of the BRAVO and CRUISE studies suggests that 92% of pts have poorer visual acuity in their study eye ((66); (84)) (see Section 6.9). In sensitivity analysis, ICERs are shown for all pt subgroups on a graph in which the % BSE and WSE is varied between 0% and 100%
Stabilisation in visual acuity	2.5 years in pts with BRVO 3 years in pts with CRVO	Brown et al (2002) (23) assumed stabilisation in BCVA from year three. Time to stabilisation in this analysis was based on the opinions of ophthalmologists at three advisory board meetings (see Table 102), who suggested pts are typically discharged at these times. Results of a survey of four UK ophthalmologists (78), also reported no routine hospital visits beyond three years.	Scenario analysis is presented in which stabilisation occurs at one year.
Re-injection	Occurs at six-monthly intervals	This is the frequency of retreatment administered in the GENEVA trials and is consistent with 1) the Phase II dose-ranging trial (46) used to inform dose selection within the GENEVA studies, in which the Ozurdex treatment effect was sustained for up to six months. 2) Consistent with the Phase IIb bridging study in which the applicator	Sensitivity analysis was not conducted around this assumption

<table>
<tr><th>Structural component</th><th>Chosen base-case assumption</th><th>Rationale</th><th>Validation / test in sensitivity analysis</th></tr>
<tr><td></td><td></td><td>formulation was also observed with sustained effct for up to six months (85) 3) Pre-clinical trials ((62))</td><td></td></tr>
<tr><td></td><td>Max. 5 injections in BRVO
Max. 6 injections in CRVO</td><td>On the basis of the assumed time to stabilisation in visual acuity (2.5 years BRVO; 3 years CRVO) and six-month retreatment period.</td><td>In the scenario analysis in which stabilisation occurs at one year, pts are assumed to have a maximum 2 injections (baseline and six months)

The cost of extended treatment in CRVO patients beyond three years is also included within sensitivity analysis. This analysis assumes no further changes in visual acuity.</td></tr>
<tr><td></td><td>
<table>
<tr><th>Txs</th><th>Timepoint</th><th>CRVO</th></tr>
<tr><td>1</td><td>Baseline</td><td>100%</td></tr>
<tr><td>2</td><td>6 mths</td><td>86%</td></tr>
<tr><td>3</td><td>12 mnths</td><td>63%</td></tr>
<tr><td>4</td><td>18 mnths</td><td>63%</td></tr>
<tr><td>5</td><td>24 mnths</td><td>36%</td></tr>
<tr><td>6</td><td>30 mnths</td><td>36%</td></tr>
<tr><th>Txs</th><th>Timepoint</th><th>BRVO</th></tr>
<tr><td>1</td><td>Baseline</td><td>100%</td></tr>
<tr><td>2</td><td>6 mths</td><td>79%</td></tr>
<tr><td>3</td><td>12 mnths</td><td>19%</td></tr>
<tr><td>4</td><td>18 mnths</td><td>19%</td></tr>
<tr><td>5</td><td>24 mnths</td><td>8%</td></tr>
<tr><td>6</td><td>30 mnths</td><td>0%</td></tr>
</table>
</td><td>The % of pts receiving the first two treatments (i.e. at baseline and six months) is based on the pooled results of the GENEVA trials (implementation of clinical data in the model).

The % of pts receiving subsequent treatments is estimated based recommended by the New York Clinical Expert Panel as being representative of pts seen in clinical practice (54).</td><td>A scenario analysis is presented - 100% of CRVO pts receive the maximum six treatments and 100% of BRVO pts receive the maximum five treatments permitted in this analysis.</td></tr>
<tr><td>Extrapolation beyond the trial until stabilisation in visual acuity</td><td>In the absence of data, the last set of available TPs were used to extrapolate outcomes beyond follow up in the GENEVA trials.</td><td rowspan="2">Available data were used in the absence of long-term data beyond follow up in the GENEVA trials.</td><td rowspan="2">A scenario analysis is presented in which no further transitions occur after maximum trial follow up at 12 months.</td></tr>
<tr><td>Observation patients</td><td>TPs from month three to month six were used to calculate three-monthly probabilities, which are applied twice per six-month period (using a transition matrix that is the product of the month three to month six transition matrix with itself).</td></tr>
</table>

Structural component	Chosen base-case assumption	Rationale	Validation / test in sensitivity analysis
Retreated Ozurdex patients	TPs from day 180-360 estimated using data for retreated pts only are applied following every re-injection until stabilization.		
Non-retreated Ozurdex patients	TPs weighted by two factors: • % pts in GENEVA 008 and GENEVA 009 who did not receive a second Ozurdex treatment because their condition had resolved. Such pts were assumed to have stable visual acuity • % pts in GENEVA 008 and GENEVA 009 who did not receive a second Ozurdex treatment but had not resolved. Such pts were assumed to receive the same TPs as observation patients, the estimation of which is described above. The presence of the stabilisation of visual acuity = % pts not treated at day 180, having a retinal thickness of ≤ 250 µm, as measured by optical coherence tomography (OCT).	At day 180, patients who were not retreated comprised two patient groups: patients who no longer met the eligibility criteria for retreatment and those who did meet the eligibility criteria. This approach was taken as the best estimate of visual acuity in this dichotomous group.	A scenario analysis is presented in which all pts not retreated with Ozurdex are subject to the TPs for observation patients.
The risk of fellow eye occurrence (FEO)	Pts are exposed to a time-dependent risk of fellow eye occurrence estimated using a Weibull curve.	The use of Weibull extrapolation to inform FEO is more conservative than the constant risk assumed in the only other economic evaluation of an intervention in RVO(23) Every parametric survival function available in Stata was tested. The decision to use the Weibull extrapolation was based on the AIC (Akaike information criterion), which was lowest with this function.	A scenario analysis is presented in which a constant risk of FEO of 3% p.a. is assumed as per Brown et al 2002 (23)
	The incidence of CRVO and BRVO in FEO is equal to the % CRVO: BRVO split at baseline in GENEVA 008 and 009. This split is applied irrespective of diagnosis in the initial event.	There is no known pathophysiological reason why this would not be the case.	No specific scenario or sensitivity analysis were conducted around this assumption. However, when the % of CRVO and BRVO at baseline is varied in sensitivity analysis, this percentage also changes to reflect the revised baseline split.

Structural component	Chosen base-case assumption	Rationale	Validation / test in sensitivity analysis
	FEO is only modelled in pts in whom the initial event occurs in the WSE	If there is damage to the BSE when the WSE has already been affected, the impact on the patient's binocular BCVA, and therefore utility, is even more significant than the initial RVO.	The inclusion of FEO in pts in whom the initial event occurs in the BSE or in the same eye were not included in a scenario analysis.
Blindness	Patients with visual acuity ≤6/60 in their BSE are assumed to experience an excess mortality risk and accrue a cost of vision loss.	This approach was taken in a previous economic evaluation by Colquitt et al (2008) in age-related macular degeneration (24). The inclusion of these parameters seeks to capture all relevant health benefits and costs (pertinent to the perspective of this analysis) associated with the treatment of patients in a condition which can result in significant loss of vision.	A scenario analysis is presented in which no excess mortality is applied to patients with visual acuity ≤6/60. The cost of blindness is varied in sensitivity analysis.

Assumptions surrounding mortality

A literature review was conducted to investigate the association between vision loss and mortality in December 2009 (86). This search was updated for the purposes of this submission in July 2010 (Appendix 15: Mortality of vision loss data search; Appendix 17: Results of literature review for excess mortality risk associated with blindness).

The identified studies consistently found that blind patients were at an increased risk of death relative to patients with good vision.

For the purposes of the model, patients with severe vision loss or blindness, defined as those patients with BSE BCVA of ≤ 38 letters, were assumed to have an increased risk of death of 1.54 times that of the general population in the base-case analysis, based on the study by Christ et al., (75). Christ et al. used structural equation modelling (SEM) to estimate the effects of vision loss on mortality risk, taking into account both direct and indirect pathways (disability and self-rated health). This estimate is derived from the largest population survey of the studies identified and adjusts for confounders on the causal pathway. Christ et al. was therefore felt to be the most robust study for the base-case analysis. A similar risk – 1.5 times that of the general population – for individuals experiencing blindness, has previously been used by Colquitt et al. in an economic evaluation of treatment for macular degeneration (24).

It was assumed that RVO patients falling into health states other than blindness would not experience an increased risk of death due to vision impairment over that of the general population (87, 88).

Gender specific general population life tables for the English and Welsh population were extracted from published sources to inform the risk of all-cause mortality (79). The starting age of patients in the model (65 years) and the proportion of males in the pooled trial population (53.4%) (Table 9) were used to calculate annual hazard rates of death for the entire model population, and subsequently per-cycle hazard rates[o].

No mortality was assumed for the first year. This has little impact on the model results as the death rate is low for patients at the age at which they enter the model. After the first year, the per-cycle hazard rates were used as follows: patients who started each model cycle were redistributed between the six BCVA health states using the appropriate transition probabilities to give the distribution of patients in these health states at the end of the cycle before taking mortality into account. The proportion of patients who survived each cycle was calculated as $\exp(-\lambda h)$, where λ is a mortality multiplier for the death rate in the patient population compared with the general population (λ=1 in the base-case, except for patients with BSE BCVA of ≤ 38 letters, λ=1.54) and h is the per-cycle hazard rate.

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 Effects of the condition on patients' quality of life

Adults experiencing sight loss incur an associated loss in quality of life (QoL) (28). It is generally accepted that RVO is associated with decreased patient-reported visual functioning (32). Patients report difficulties with many aspects of daily life, distance vision, driving and general health (32, 33).

Vision loss in the WSE compared with the BSE differentially impacts health-related quality of life (HRQL) (89). The HRQL impact of an RVO in a WSE may be limited due to the remaining eye (the BSE) generally having reasonable BCVA. However, if a second RVO occurs in the BSE, the impact on the patient's binocular BCVA, and therefore HRQL, may be greater than the effect of the initial RVO. Importantly, independent studies have confirmed that retinal vein occlusions in either the WSE or BSE have significant and measurable impact on HRQL (32, 33).

The differential effect on HRQL observed in WSE and BSE patients was applied to the model by using different utility weights for the WSE and the BSE[p], and is described further in Section 6.4.9. By modelling the incidence of a second RVO in a patient's BSE, it is also possible to incorporate the impact of deterioration in the BSE, when the WSE has already been affected by an RVO. This approach has been described in Section 6.3.7 (fellow eye occurrence).

[o] The annual probability of death by gender was converted to a cumulative survival rate for all patients, weighted by the proportion of males and females, and starting at the average age of RVO diagnosis (65 years). From this the annual hazard of death for all patients was calculated using the equation -log(cumulative survival^{t}/cumulative survival^{t-1}), and converted into a hazard rate per cycle based on the length of each cycle.

[p] BSE was defined as baseline study eye BCVA greater than or equal to baseline non-study eye BCVA and WSE was defined as baseline study eye BCVA less than baseline non-study eye BCVA.

6.4.2 Change in HRQL over time

Small changes in visual acuity are expected to occur for up to 2.5 years in BRVO and 3 years in CRVO (see Extrapolating visual acuity).; consequently leading to changes in HRQL over this period. However, after this period, stabilisation in visual acuity is assumed to occur and therefore no further changes in HRQL resulting from the RVO event are assumed beyond this time.

HRQL data derived from clinical trials

6.4.3 Description of trial based HRQL data

HRQL data were collected throughout the trial using the NEI-VFQ-25 instrument, a commonly used disease-targeted measure of health status. The NEI-VFQ-25 is a non-preference based, vision-specific QoL measure, which does not include the direct estimation of utility weights. Therefore, for the purposes of this evaluation, utility values were derived from a preference-based scoring algorithm produced through direct valuation from the general population (see study details in Section 6.4.4). Previous literature estimates permit only valuation of health states driven by BCVA in the BSE (see Section 9.17).

Mapping

6.4.4 Description of mapping exercise

Although this section details the methods used to estimate utility values from a disease-specific measure, the study detailed included an extensive and rigorous study to elicit preferences of the general population. It therefore does not conform strictly to the common definition of mapping.

The approach used permits utility values to be estimated from a subset of six-items from the NEI-VFQ-25, a vision-specific health-related quality of life measure that assesses binocular visual functioning. The subset of six items define a recently developed health state classification system, the Visual Function Questionnaire Utility Index (VFQ-UI) (90).

Eight binocular visual-functioning health states defined by the VFQ-UI were previously valued using time-trade off (TTO) by 607 members of the general population in the UK, Canada, Australia, and the US to elicit preference scores (91). Each participant was asked to value all eight health states. Using the resulting database of general population preferences, econometric modelling was used to create an algorithm (the VFQ-UI algorithm), whereby a utility score could be estimated for any possible health state defined by the six NEI VFQ-25 items that comprise the VFQ-UI classification system.

The development of the VFQ-UI classification system and algorithm was a multi-year research project sponsored by Allergan and conducted in collaboration with United BioSource Corporation and academic research groups, which included Professor John Brazier and Professor Ron Hays.

For the purpose of valuing the six health states in the cost utility model, regression analyses were performed whereby the study BCVA score at Day 180 in the GENEVA studies was set as the independent variable to predict the VFQ-UI utility score (dependent variable) at Day 180. Separate analyses were performed for those patients whose study eye was their WSE and for those whose study eye was their BSE. The resulting separate equations from the regressions for WSE and BSE study-eye patients were then used to estimate the utility score values for each of the six model health states, by WSE and BSE [redacted]

The mean visual acuity in each health state and the regression coefficient used to predict utility for a given level of visual acuity are also varied independently in sensitivity analysis.

An alternative methodology (the Sharma equation) was used in sensitivity analysis (Section See Section 6.6.2 Sharma equation). The Sharma equation has been used previously by economic evaluations in retinal conditions, such as Colquitt et al, 2008 (24). Compared to the VFQ-UI BSE cohort health state valuations in the reference case using the VFQ-UI, the Sharma equation provides lower (worse) valuations for each of the six model health states and supports that the VFQ-UI BSE health state valuations are reasonable and potentially conservative.

HRQL studies

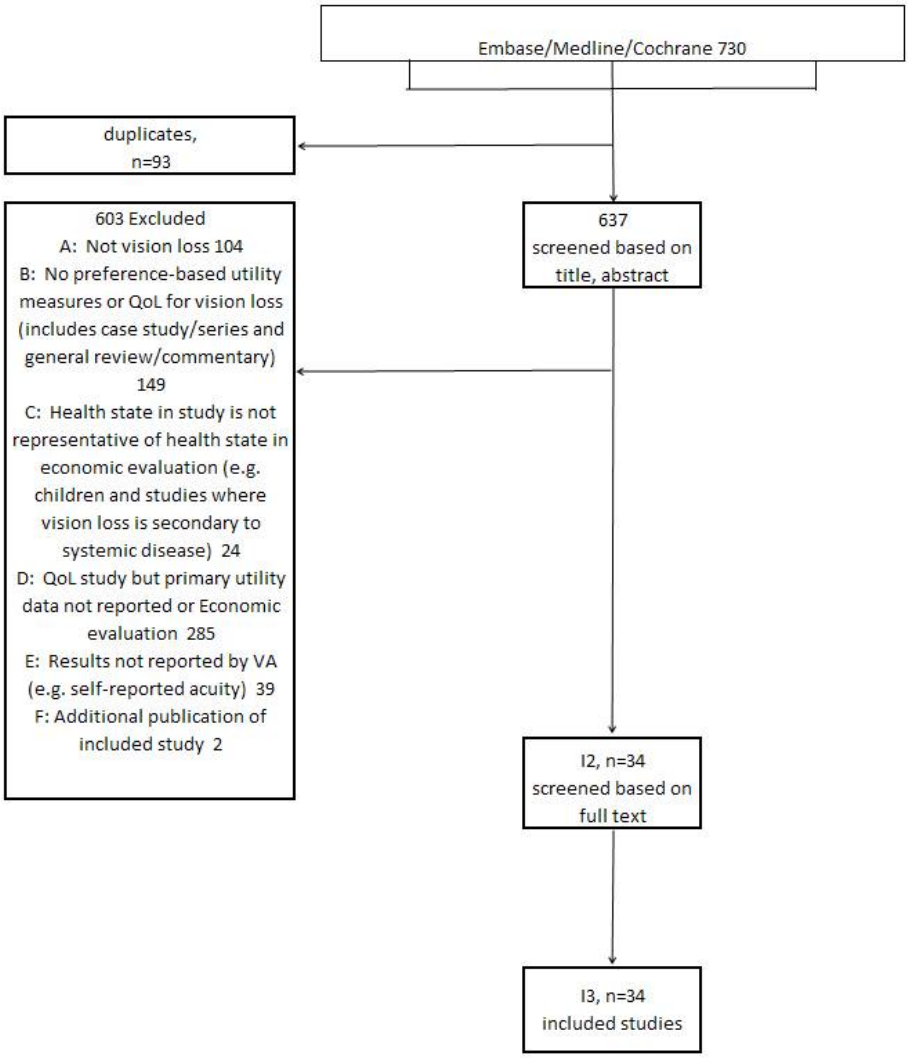
6.4.5 Literature search to identify HRQL studies

6.4.6 HRQL studies identified

Two systematic literature searches were undertaken to identify published HRQL data. The first was in December 2009 during model scoping and the second was an update of the initial literature review to present day and in order to capture all relevant data in the format requested by NICE. HRQL search terms were combined with terms for the disease area specified in Section 9.12.

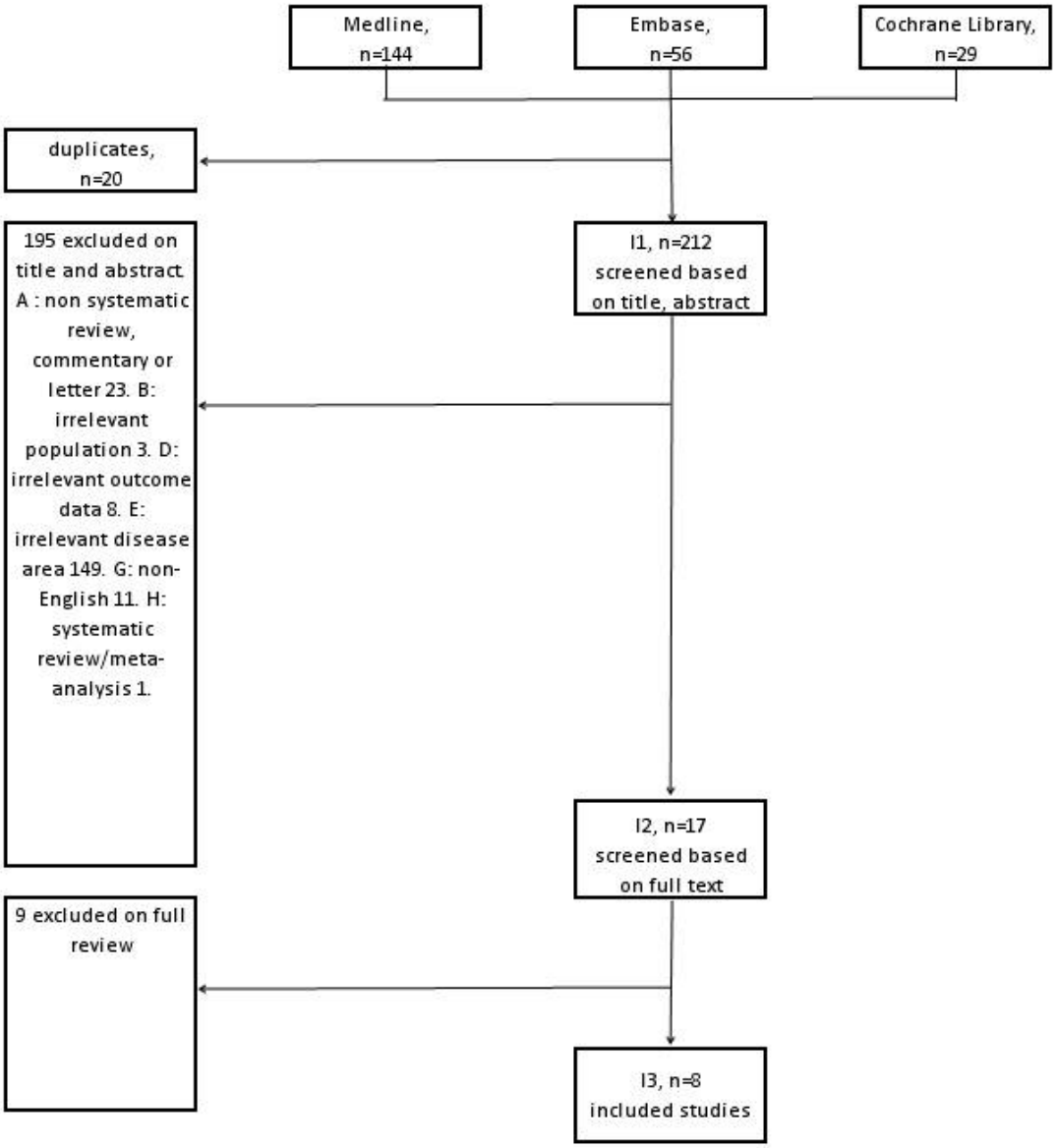
The inclusion and exclusion criteria were chosen to identify all preference-based measures of quality of life, either generic or valued in a separate study with appropriate methods (i.e. standard gamble or time trade off) or one of the following non-preference quality of life measures: SF-12 or SF-36. Studies were excluded from the review if they did not investigate vision loss or if quality of life data was not reported. The results of these searches are reported within this section.

Figure 20: Consort flow diagram for HRQL studies (search December 2009)



A total of 637 potentially relevant publications were identified for inclusion in the systematic review of HRQL studies in December 2009, of which 603 were excluded on the basis of title and abstract. After review of 34 full text papers, 34 papers were identified as appropriate for inclusion.

Figure 21: Consort flow diagram for HRQL studies (updated search July 2010)



A total of 218 potentially relevant publications were identified for inclusion in the update of the systematic review of HRQL studies in July 2010, of which 201 were excluded on the basis of title and abstract. After review of 17 full text papers, eight further papers were excluded, leaving eight included papers. For suitability for inclusion in this analysis, see Section 9.17.

6.4.7 Comparison of HRQL data

The HRQL data used in this analysis (see mapping) have a number of advantages that were not present in any single study identified in the literature. The majority of studies identified in the systematic review anchored utilities between existing health and perfect health/vision and did not provide differential utility data for BSE and WSE patients. The utility data used in this analysis:

- Were obtained using methods which meet the NICE reference case, being valued using time-trade off (TTO) by members of the general public
- Are anchored between death and perfect health
- Are based on the VFQ-UI, which is a vision-specific instrument measuring the effects of binocular vision on HRQL
- Provide utility data that map directly to the health states used in this model
- Allow differential estimation of utility impact based on whether the WSE or BSE is involved

Adverse events

6.4.8 The impact of adverse events on HRQL

Adverse events associated with Ozurdex treatment have little impact on HRQL due to their nature and low incidence. The main adverse events associated with Ozurdex treatment in GENEVA 008 and 009 were increases in IOP and a higher incidence of cataracts. Increases in IOP were predictable, transient and mainly required no treatment or were managed successfully with standard topical IOP-lowering medications. The impact of Ozurdex-related increases in IOP on HRQL was considered minimal and was therefore not incorporated in the model. The incidence of cataracts was considered low in the GENEVA studies with only 1/368 phakic eyes (0.27%) treated with Ozurdex requiring surgery in the study eye. Cataracts are likely to have a detrimental effect on a patient's HRQL due to the impact on the patient's visual acuity. However, as the model maps changes in patients' visual acuity using data from the GENEVA studies and the corresponding impact on patient HRQL, it was deemed unnecessary to apply a further disutility to patient's experiencing cataract extraction. Any disutility associated with the cataract extraction procedure is experienced for a very short period of time and was therefore not considered.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Summary of HRQL values used

The base-case analysis assumed that RVO would occur in the BSE and WSE in 10% and 90% of patients, respectively, a ratio recommended by clinical experts as representative of patients seen in clinical practice (54). Due to uncertainty surrounding the distribution of WSE/BSE disease in clinical practice, this was varied through sensitivity analysis. For discussion around this split, please see Table 105.

For the purposes of this evaluation, utility values were derived from a preference-based scoring algorithm produced through direct valuation from the general population. [redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

6.4.10 Input from clinical experts

N/A

6.4.11 HRQL experienced in each health state

HRQL was assumed to remain constant within each health state, as per previous economic evaluations in ocular conditions (24).

6.4.12 Health effects excluded from the analysis

See Section 6.4.8.

6.4.13 Baseline HRQL

N/A

6.4.14 Changes in HRQL over time

Small changes in visual acuity are expected to occur for up to 2.5 years in BRVO and 3 years in CRVO; consequently leading to changes in HRQL over this period. However, after this period, changes in visual acuity are no longer applied within the model and therefore HRQL is assumed to remain constant.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

N/A

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 How is the clinical management of the condition currently costed in the NHS?

Observation is currently the clinical management strategy for patients with CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage or in patients who have previously been treated with laser photocoagulation but have not achieved therapeutic response. Ozurdex is the only licensed pharmacological intervention for the treatment of ME following CRVO or BRVO.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Ozurdex is the first licensed pharmacological intervention for the treatment of ME following CRVO or BRVO. Therefore, the costs associated with Ozurdex treatment are not reflected in current NHS reference costs or PbR tariffs. Current NHS reference costs and PbR tariffs are below the cost of an Ozurdex implant and would not adequately cover the cost of the procedure.

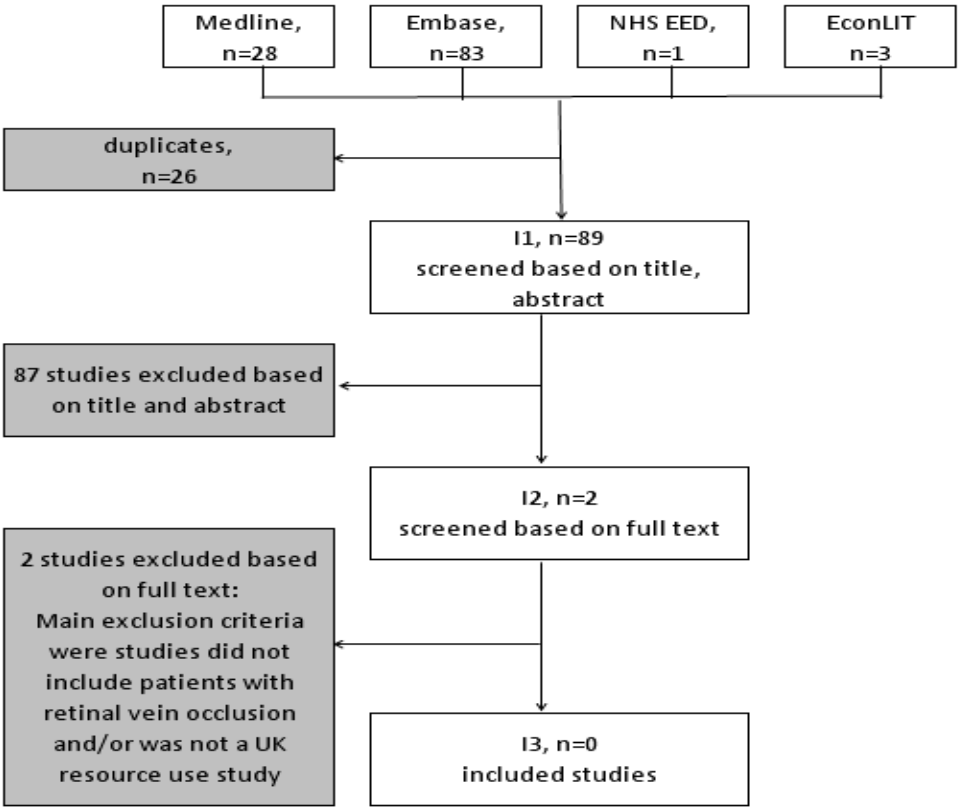
Resource identification, measurement and valuation studies

6.5.3 Literature search to identify resource data

A systematic review of the literature was carried out in order to identify existing medical resource use studies in the treatment of macular oedema secondary to retinal vein occlusion. Resource cost search terms were combined with terms for the disease area detailed in Section 9.13.

The inclusion and exclusion criteria were chosen to identify all medical resource use studies for macular oedema secondary to retinal vein occlusion. The results of these searches are reported within this section. The methods used are reported in Section 9.13.

Figure 22: Consort flow diagram for resource use studies



A total of 89 potentially relevant publications were identified for inclusion in the systematic review of resource use studies, of which 87 were excluded on the basis of title and abstract. After review of 2 full text papers, no studies were found that reported medical resource use for the UK for patients with macular oedema secondary to retinal vein occlusion.

6.5.4 Input from clinical experts

Estimates of medical resource use for observation were obtained through a survey of four ophthalmologists practising in the UK (see Table 102) (78). For details of questions and responses, see Section 9.19. Additional clinical experts asked to validate the resource use estimates confirmed them as reasonable with the exception of OCT. It was felt that OCT would be performed once more than estimated during the first six-months (at presentation, two months and six months) in both observation and Ozurdex patients. As the additional OCT would be seen in both treatment arms, this can be expected to have minimal impact on the ICERs reported in this analysis.

Intervention and comparator costs

6.5.5 Summary of costs used

Ozurdex treatment

Ozurdex biodegradable intravitreal implant in applicator delivers 700 µg of the corticosteroid dexamethasone (DEX) through a solid polymer drug delivery system to the posterior segment of the eye. The procedure cost to administer Ozurdex was

based on the Office of Population Censuses and Surveys (OPCS) code C89.2 "Insertion of steroid into posterior segment of eye" (92)[q]. The administration of Ozurdex was assumed to be as a day case procedure, and the corresponding NHS reference costs were extracted (HRG code BZ23Z, Vitreous Retinal Procedures - category 1 (£648) (93)) (Table 107). The total per-treatment cost of Ozurdex was estimated to be £1,518, based on a unit cost of Ozurdex of £870 and the cost of the procedure to administer Ozurdex of £648.

Routine hospital visits and monitoring procedures

Observation and Ozurdex treatment are both associated with routine outpatient visits for eye examinations with an ophthalmologist, as well as costs for OCT, fluorescein angiography and ophthalmoscopy. Estimates of resource use were based on a survey of four ophthalmologists in Scottish practice (78).

Based on this expert opinion, the frequency of hospital visits and monitoring procedures was assumed to be the same for observation as for Ozurdex, with the exception of one additional outpatient visit per six-month period for IOP measurements (tonometry) in Ozurdex-treated patients. The unit cost of a routine ophthalmologist outpatient appointment was taken to be £73 (Service code 130, follow up attendance non-admitted face-to-face (93)).

As such, the six-month per-patient costs applied to all patients who did not receive Ozurdex were £73 less than in the Ozurdex treated arm. Table 108 details the costs applied to all patients in each six-month period. These costs do not include the additional ophthalmologist consultation, which was considered to be an adverse-event-related cost and is detailed in Section 6.5.7.

NHS Reference costs were used to provide estimates of resource costs for OCT, fluorescein angiography and ophthalmoscopy (92, 93). Two different outpatient procedure costs are appropriate, depending on:

- the combination of procedures performed at any one hospital visit and
- the complexity rating – VR band – applied to each procedure (Table 107)

OCT and ophthalmoscopy have a VR band rating of 1 and fluorescein angiography a VR band rating of 2, such that the cost of OCT alone (VR total 1), for example, would be £150, OCT and ophthalmoscopy (VR total 2) would be £150, and OCT, angiography and ophthalmoscopy (VR total 4) would be assigned a cost of £184. This is a complicating factor, because estimates of resource use were required to be converted into units of services.[r]

[q] Please note that there is an OPCS code "insertion of sustained delivery device to the posterior of the eye". This was not considered to be the appropriate code following discussion with a UK-based ophthalmologist who suggested that this code may be more applicable to a surgical intervention.

[r] For example, if the mean number of OCTs was 2, mean number of angiographies was 1, and the mean number of ophthalmoscopys was 3, we assumed this to be equivalent to 1 visit in which an OCT, ophthalmoscopy and angiograpy would be administered (VR total 4), 1 visit in which an OCT and ophthalmoscopy would be administered (VR total 2), and one visit in

Table 107: Unit costs of monitoring procedures

HRG code†	Sum of VR bands†	Unit cost‡
BZ22Z, Vitreous Retinal Procedures - category 2	3-5	£184
BZ23Z, Vitreous Retinal Procedures - category 1	< 3	£150

HRG, Healthcare Resource Group; VR, vitreous retina. † Based on the OPCS codes C87.3 for OCT, C86.5 for fluorescein angiography and C87.5 for ophthalmoscopy (92); ‡ Based on NHS reference costs for Outpatient procedures (93).

Medical resource utilisation costs were applied to each six-month period (Table 108) whilst on treatment. Beyond stabilisation, it was assumed that no further routine hospital visits and monitoring procedures would be required.

Table 108: Medical resource utilisation, all patients

Resource	CRVO		BRVO	
	Units/6 mths	Cost/6 mths†	Units/6 mths	Cost/6 mths†
0-6 mths				
Ophthalmologist consultation	3	£292	3	£292
OCT	2	£484	2	£334
Fluorescein angiography	1		1	
Ophthalmoscopy	3		2	
	Total cost/pt	£703	Total cost/pt	£553
+6 mths (before visual acuity stabilization)				
Ophthalmologist consultation	2	£219	2	£219
OCT	1	£300	1	£300
Fluorescein angiography	0		0	
Ophthalmoscopy	2		2	
	Total cost/pt	£446	Total cost/pt	£446

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; FU, follow up; mth, month; OCT, optical coherence tomography; pt, patient; tx, treatment; yr, year. †Total cost/pt in each 6-month period comprises the number of ophthalmologist outpatient appointments multiplied by a unit cost of £73 (93) and the cost of monitoring procedures performed, based on the combination of procedures performed at any one hospital visit and the VR band rating applied to each procedure (92, 93).

The model assumed that patients could receive a maximum of 5 (BRVO) or 6 (CRVO) Ozurdex treatments, based on expert clinical opinion from the New York Clinical Expert Panel(54). This assumption is based on six-monthly treatments over 2.5 years in patients with BRVO and 3 years in patients with CRVO (see Extrapolating visual acuity). This assumption is investigated in sensitivity analysis (see Table 115).

The proportion of patients who received the first two treatments of Ozurdex (at baseline and six months) was based on the pooled results of the GENEVA 008 and GENEVA 009 trials (Table 109). The percentage of patients that require additional treatments with Ozurdex at six-monthly intervals beyond six months was taken form the New York Clinical Expert Panel(54).

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which only an ophthalmoscopy would be administered (VR band 1). This would provide an estimated total cost of £484.

Based on the assumed proportion of CRVO and BRVO patients receiving treatments at each time point, the total average cost per CRVO and BRVO patient treated with Ozurdex was estimated to be approximately £5,768 and £3,491 respectively (Table 109).

Table 109: Cost of Ozurdex treatment

Number of Ozurdex txs	Time-point	CRVO		BRVO	
		Pts †	Cost/pt	Pts †	Cost/pt
1	Baseline	100%	£1,518	100%	£1,518
2	6 mths	86%	£1,301	79%	£1,196
3	12 mths	63%	£956	19%	£281
4	18 mths	63%	£956	19%	£281
5	24 mths	37%	£554	8%	£121
6	30 mths	37%	£554	0%	£0
		Total cost/pt	£5,839	Total cost/pt	£3,397

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; mth, month; pt, patient; tx, treatment.
† % of pts receiving two Ozurdex treatments was based on pooled data from GENEVA 008 and GENEVA 009 trials (Section 3.5.1), and further estimates provided by expert clinical opinion (New York Clinical Expert Panel)

Health-state costs

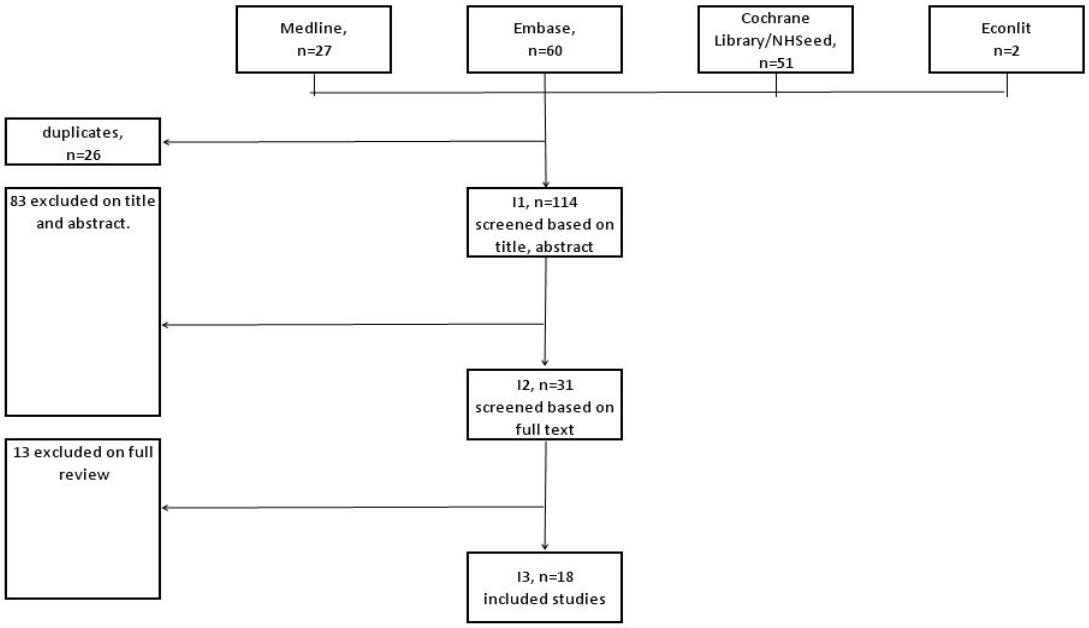
6.5.6 Summary of costs used

In the base-case, the cost of blindness was applied to all patients in the worst health state (BCVA ≤ 38 letters), who had an RVO in their BSE. These costs were not applied to patients in the worst health state who had an RVO in their WSE.

A systematic literature review was undertaken to identify studies reporting the cost of blindness. Cost terms were combined with terms for blindness and low vision detailed in Section 9.16.

The inclusion and exclusion criteria were chosen to identify all studies reporting the cost of blindness for the UK.

Figure 23: Consort flow diagram for cost of blindness



A total of 114 potentially relevant publications were identified for inclusion in the systematic review of resource use studies, of which 83 were excluded on the basis of title and abstract. After review of 31 full text papers, 18 studies met the inclusion criteria.

Of these studies, 14 met the NICE reference case with costs reported from the perspective of the UK NHS and personal social services. Ten of the 14 studies adopted the approach set out by Meads et al., (48). This analysis also adopts this methodology, updating relevant costs with the latest available published estimates (Table 110) and including only those cost items presented in the most recently published NICE technology appraisal of a retinal condition (TA155) (24).The cost items associated with blindness used include community care, residential care, depression and hip replacement (24).

Additional one-off costs including blind registration, low vision aids and low vision rehabilitation may also be anticipated (24) but are conservatively excluded from this analysis.

Table 110: Costs of blindness

Service †	% receiving services†	Unit cost (annual)	Cost/pt (annual)
Community care	6%	£6,708‡	£402
Residential care	30%	£23,972§	£7,192
Depression	39%	£498¶	£194
Hip replacement	5%	£5,336††	£267
		Total cost/pt with blindness	£8,055

Pt, patient.† as reported by Colquitt et al., (24); ‡ based on weekly low cost community care package for the elderly (excluding accommodation costs) (94); § based on weekly cost of voluntary residential care for the elderly (94); ¶ as reported by Colquitt et al. and uplifted to 2008/09 prices assuming reported costs are 2004/05 using pay and prices index (24); †† NHS reference cost for non-elective inpatient HRG code HA13C Intermediate hip procedures for trauma without CC (93).

The approach taken in sensitivity analysis around the costs of blindness mirrors that of Meads and Hyde (95) and Colquitt et al., (24). Upper and lower bounds for each set of parameters (uptake of services and annual unit costs) are estimated and results of scenarios based on the highest and lowest parameter values are presented.

Upper and lower limits for the percentage uptake of services are taken directly from Colquitt et al., (24), whilst upper and lower limits for the annual cost of services is estimated using the same methodology as detailed by Meads and Hyde (95). Estimates are detailed in Table 117 and provide a range of £1,235 - £31,300 per year. Note that this range is wider than those reported by the studies above.

Adverse-event costs

6.5.7 Summary of cost used

The cost of treating Ozurdex-related adverse events included increased IOP, cataract removal, and retinal tear/detachment.

Increased IOP

Costs of treatment associated with elevated IOP as a result of Ozurdex treatment, included the cost of topical IOP lowering medication and surgical procedures. The proportion of patients requiring treatment were derived from pooled data for the GENEVA 008 and GENEVA 009 trials, in which patients could receive up to two Ozurdex treatments.

The costs of IOP measurements (tonometry) have been accounted for in Table 107 and Table 108, as part of routine hospital visits and monitoring procedures. The cost of an additional ophthalmology follow up attendance for surgical procedures associated with raised IOP were also included (Table 112).

The incidence and associated costs of pharmacological treatment for increased IOP and surgical procedures for increased IOP are shown in Table 111 and Table 112, respectively. The average weighted cost per patient treated with Ozurdex for IOP medication was estimated to be £14.13 and £19.94, following initial Ozurdex treatment and any subsequent re-treatment, respectively (Table 111). The average weighted cost per Ozurdex patient for IOP lowering surgical procedures was estimated to be £12.58 and £7.09, following initial Ozurdex treatment and any subsequent re-treatment, respectively (Table 112). Note that the cost per patient estimates include the cost of an additional ophthalmology follow up attendance (£73) (93).

Table 111: Incidence and cost of pharmacological treatment for increased IOP

Class	Most common tx in class	Unit cost†	Days/ Bottle§	Initial tx (0–6 months)				Re-tx (every 6 months)			
				Pts on tx‡	Days of tx‡	Units/pt	Cost/ pt	Pts on tx‡	Days of tx‡	Units/ Pt	Cost/ pt
Beta-blockers	Timolol	£1.55	28	14.3%	92.3	4	£0.89	16.7%	127.3	5	£1.29
Prostaglandins	Latanaprost	£12.48	28	8.8%	103.4	4	£4.39	11.7%	113.6	5	£7.30
CA inhibitors	Brinzolamide	£6.56	28	5.0%	80.4	3	£0.98	4.7%	105.3	4	£1.23
Combination	Dorzolamide & timolol maleate	£10.05	28	10.2%	115.2	5	£5.13	12.9%	135.8	5	£6.48
Brimonidine	Brimonidine tartrate ¶	£6.85	28	10.0%	90.0	4	£2.74	10.6%	127.5	5	£3.63
				Total cost/pt (initial tx)			£14.13	Total cost/pt (re-tx)			£19.94

Pts, patients; tx, treatment. † unit costs from BNF (96) for most commonly prescribed therapy within the most commonly prescribed chemical class (97); ‡ derived from pooled safety data from GENEVA 008 and GENEVA 009 trials; § based on shelf life of product as detailed in the relevant product SPC; ¶ the cost for the generic version of this treatment could not be obtained, therefore equivalent branded costs assumed (Alphagan®)

Table 112: Incidence and cost of surgical procedures for increased IOP

Procedure	Unit cost/procedure†	Initial tx (0–6 months)		Re-tx (every 6 months)	
		Pts on tx‡	Cost/pt§	Pts on tx‡	Cost/pt§
Trabeculoplasty	£571	0.24%	£1.55	0.59%	£3.80
Sclerectomy	£1,278	0.24%	£3.24	0.00%	£0.00
Aqueous shunt	£1,278	0.24%	£3.24	0.00%	£0.00
Cryotherapy	£1,061	0.24%	£2.72	0.00%	£0.00
Iridectomy	£1,061	0.00%	£0.00	0.29%	£3.29
Scleral reinforcement	£689	0.24%	£1.83	0.00%	£0.00
		Total cost/pt (Initial tx)	£12.58	Total cost/pt (Re-tx)	£7.09

Pts, patients; tx, treatment. † Based on NHS reference costs, weighted by activity across elective inpatient, non-elective inpatient (long and short stay), and day cases (93) (relevant HRG codes for each procedure as follows: Sclerectomy, BZ17Z glaucoma category 3; Trabeculoplasty, BZ19Z glaucoma category 1; Aqueous shunt, BZ17Z glaucoma category 3; Cryotherapy, BZ18Z glaucoma category 2; Iridectomy, BZ18Z glaucoma category 2; Scleral reinforcement, BZ23Z vitreous retinal procedures category 1); ‡ Derived from pooled safety data from GENEVA 008 and GENEVA 009 trials; § Includes cost of ophthalmology follow up attendance (non-admitted face to face) per procedure (£73).

Cataract extraction

The proportion of Ozurdex patients receiving treatment for cataracts – cataract extraction and insertion of intraocular lens – was based on the 12-month pooled results of the GENEVA 008 and GENEVA 009 trials; 87.4% of patients were phakic at baseline, meaning that they still had their natural lens, and thus could potentially be affected by cataracts. During the first six months of the trials, 0.27% of phakic eyes (1 patient; Procedures for cataracts - 180 days) required cataract removal, whilst 0.99% of phakic eyes (3 patients; Procedures for cataracts - 360 days) required cataract removal during the second six-month, open label phase. For patients who received more than two Ozurdex treatments, it was conservatively assumed that the risk of cataracts doubled with each subsequent treatment. This assumption is varied in sensitivity analysis.

In addition to procedure costs, we assumed one additional outpatient attendance per procedure, as in Meads et al., (48).

The incidence of cataract extraction and associated costs are shown in Table 113.

Table 113: Incidence and cost of cataract extraction

Ozurdex treatment number	Phakic pts†	Cataract extraction for phakic eyes‡	Unit cost/procedure §	Cost/pt
1	87.4%	0.27%	£965	£2.28
2	87.16%	0.99%	£965	£8.33
3	86.30%	1.98%	£965	£16.49
4	84.59%	3.96%	£965	£32.33
5	81.24%	7.92%	£965	£62.09
6	74.81%	15.84%	£965	£114.35

Pts, patients; tx, treatment. † 87.4% of pts were phakic at baseline as derived from pooled safety data from GENEVA 008 and GENEVA 009 trials. For subsequent txs the % who were phakic was reduced by the proportion of patients who had cataract extraction following the previous Ozurdex tx; ‡ derived from pooled safety data from GENEVA 008 and GENEVA 009 trials for the first two Ozurdex txs. For three or more txs it was assumed that the risk of cataract doubled with each additional tx (54); § Consisting of the cataract procedure and an outpatient ophthalmologist consultation. Procedure cost based on NHS reference cost, weighted by activity across elective inpatient, non-elective inpatient, and day cases (93), using HRG codes BZ24A Non-surgical ophthalmology with length of stay 2 days or more and age ≥ 19, and BZ24C Non-surgical ophthalmology with length of stay 1 day or less and age ≥ 19. Outpatient cost based on Service code 130, follow up attendance non-admitted face to face (93).

Retinal tear/detachment

The proportion of Ozurdex patients receiving treatment for retinal tears and detachments was based on the pooled results of the GENEVA 008 and 009 trials. During the first six months of the trial, 0.48% and 0.24% of patients suffered a retinal tear or detachment respectively (98). During the second six-month, open label phase, 0.29% and 0.29% suffered a retinal tear or detachment respectively (98). These latter probabilities of tears/detachments (from the open label phase) were re-applied to treated patients in subsequent treatments of Ozurdex. All patients suffering from retinal tear or detachment were conservatively assumed to receive buckling operations. During GENEVA 008 and 009 trials only one of five patients with retinal tear/detachment underwent surgical intervention (retinopexy which falls under the same HRG as buckling operations).

The cost of treatment was taken from NHS Reference costs (£689 National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures Category 1. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay) and day case)(93).

Miscellaneous costs

6.5.8 Summary of cost used

Because treatment with Ozurdex may persist beyond the time-period for which data were available, it was necessary to make an assumption regarding how costs associated with adverse events may change over multiple administrations. This parameter was included in order to test whether it was a driver of cost-effectiveness in the absence of long-term data. Assumptions regarding the increase in adverse event costs with each additional Ozurdex treatment were validated at two UK advisory board meetings in Edinburgh (see Table 102).

Table 114: Assumed uplift in costs over multiple Ozurdex treatments

Ozurdex treatment	Assumed increase in adverse event costs
1	0%
2	0%
3	15%
4	40%
5	40%
6	40%

6.6 Sensitivity analysis

6.6.1 Uncertainty around structural assumptions

Scenario analyses were performed whereby key structural assumptions were varied and costs and QALYs recorded. Scenarios considered are listed in Table 115.

Table 115: Scenarios considered

Scenario name	Base-case/Default	Scenario
Source of utility estimates / 100% BSE patients	VFQ-UI for BSE/WSE	Sharma equation as source of utilities and 100% of patients BSE (detailed in Sharma equation)
Costs of vision loss: High service uptake/High cost	£8,055 per year	£31,300 (detailed in Table 117)
Costs of vision loss: Low service uptake/Low cost	£8,055 per year	£1,235 (detailed in Table 117)
Stabilisation of visual acuity at day 360	Stabilisation at year 2.5 (BRVO) and year 3 (CRVO)	Stabilisation at year 1 (no further Ozurdex retreatment beyond year 1)
Not treated extrapolation assumptions	Not treated patients experience TPs weighted by proportion of not treated patients resolved at day 180 (See Table 101)	All not treated patients receive same TPs as observation group (product matrix of day 90-180) (See Table 101)
Excess mortality of blindness	Excess mortality of 1.54	No excess mortality
Fellow eye occurrence	Probability of FEO based on Weibull extrapolation	FEO risk of 2.5% per year
Discounting	3.5% for both costs and benefits	6% for costs, 1% for benefits
Constant trial proportion retreated	Absolute numbers of retreated patients based on New York Clinical Expert Panel(54)	Assuming 78.8% of BRVO patients receive the maximum five injections and 85.7% of CRVO patients receive the maximum six injections
All patients start in ETDRS 39-43 letters	Distribution at baseline is weighted average of baseline distributions for BRVO and CRVO populations of interest	All patients start model in ETDRS 39-43 letters
Visual decline of 1.5% per 6 months	Visual acuity is assumed to be constant from year 2.5 (BRVO) and year 3 (CRVO)	6 month probability of moving to next poorest health state of 1.5% in place of stabilisation (99).
84% FEO results in ME	100% of RVOs in Hayreh et al. assumed to result in macular oedema (71)	84% of RVOs assumed to result in macular oedema (5)

CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; pts, patients; BSE, best-seeing eye; WSE, worse-seeing eye.

Sharma equation

Econometric modelling was used to create an algorithm (the VFQ-UI algorithm), whereby a utility score could be estimated for any possible health state using the

VFQ-UI health state classification (Section 6.4.4). An alternative method for deriving utility scores (the Sharma equation) was explored in sensitivity analysis.

The study published by Sharma et al (100) was conducted in 254 patients with varying degrees of vision loss. Patients' BCVA was measured using the Snellen chart. Patients underwent a TTO interview to determine the utility value associated with their BCVA. Univariate and multivariate regression analyses demonstrated that only BCVA in the BSE was significantly associated with utility ($P < 0.001$), with the duration of vision loss approaching statistical significance ($P = 0.075$). Based on the results of this study, Sharma et al developed the following equation for converting vision in the BSE to a utility value (U):

$$U = (0.374)(MAR) + 0.514$$

Converting the magnification requirement (MAR) to ETDRS provides the following equation:

$$U = 0.514 + 0.374 \times 10^{(-(1.7 - 0.02 \times (\text{BCVA in BSE})))}$$

Abbreviations: MAR, magnification requirement; U, utility; BCVA, best-corrected visual acuity; BSE, better seeing eye.

Utility values for BSE derived using this equation are shown in Table 116. A scenario analysis is presented whereby all patients are assumed to be BSE and the Sharma equation is used to estimate utility in each health state (Table 116). This makes the results of the analysis comparable to previous economic evaluations which considered only BSE patients (for example Colquitt et al. (24)).

Table 116: Sensitivity analysis utility values (Sharma equation)

BCVA Health State	HS0	HS1	HS2	HS3	HS4	HS5
ETDRS, number of letters	≥ 69	58–68	54–58	44–53	39–43	≤ 38
Utility in BSE	0.749978	0.652954	0.612372	0.583642	0.563303	0.548109

ETDRS, Early Treatment in Diabetic Retinopathy Study; WSE, worse seeing eye; BSE, Better seeing eye.† as derived using the VFQ-UI, since the Sharma equation relates only to the BSE.

The association between BCVA and the utilities calculated from the VFQ-UI (Section and the Sharma equation are shown in Figure 24.

Cost of blindness

Table 117 presents the upper and lower parameter estimates associated with the costs of vision loss. The upper and lower values used in sensitivity analysis are based on the lowest estimates of service uptake and lowest unit costs of service (£1,235), and the highest estimates of service uptake and highest unit costs (£31,300) respectively.

Table 117: Costs of blindness parameter upper and lower bounds in sensitivity analysis

	Uptake of services (%)‡			Unit costs of services (£)		
Service	**Base-case**	**High**	**Low**	**Base-case**	**High**	**Low**
Community care	6.0%	40.0%	6.0%	£6,708	£6,708	£2,548†
Residential care	30.0%	56.0%	13.0%	£23,972	£47,996§	£6,864¶
Depression	38.6%	50.0%	6.0%	£498	£498	£498
Hip replacement	5.0%	24.7%	0.5%	£5,336	£6,033††	£4,499††

† based on weekly very low cost community care package for the elderly (excluding accommodation costs) (94); § Annual cost for local authority residential care (94); ¶ Annual cost for local authority sheltered housing for older people (housing costs only) (94); †† NHS reference cost for non-elective inpatient HRG code HA13C Intermediate hip procedures for trauma without CC, upper and lower quartiles (93); ‡ Taken from Colquitt et al.

6.6.2 Deterministic sensitivity analysis

All data inputs were independently varied over a plausible range determined by a) the 95% confidence interval surrounding the point estimate or b) a sensible range of values where there is no sampling uncertainty (such as the discount rate applied to costs and benefits). For those parameters for which a measure of uncertainty was not available, the range was estimated as ± 25% of the point estimate.

The ICER was recorded at the upper and lower value for all parameters and tornado diagrams were produced.

6.6.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken whereby parameters were assigned distributions and 10,000 Monte Carlo simulations were performed. Costs, QALYs and parameter values were recorded and plotted on the cost-effectiveness plane.

The following inputs were not varied in PSA: the baseline distribution of patients; annual mortality; costs of IOP medications, the percentage of patients affected in their WSE.

The distributions assigned were as follows:

- Efficacy transition probabilities: Dirichlet sampling using a random gamma distribution and reweighting to ensure probabilities sum to one.
- Other probabilities[19]: Beta distributions
- NHS reference costs: NHS reference costs only report the interquartile range (IQR). In order to vary these estimates in PSA, it was assumed that the natural logarithm of these parameters followed a Gaussian distribution, and estimates of the standard error were then derived on this scale.
- FEO: Weibull regression coefficients were assumed to follow multivariate normal distributions, with a Cholesky decomposition used to allow for correlation between these parameters.
- Medical resource use estimates provided by clinicians: as clinician estimates were used to define routine medical resource use (Table 108), it was not possible to accurately estimate uncertainty around these estimates. It was therefore assumed that the 95% confidence interval lay +/-25% of the point estimate, and each parameter estimate was varied independently assuming a gamma distribution.
- Other parameters: see Table 153.

6.7 Results

Clinical outcomes from the model

6.7.1 Summary of clinical outcomes from the model

A comparison of outcomes from GENEVA with corresponding results from the model in the treated population of patients with ME following CRVO, BRVO-macular

[19] Probabilities of adverse events, probabilities of resolution in patients who are not retreated with Ozurdex, the percentage of patients who were male.

haemorrhage and BRVO with previous laser is provided in Table 118, Table 119, and Table 120, respectively. Note these results were achieved by assuming that the respective patient population was equal to 100% of the cohort (for example, the CRVO results assume 100% of patients are CRVO). This will lead to slightly different results to those used in the estimation of the ICERs, which use a weighted average baseline assuming 34.5% of patients were CRVO. Baseline distribution differs slightly between the model and the GENEVA trials as the baseline distribution in the model included observation (Sham) patients in addition to Ozurdex-treated patients.

Table 118: Comparison of trial and model outcomes in treated patients with CRVO.

Health state	Baseline		Day 180		Day 360	
	GENEVA result	Model result	GENEVA result	Model result	GENEVA result	Model result
≤ 69	0.0%	0.4%	20.3%	20.8%	20.2%	20.9%
59-68	35.3%	36.4%	19.5%	19.9%	24.6%	19.0%
54-58	18.0%	21.1%	14.3%	14.3%	13.2%	9.2%
44-53	18.0%	16.4%	17.3%	17.2%	21.9%	22.2%
39-43	12.0%	8.9%	6.0%	5.9%	3.5%	2.0%
≤ 38	16.5%	16.8%	22.6%	21.9%	16.7%	26.7%

Table 119: Comparison of trial and model outcomes in treated patients with BRVO-macular haemorrhage.

Health state	Baseline		Day 180		Day 360	
	GENEVA result	Model result	GENEVA result	Model result	GENEVA result	Model result
≤ 69	0.0%	0.6%	36.5%	36.7%	38.6%	40.6%
59-68	42.0%	41.2%	30.2%	30.3%	21.8%	28.9%
54-58	16.9%	18.6%	10.2%	10.2%	13.4%	8.2%
44-53	25.1%	23.7%	12.5%	12.5%	14.9%	11.0%
39-43	6.7%	7.6%	4.7%	4.6%	4.5%	3.5%
≤ 38	9.4%	8.3%	5.9%	5.7%	6.9%	7.8%

Table 120: Comparison of trial and model outcomes in treated patients with BRVO with previous laser.

Health state	Baseline		Day 180		Day 360	
	GENEVA result	Model result	GENEVA result	Model result	GENEVA result	Model result
≤ 69	0.0%	0.0%	22.2%	23.6%	22.6%	24.1%
59-68	27.8%	31.9%	36.1%	37.3%	22.6%	32.7%
54-58	19.4%	22.2%	11.1%	10.9%	16.1%	14.4%
44-53	27.8%	25.0%	11.1%	10.7%	22.6%	7.6%
39-43	16.7%	13.9%	5.6%	5.3%	6.5%	5.4%
≤ 38	8.3%	6.9%	13.9%	12.2%	9.7%	15.9%

A comparison of outcomes from GENEVA with corresponding results from the model in the observation (Sham) group of patients with ME following CRVO, BRVO-macular haemorrhage and BRVO with previous laser is provided in Table 121,

Table 122, and Table 123 respectively. As above, these results were produced assuming the respective patient population represented 100% of the cohort in the model.

Table 121: Comparison of trial and model outcomes in observation patients with CRVO

Health state	Baseline		Day 180	
	GENEVA result	Model result	GENEVA result	Model result
≤ 69	0.68%	0.36%	23.81%	23.22%
59-68	37.41%	36.43%	17.01%	16.76%
54-58	23.81%	21.07%	10.20%	10.16%
44-53	14.97%	16.43%	15.65%	15.80%
39-43	6.12%	8.93%	4.76%	4.87%
≤ 38	17.01%	16.79%	28.57%	29.19%

Table 122: Comparison of trial and model outcomes in observation patients with BRVO-macular haemorrhage

Health state	Baseline		Day 180	
	GENEVA result	Model result	GENEVA result	Model result
≤ 69	1.15%	0.58%	29.62%	29.28%
59-68	40.38%	41.17%	30.00%	29.86%
54-58	20.38%	18.64%	11.54%	11.58%
44-53	22.31%	23.69%	14.62%	14.74%
39-43	8.46%	7.57%	5.00%	5.09%
≤ 38	7.31%	8.35%	9.23%	9.45%

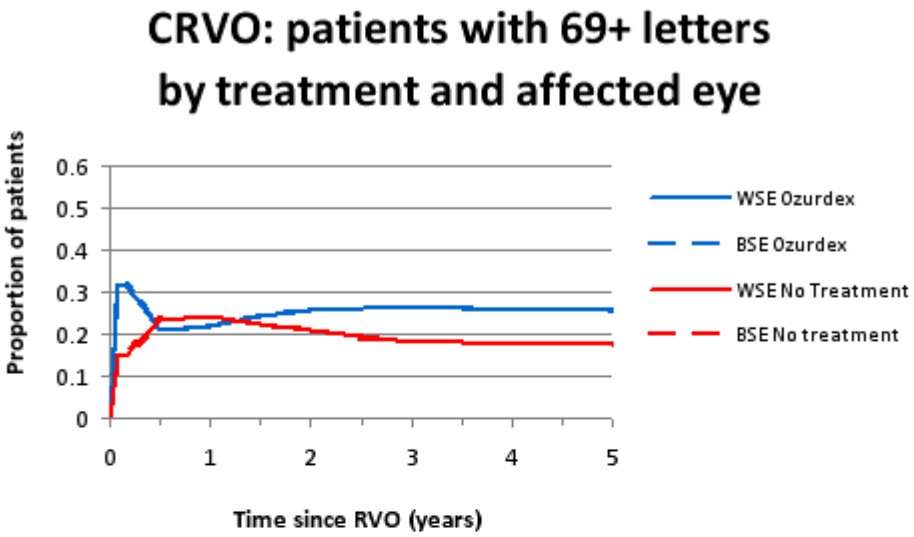
Table 123: Comparison of trial and model outcomes in observation patients with BRVO with previous laser

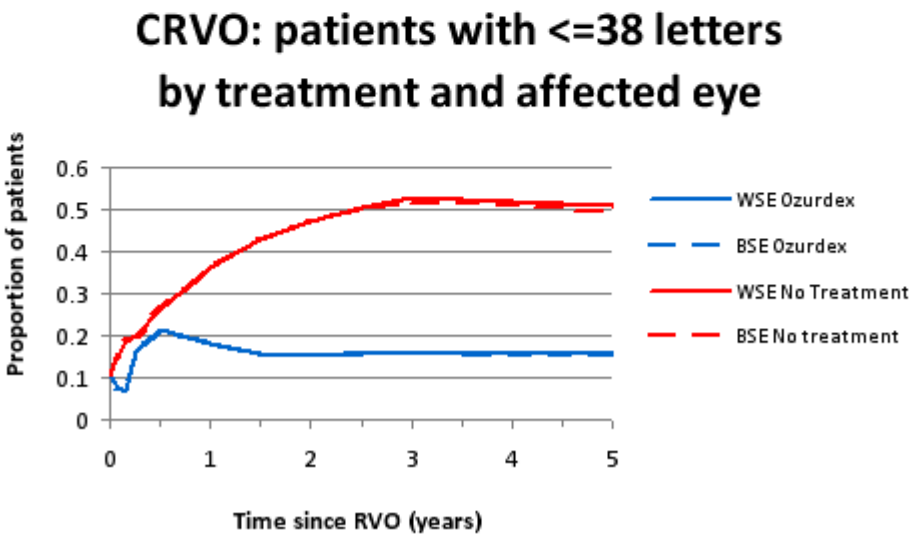
Health state	Baseline		Day 180	
	GENEVA result	Model result	GENEVA result	Model result
≤ 69	0.00%	0.00%	13.89%	12.89%
59-68	36.11%	31.94%	30.56%	28.70%
54-58	25.00%	22.22%	22.22%	21.91%
44-53	22.22%	25.00%	11.11%	11.02%
39-43	11.11%	13.89%	11.11%	12.28%
≤ 38	5.56%	6.94%	11.11%	13.22%

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure 25 to Figure 27 illustrate the proportion of the cohort in the best and poorest states (69+ letters and ≤ 38 letters respectively) for relevant patient populations. Note that because the model treats BRVO and CRVO differentially, it was not possible to achieve an equivalent figure for all RVO. Markov traces for states not presented below are included in Appendix 9.23.

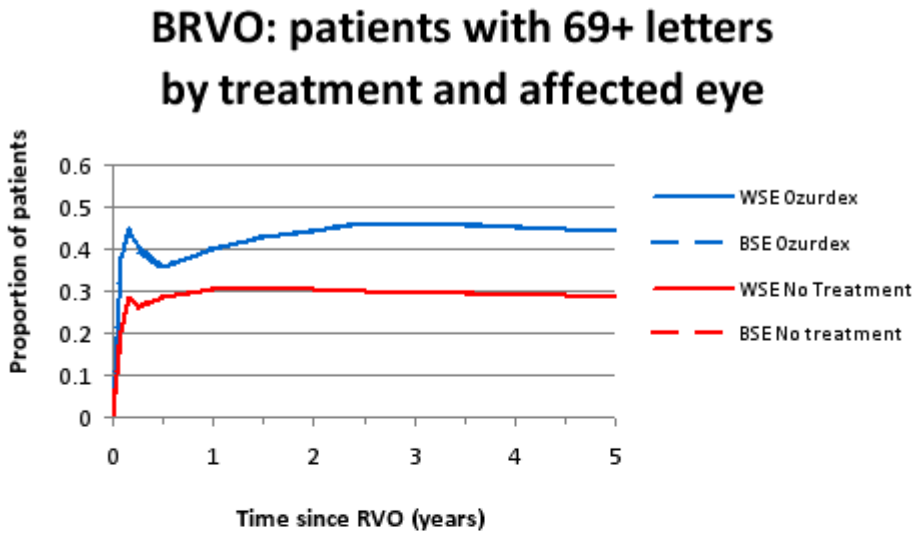
Figure 25: CRVO, Markov traces for best and poorest states

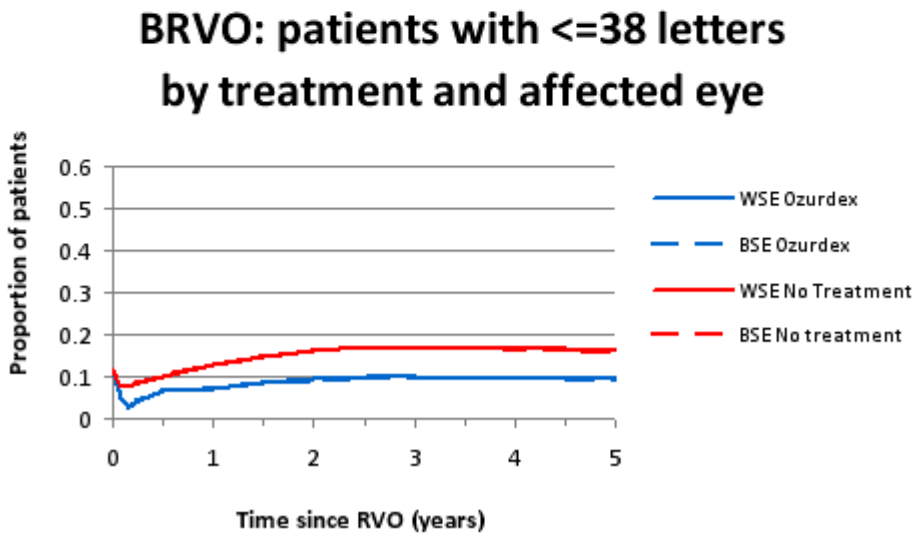




Abbreviations: WSE, worse seeing eye; BSE, better seeing eye; CRVO, central retinal vein occlusion.

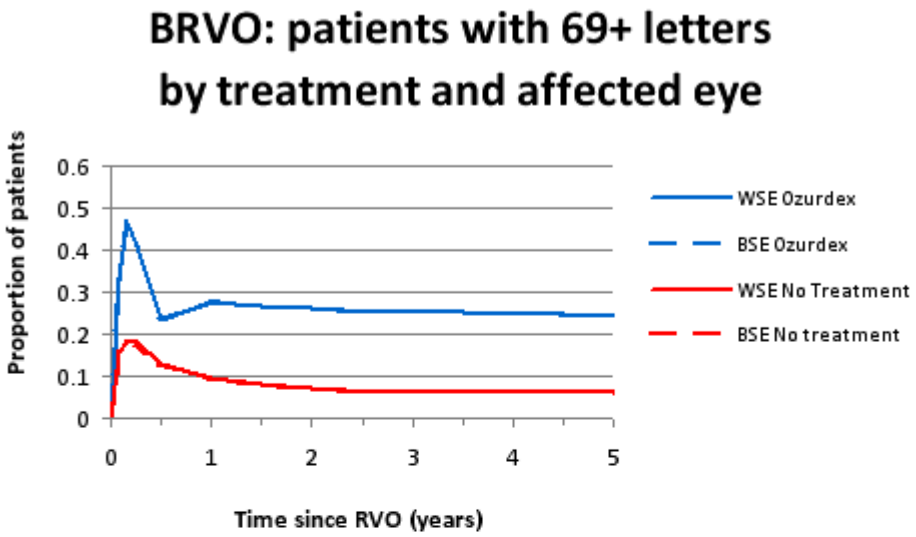
Figure 26: BRVO-macular haemorrhage, Markov traces for best and poorest states

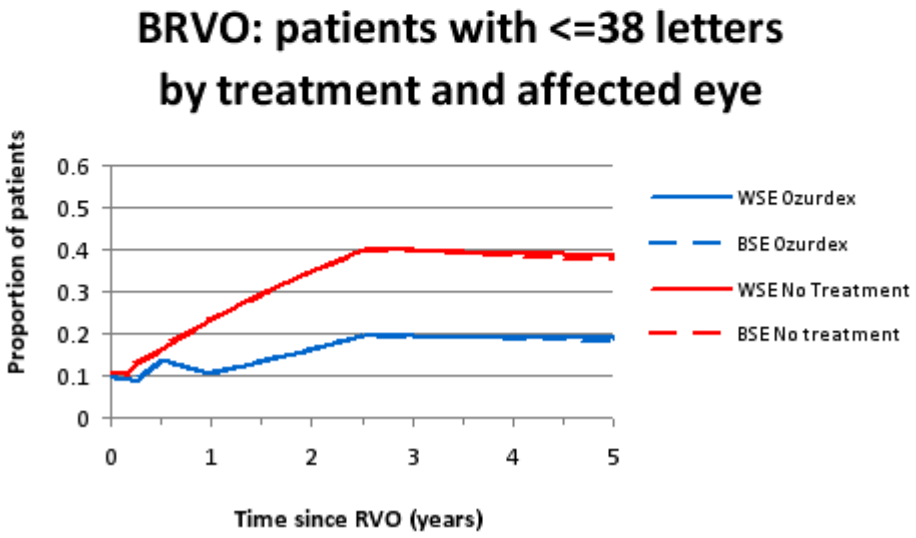




Abbreviations: WSE, worse seeing eye; BSE, better seeing eye; BRVO, branch retinal vein occlusion.

Figure 27: BRVO with previous laser therapy, Markov traces for best and poorest states





Abbreviations: WSE, worse seeing eye; BSE, better seeing eye; BRVO, branch retinal vein occlusion.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

See Markov traces above.

6.7.4 Life years and QALYs accrued for each clinical outcome

The life years (LYs) and QALYs accrued for each health state by WSE and BSE for Ozurdex compared with observation (Sham) in patients with ME following RVO, CRVO, BRVO-macular haemorrhage, and BRVO with previous laser are shown in Table 124, Table 125, Table 126, and Table 127, respectively.

Table 124: Life years and QALYs by health state in patients with RVO

Treated eye	Health state	Ozurdex		Observation	
		LYs	QALYs	LYs	QALYS
WSE	≤ 69	4.05	3.49	2.70	2.33
	59-68	2.65	2.25	2.38	2.02
	54-58	0.80	0.67	0.82	0.69
	44-53	1.54	1.28	1.21	1.01
	39-43	0.28	0.23	0.50	0.42
	≤ 38	1.19	0.97	2.91	2.37
BSE	≤ 69	1.53	1.17	1.01	0.78
	59-68	1.00	0.72	0.89	0.64
	54-58	0.30	0.21	0.31	0.21
	44-53	0.58	0.38	0.45	0.30
	39-43	0.11	0.07	0.19	0.12
	≤ 38	0.40	0.24	0.98	0.58

Abbreviations: LYs, life years; QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

Table 125: Life years and QALYs by health state in patients with CRVO

Treated eye	Health state	Ozurdex		Observation	
		LYs	QALYs	LYs	QALYS
WSE	≤ 69	2.87	2.47	2.07	1.79
	59-68	2.60	2.21	1.09	0.93
	54-58	0.79	0.67	0.55	0.47
	44-53	2.44	2.03	1.06	0.88
	39-43	0.18	0.15	0.46	0.38
	≤ 38	1.64	1.33	5.28	4.31
BSE	≤ 69	1.37	1.05	0.93	0.71
	59-68	0.99	0.72	0.72	0.52
	54-58	0.30	0.21	0.27	0.19
	44-53	0.70	0.46	0.43	0.29
	39-43	0.09	0.06	0.18	0.12
	≤ 38	0.45	0.27	1.25	0.75

Abbreviations: LYs, life years; QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

Table 126: Life years and QALYs by health state in patients with BRVO-macular haemorrhage

Treated eye	Health state	Ozurdex		Observation	
		LYs	QALYs	LYs	QALYS
WSE	≤ 69	4.85	4.19	3.19	2.75
	59-68	2.44	2.07	2.76	2.34
	54-58	0.79	0.67	0.95	0.80
	44-53	1.05	0.88	1.31	1.09
	39-43	0.35	0.29	0.56	0.46
	≤ 38	1.02	0.83	1.75	1.43
BSE	≤ 69	1.66	1.28	1.10	0.85
	59-68	0.93	0.67	0.89	0.65
	54-58	0.30	0.20	0.32	0.22
	44-53	0.51	0.34	0.47	0.31
	39-43	0.12	0.07	0.20	0.13
	≤ 38	0.39	0.23	0.85	0.51

Abbreviations: LYs, life years; QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

Table 127: Life years and QALYs by health state in patients with BRVO with previous laser

Treated eye	Health state	Ozurdex		Observation	
		LYs	QALYs	LYs	QALYS
WSE	≤ 69	2.75	2.37	0.73	0.63
	59-68	2.53	2.15	2.01	1.71
	54-58	1.71	1.44	2.02	1.70
	44-53	0.98	0.82	0.89	0.74
	39-43	0.53	0.44	0.84	0.69
	≤ 38	2.01	1.64	4.02	3.28
BSE	≤ 69	1.04	0.80	0.38	0.29
	59-68	0.95	0.69	0.67	0.49
	54-58	0.57	0.39	0.63	0.44
	44-53	0.49	0.33	0.35	0.23
	39-43	0.17	0.11	0.28	0.18
	≤ 38	0.65	0.39	1.45	0.87

Abbreviations: LYs, life years; QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

6.7.5 Disaggregated incremental QALYs and costs

Disaggregated QALYs are presented in all RVO, CRVO, BRVO-macular haemorrhage and BRVO with previous laser in Table 128, Table 129, Table 130, and Table 131, respectively. The model was not configured to allow the disaggregation of costs in the same manner; however, a breakdown of costs by category is presented in Table 132 to Table 135.

Table 128: Disaggregated QALYs – all RVO

Treated eye	Health state	QALY Observation	QALY Ozurdex	Increment	Absolute increment	% absolute increment
WSE	>=69	2.33	3.49	1.17	1.17	50.1%
	59-68	2.02	2.25	0.23	0.23	11.6%
	54-58	0.69	0.67	-0.02	0.02	2.2%
	44-53	1.01	1.28	0.27	0.27	27.1%
	39-43	0.42	0.23	-0.18	0.18	43.5%
	<=38	2.37	0.97	-1.40	1.40	59.0%
BSE	>=69	0.78	1.17	0.39	0.39	50.6%
	59-68	0.64	0.72	0.08	0.08	11.9%
	54-58	0.21	0.21	-0.01	0.01	2.6%
	44-53	0.30	0.38	0.08	0.08	27.6%
	39-43	0.12	0.07	-0.05	0.05	43.9%
	<=38	0.58	0.24	-0.35	0.35	59.0%

Abbreviations: QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

Table 129: Disaggregated QALYs - CRVO

Treated eye	Health state	QALY Observation	QALY Ozurdex	Increment	Absolute increment	% absolute increment
WSE	>=69	1.79	2.47	0.68	0.68	38.3%
	59-68	0.93	2.21	1.28	1.28	138.6%
	54-58	0.47	0.67	0.20	0.20	43.0%
	44-53	0.88	2.03	1.15	1.15	130.6%
	39-43	0.38	0.15	-0.23	0.23	60.9%
	<=38	4.31	1.33	-2.97	2.97	69.0%
BSE	>=69	0.71	1.05	0.34	0.34	47.2%
	59-68	0.52	0.72	0.20	0.20	37.5%
	54-58	0.19	0.21	0.02	0.02	9.7%
	44-53	0.29	0.46	0.18	0.18	61.8%
	39-43	0.12	0.06	-0.06	0.06	49.8%
	<=38	0.75	0.27	-0.48	0.48	64.0%

Abbreviations: QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

Table 130: Disaggregated QALYs - BRVO- macular haemorrhage

Treated eye	Health state	QALY Observation	QALY Ozurdex	Increment	Absolute increment	% absolute increment
WSE	>=69	2.75	4.19	1.44	1.44	52.3%
	59-68	2.34	2.07	-0.27	0.27	11.5%
	54-58	0.80	0.67	-0.13	0.13	16.7%
	44-53	1.09	0.88	-0.21	0.21	19.6%
	39-43	0.46	0.29	-0.17	0.17	36.1%
	<=38	1.43	0.83	-0.60	0.60	41.8%
BSE	>=69	0.85	1.28	0.43	0.43	50.5%
	59-68	0.65	0.67	0.03	0.03	4.0%
	54-58	0.22	0.20	-0.02	0.02	8.4%
	44-53	0.31	0.34	0.03	0.03	9.1%
	39-43	0.13	0.07	-0.05	0.05	41.2%
	<=38	0.51	0.23	-0.28	0.28	54.5%

Abbreviations: QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

Table 131: Disaggregated QALYs - BRVO with previous laser

Treated eye	Health state	QALY Observation	QALY Ozurdex	Increment	Absolute increment	% absolute increment
WSE	>=69	0.63	2.37	1.74	1.74	277.3%
	59-68	1.71	2.15	0.44	0.44	25.7%
	54-58	1.70	1.44	-0.26	0.26	15.2%
	44-53	0.74	0.82	0.07	0.07	10.1%
	39-43	0.69	0.44	-0.25	0.25	36.4%
	<=38	3.28	1.64	-1.64	1.64	50.1%
BSE	>=69	0.29	0.80	0.51	0.51	174.3%
	59-68	0.49	0.69	0.20	0.20	41.7%
	54-58	0.44	0.39	-0.05	0.05	10.4%
	44-53	0.23	0.33	0.10	0.10	42.5%
	39-43	0.18	0.11	-0.07	0.07	39.6%
	<=38	0.87	0.39	-0.48	0.48	55.3%

Abbreviations: QALY, quality-adjusted life year; WSE, worse seeing eye; BSE, better seeing eye

In all RVO, Ozurdex treatment was associated with a total cost of approximately £12,245 versus £10,578 with observation. The incremental cost of Ozurdex versus observation was £1,667 (Table 132).

Table 132: Costs by category – all RVO

Item	Cost Ozurdex	Cost Observation	Increment	Absolute increment	% absolute increment
Drug acquisition	£2,785.51	£0.00	£2,785.51	£2,785.51	-
Drug administration	£2,074.72	£0.00	£2,074.72	£2,074.72	-
Routine visits and monitoring	£3,725.73	£2,740.29	£985.44	£985.44	36%
Adverse events	£409.49	£0.00	£409.49	£409.49	-
Vision loss: Community care	£162.37	£391.62	-£229.24	£229.24	59%
Vision loss: Residential care	£2,901.28	£6,997.48	-£4,096.19	£4,096.19	59%
Vision loss: Depression	£78.35	£188.98	-£110.62	£110.62	59%
Vision loss: Hip replacement	£107.63	£259.60	-£151.96	£151.96	59%
Total	**£12,245.09**	**£10,577.96**	**£1,667.14**	**£1,667.14**	**16%**

In CRVO, Ozurdex treatment was associated with a total cost of approximately £14,962 versus £13,126 with observation. The incremental cost of Ozurdex versus observation was £1,836 (Table 133).

Table 133: Costs by category - CRVO

Item	Cost Ozurdex	Cost Observation	Increment	Absolute increment	% absolute increment
Drug acquisition	£3,597.38	£0.00	£3,597.38	£3,597.38	-
Drug administration	£2,679.43	£0.00	£2,679.43	£2,679.43	-
Routine visits and monitoring	£4,485.27	£3,078.52	£1,406.75	£1,406.75	46%
Adverse events	£560.30	£0.00	£560.30	£560.30	-
Vision loss: Community care	£181.85	£502.02	-£320.18	£320.18	64%
Vision loss: Residential care	£3,249.31	£8,970.27	-£5,720.96	£5,720.96	64%
Vision loss: Depression	£87.75	£242.26	-£154.50	£154.50	64%
Vision loss: Hip replacement	£120.55	£332.79	-£212.24	£212.24	64%
Total	**£14,961.83**	**£13,125.86**	**£1,835.97**	**£1,835.97**	**14%**

In BRVO-macular haemorrhage, Ozurdex treatment was associated with a total cost of approximately £10,943 versus £9,434 with observation. The incremental cost of Ozurdex versus observation was £1,510 (Table 134).

Table 134: Costs by category - BRVO- macular haemorrhage

Item	Cost Ozurdex	Cost Observation	Increment	Absolute increment	% absolute increment
Drug acquisition	£2,358.05	£0.00	£2,358.05	£2,358.05	-
Drug administration	£1,756.34	£0.00	£1,756.34	£1,756.34	-
Routine visits and monitoring	£3,325.81	£2,562.19	£763.63	£763.63	30%
Adverse events	£330.09	£0.00	£330.09	£330.09	-
Vision loss: Community care	£158.54	£343.34	-£184.80	£184.80	54%
Vision loss: Residential care	£2,832.88	£6,134.87	-£3,301.99	£3,301.99	54%
Vision loss: Depression	£76.51	£165.68	-£89.18	£89.18	54%
Vision loss: Hip replacement	£105.10	£227.60	-£122.50	£122.50	54%
Total	**£10,943.32**	**£9,433.67**	**£1,509.65**	**£1,509.65**	**16%**

In BRVO with previous laser, Ozurdex treatment was associated with a total cost of approximately £12,966 versus £14,184 with observation. The incremental cost saving with Ozurdex versus observation was £1,218 (Table 135).

Table 135: Costs by category - BRVO with previous laser

Item	Cost Ozurdex	Cost Observation	Increment	Absolute increment	% absolute increment
Drug acquisition	£2,358.05	£0.00	£2,358.05	£2,358.05	-
Drug administration	£1,756.34	£0.00	£1,756.34	£1,756.34	-
Routine visits and monitoring	£3,325.73	£2,561.95	£763.78	£763.78	30%
Adverse events	£330.09	£0.00	£330.09	£330.09	-
Vision loss: Community care	£259.63	£580.71	-£321.08	£321.08	55%
Vision loss: Residential care	£4,639.14	£10,376.28	-£5,737.14	£5,737.14	55%
Vision loss: Depression	£125.29	£280.23	-£154.94	£154.94	55%
Vision loss: Hip replacement	£172.11	£384.95	-£212.84	£212.84	55%
Total	**£12,966.38**	**£14,184.12**	**-£1,217.74**	**£1,217.74**	**9%**

Base-case analysis

6.7.6 Summary of results

In the base-case for Ozurdex in all RVO, the incremental total cost over a patient's lifetime was £1,667 and the incremental QALYs were 0.23. Therefore, the incremental cost per QALY was **£7,368** for Ozurdex in all RVO (Table 136).

Table 136: Base-case results - all RVO

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Observation	£10,578	14.34	11.47	-	-	-	-
Ozurdex	£12,245	14.42	11.69	£1,667	0.08	0.23	£7,368

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

In the base-case for Ozurdex in CRVO, the incremental total cost over a patient's lifetime was £1,836 and the incremental QALYs were 0.31. Therefore, the incremental cost per QALY was **£6,008** for Ozurdex in CRVO (Table 137).

Table 137: Base-case results - CRVO

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Observation	£13,126	14.31	11.32	-	-	-	-
Ozurdex	£14,962	14.41	11.62	£1,836	0.11	0.31	£6,008

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

In the base-case for Ozurdex in BRVO-macular haemorrhage, the incremental total cost over a patient's lifetime was £1,510 and the incremental QALYs were 0.19. Therefore, the incremental cost per QALY was **£7,953** for Ozurdex in BRVO-macular haemorrhage (Table 138).

Table 138: Base-case results - BRVO-macular haemorrhage

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Observation	£9,434	14.36	11.54	-	-	-	-
Ozurdex	£10,943	14.42	11.73	£1,510	0.06	0.19	£7,953

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

In the base-case for Ozurdex in BRVO with previous laser, the incremental total cost over a patient's lifetime was -£1,218 and the incremental QALYs were 0.31. Therefore, Ozurdex was **dominant** when compared to observation in BRVO with previous laser (Table 139).

Table 139: Base-case results - BRVO with previous laser

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Observation	£14,184	14.28	11.24	-	-	-	-
Ozurdex	£12,966	14.39	11.56	-£1,218	0.11	0.31	Dominant

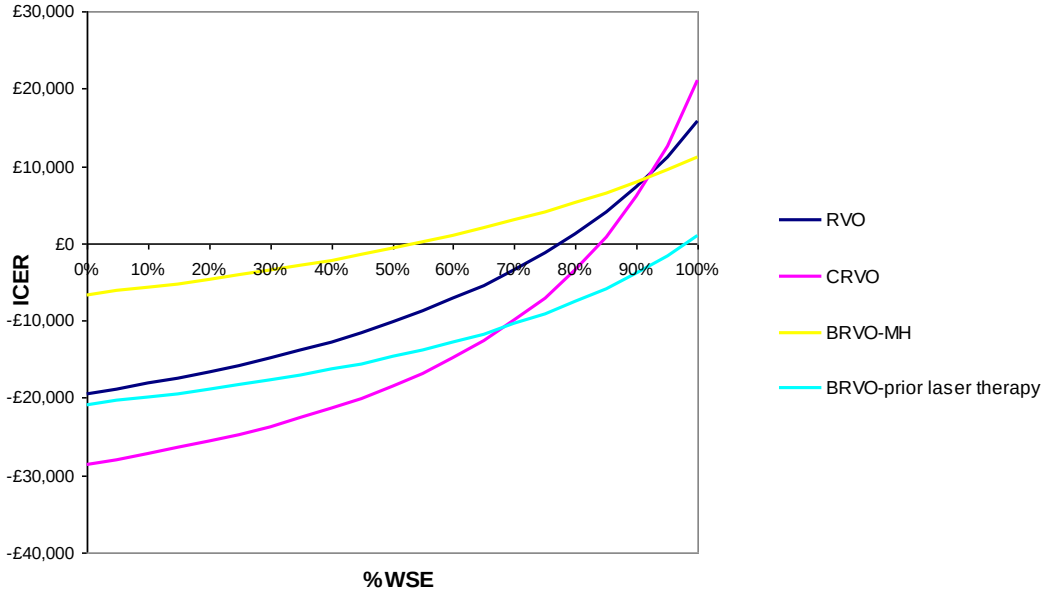
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

6.7.7 Deterministic sensitivity analysis

Results of varying the BSE:WSE ratio are presented in Figure 28 for all patient populations. Note that in all cases, negative ICERs relate to reduced incremental costs and QALYs (Ozurdex is dominant).

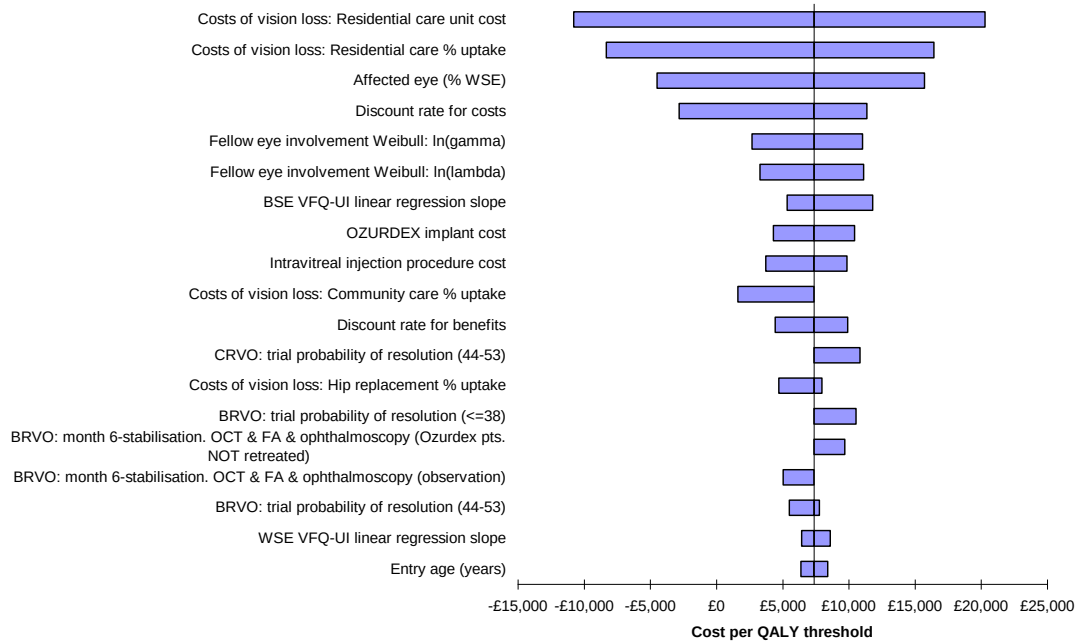
Figure 28: Changes in ICER with changes in WSE:BSE ratio



Abbreviations: CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; MH, macular haemorrhage, ICER, incremental cost-effectiveness ratio; % WSE, percentage of patients.

Results for the univariate sensitivity analysis are presented as tornado diagrams in Figure 29 to Figure 32 for the following patient groups: all RVO, CRVO, BRVO-macular haemorrhage and BRVO with previous laser.

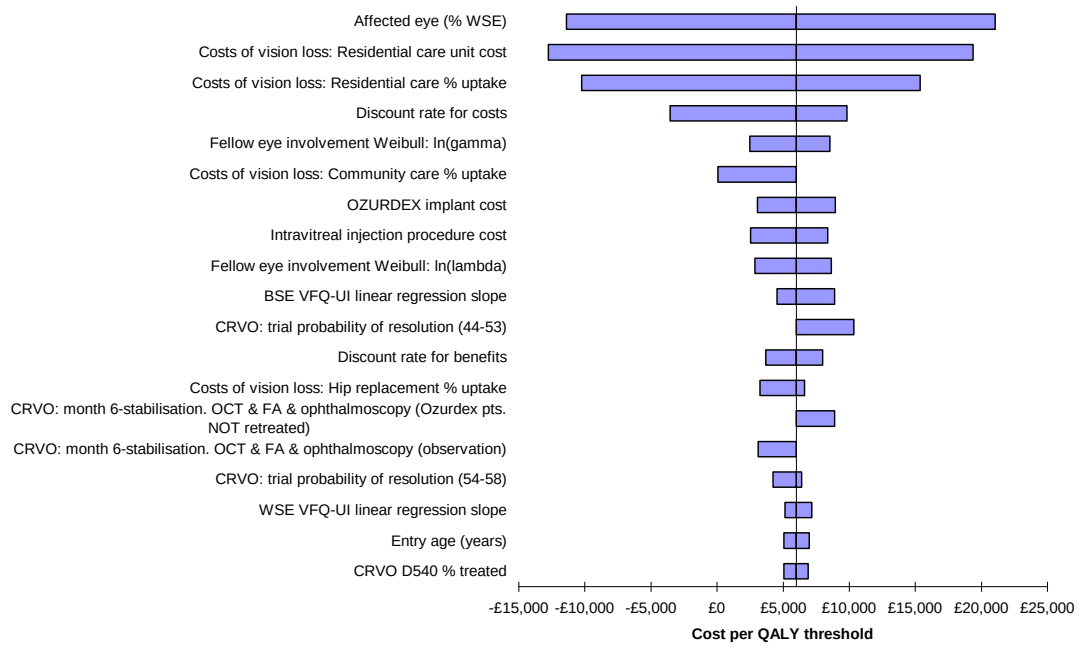
Figure 29: all RVO. Univariate sensitivity analysis



Abbreviations: BSE, better seeing eye;

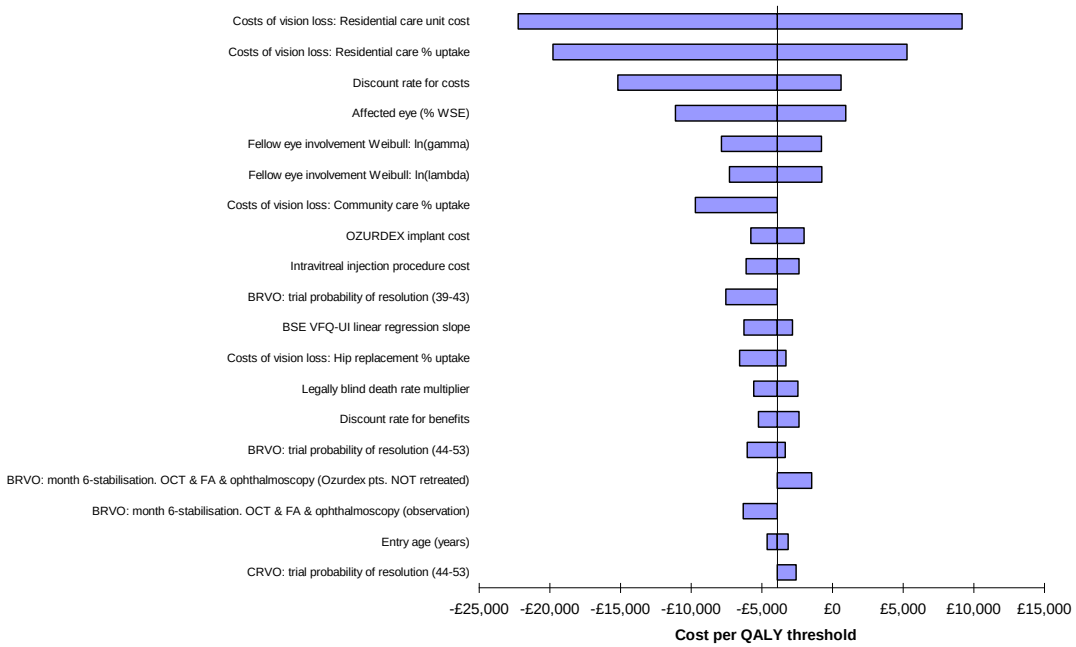
For Ozurdex in all RVO, the incremental cost-effectiveness ratio (ICER) is most sensitive to changes in the annual cost of residential care. At the lower estimate of the annual cost of residential care, the ICER increases to **£20,288**. At the higher estimate of the annual cost of residential care, Ozurdex is dominant. No other parameter was able to produce an ICER, which exceeded £20,000 per QALY when varied.

Figure 30: CRVO. Univariate sensitivity analysis



In CRVO, the ICER is most sensitive to changes in the percentage of patients affected in their WSE; at the upper estimate of the percentage of patients affected in their WSE (100%), the ICER increases to **£21,043**. At the lower estimate (68%), Ozurdex is dominant. No other parameter was able to produce an ICER, which exceeded £20,000 per QALY when varied.

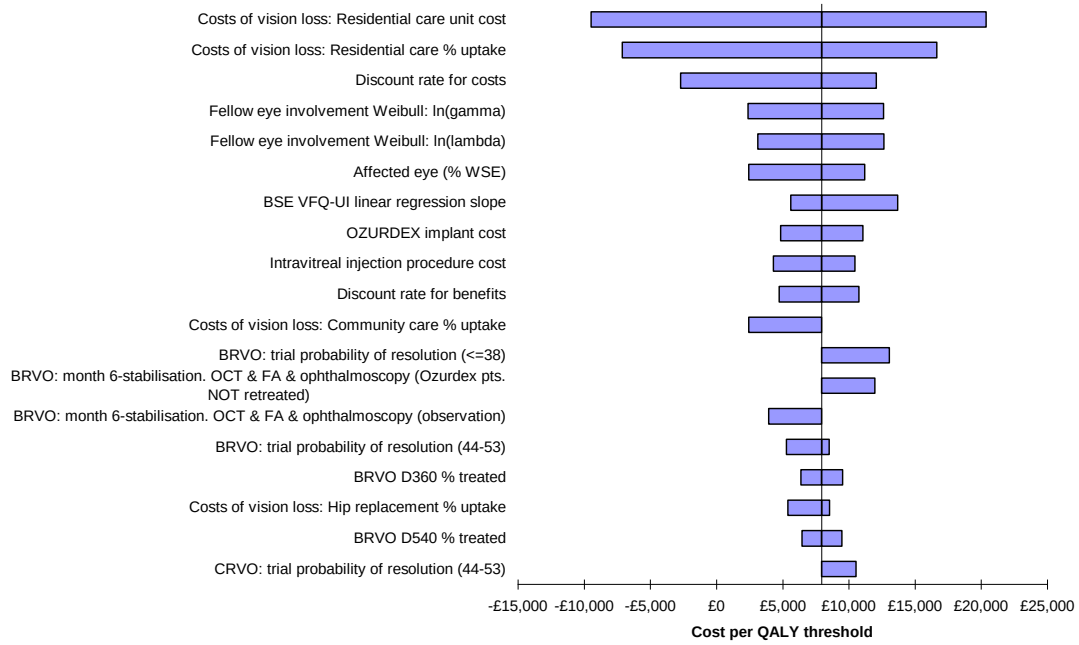
Figure 31: BRVO with previous laser. Univariate sensitivity analysis



For Ozurdex in BRVO with previous laser, no variables increase the ICER above £20,000.

The ICER for Ozurdex in BRVO with previous laser is most sensitive to changes in the annual cost of residential care.

Figure 32: BRVO-macular haemorrhage. Univariate sensitivity analysis



For Ozurdex in BRVO-macular haemorrhage the ICER is most sensitive to changes in the annual cost of residential care. At the lower estimate of cost of the annual cost of residential care, the ICER increases to **£20,367**. At the higher estimate of cost of in the annual cost of residential care, Ozurdex is dominant.

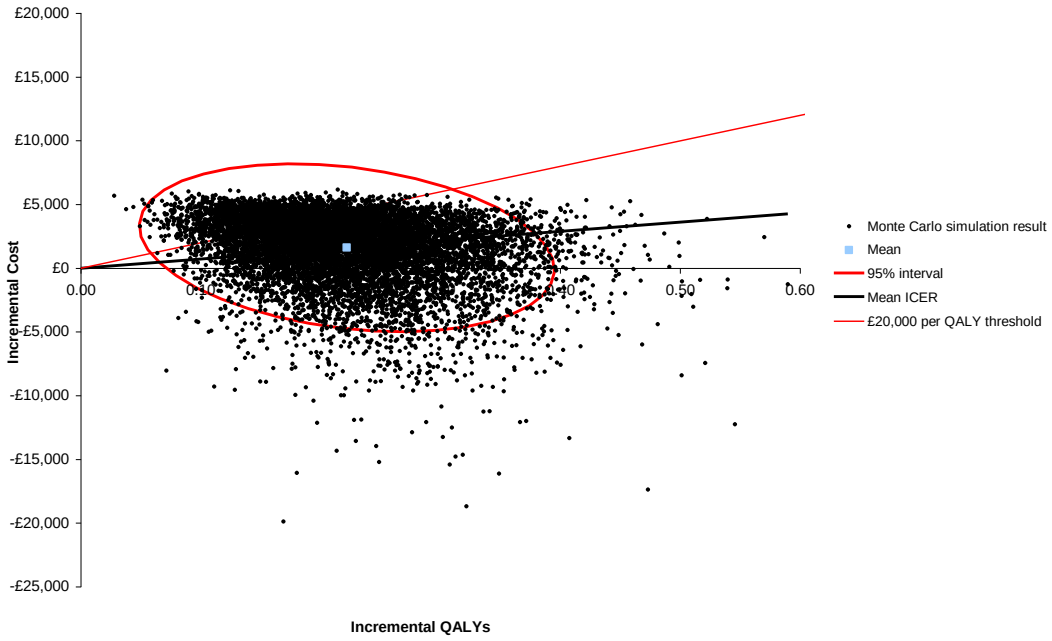
6.7.8 Probabilistic sensitivity analysis (PSA)

Scatter plot results for the PSA are presented in Figure 33 to Figure 36 for the following patient groups: all RVO, CRVO, BRVO-macular haemorrhage and BRVO with previous laser.

The scatter plots indicate that for Ozurdex in all RVO, CRVO, and BRVO-macular haemorrhage the majority of simulations lie in the north-east quadrant (incremental cost and incremental QALY) with a mean ICER less than the £20,000 per QALY threshold. For Ozurdex in BRVO with previous laser, the mean ICER is dominant, i.e. Ozurdex results in incremental QALYs and reduced cost when compared against observation.

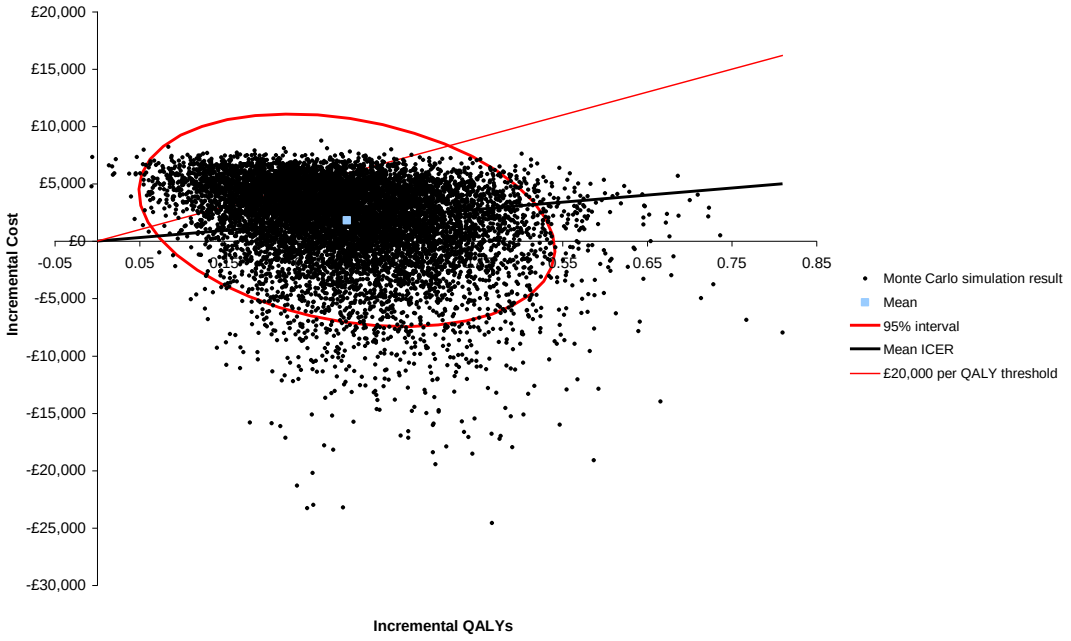
Scatter plots

Figure 33: all RVO. Results of probabilistic sensitivity analysis (10,000 simulations). Mean ICER is £7,208



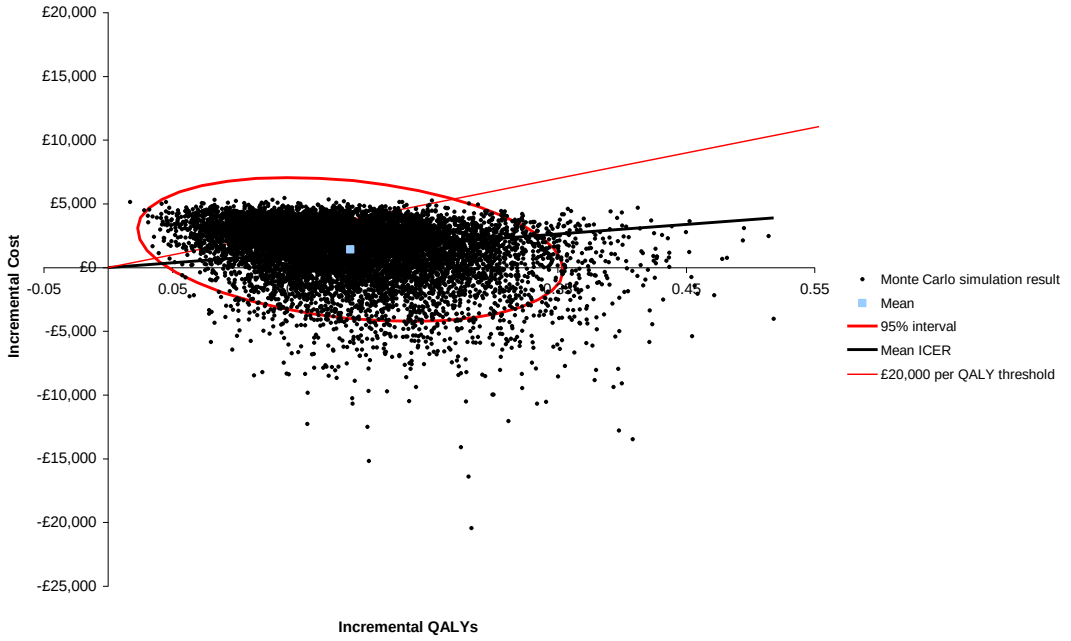
Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Figure 34: CRVO. Results of probabilistic sensitivity analysis (10,000 simulations). Mean ICER is £6,188



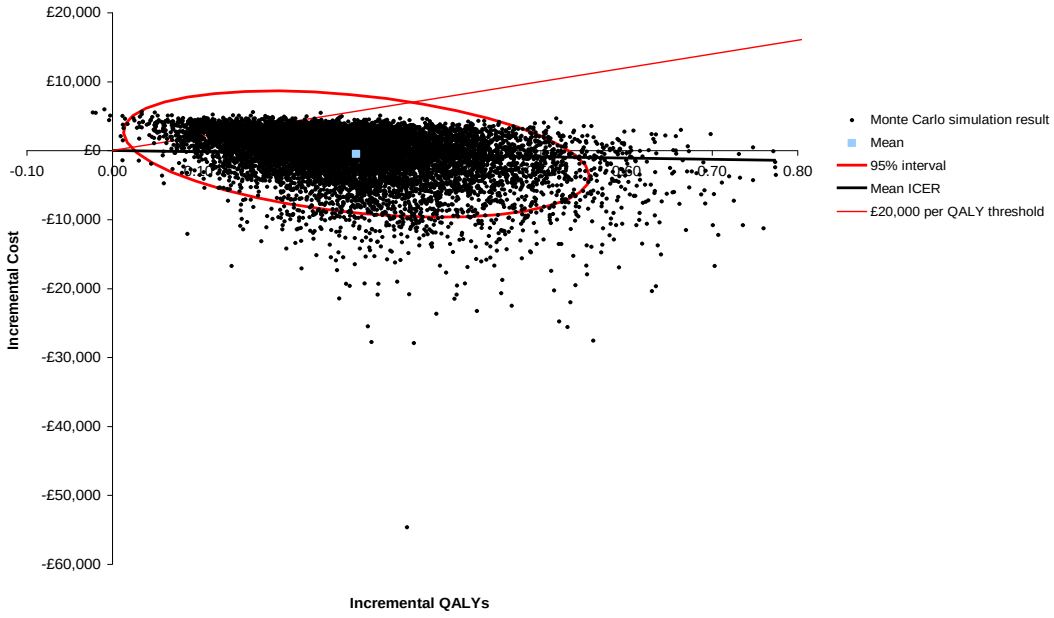
Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Figure 35: BRVO-macular haemorrhage. Results of probabilistic sensitivity analysis (10,000 simulations). Mean ICER is £7,495



Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Figure 36: BRVO with previous laser. Results of probabilistic sensitivity analysis (10,000 simulations). Mean ICER shows that Ozurdex is dominant

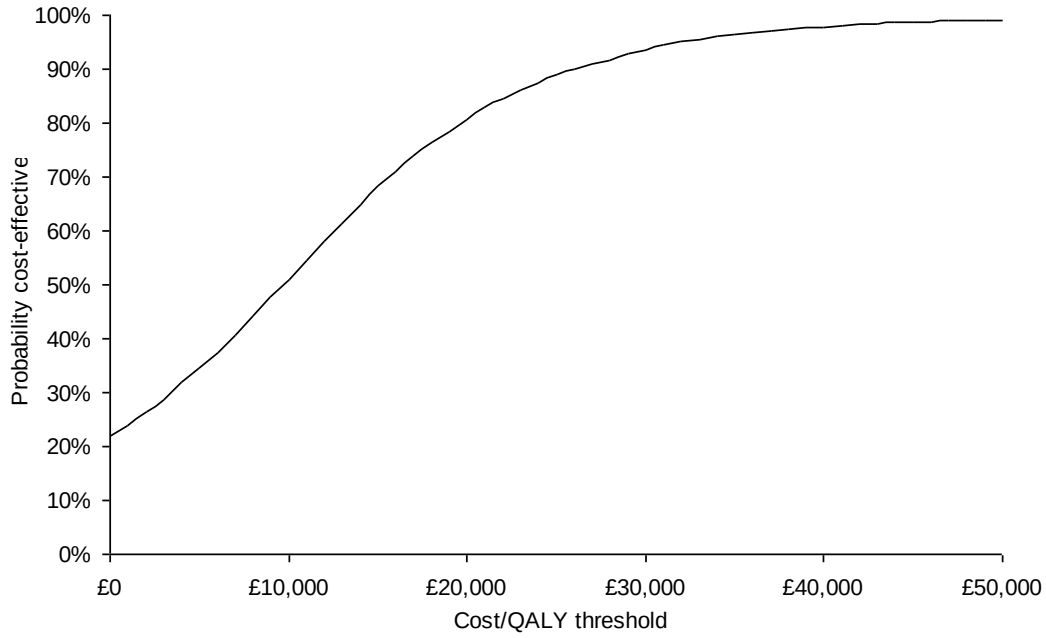


Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Cost-effectiveness acceptability curves (CEACs)

CEACs for the PSA are presented in Figure 37 to Figure 40 for the following patient groups: all RVO, CRVO, BRVO-macular haemorrhage and BRVO with previous laser.

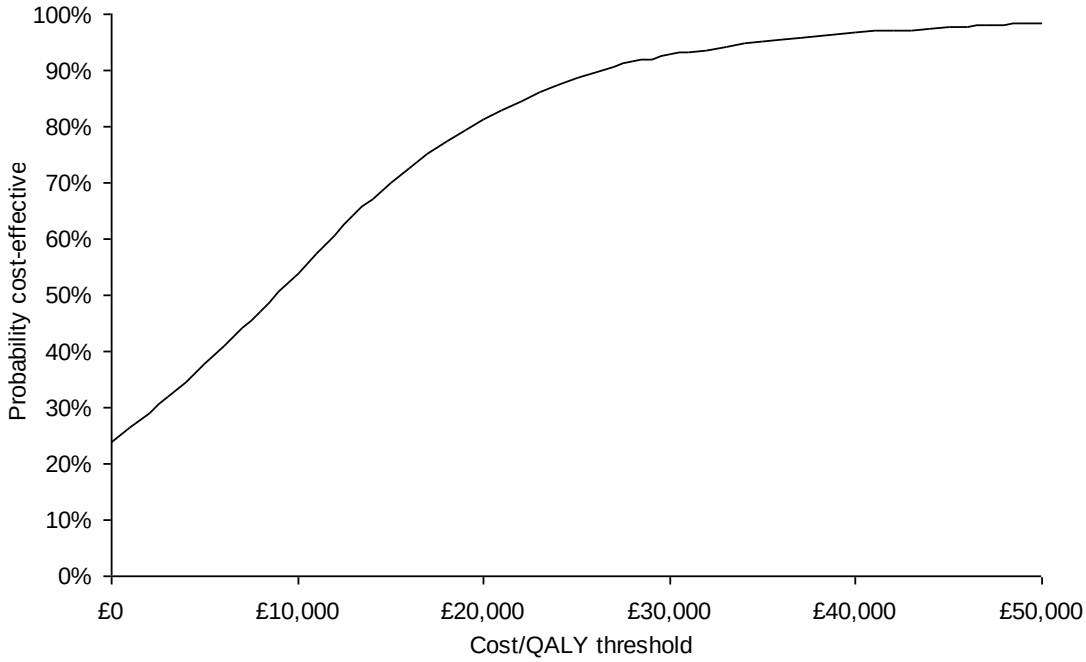
Figure 37: all RVO. Cost-effectiveness acceptability curve (CEAC)



Abbreviations: QALY, quality-adjusted life-year

In all RVO, the CEAC indicates that at a willingness to pay threshold of £20,000 per incremental QALY gained, approximately **81%** of simulations were cost-effective. At a willingness to pay threshold of £30,000 per incremental QALY gained, approximately **93%** of simulations were cost-effective (Figure 37).

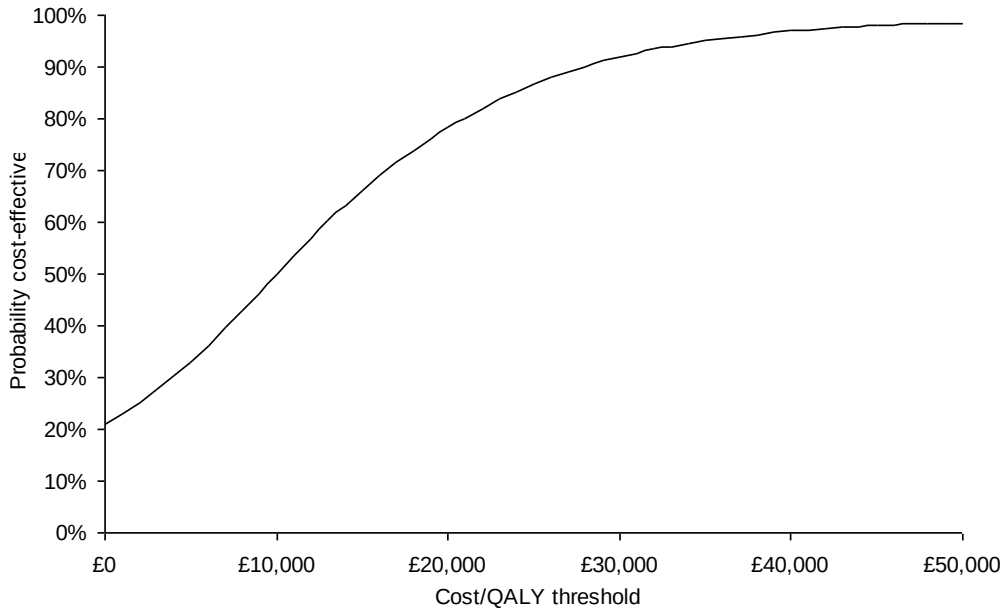
Figure 38: CRVO. Cost-effectiveness acceptability curve (CEAC)



Abbreviations: QALY, quality-adjusted life-year

In CRVO, the CEAC indicates that at a willingness to pay threshold of £20,000 per incremental QALY gained, approximately **81%** of simulations were cost-effective. At a willingness to pay threshold of £30,000 per incremental QALY gained, approximately **93%** of simulations were cost-effective (Figure 38).

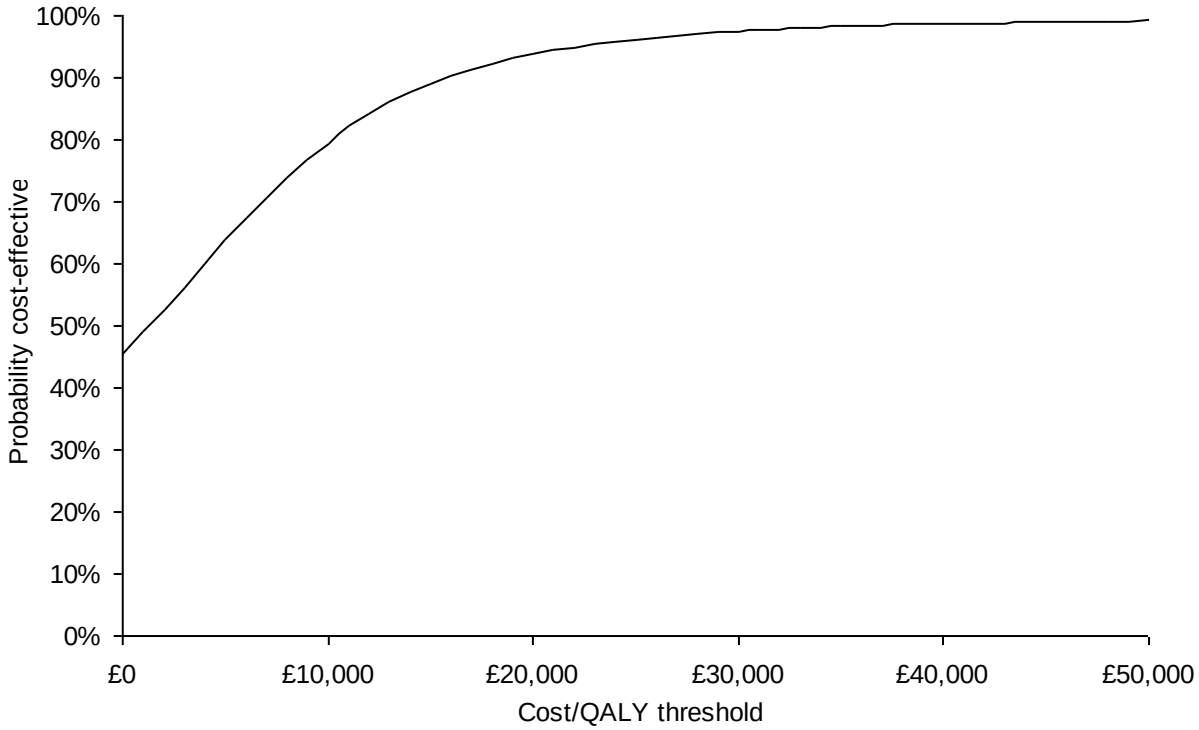
Figure 39: BRVO - macular haemorrhage. Cost-effectiveness acceptability curve (CEAC)



Abbreviations: QALY, quality-adjusted life-year

In BRVO-macular haemorrhage, the CEAC indicates that at a willingness to pay threshold of £20,000 per incremental QALY gained, approximately **78%** of simulations were cost-effective. At a willingness to pay threshold of £30,000 per incremental QALY gained, approximately **92%** of simulations were cost-effective (Figure 39).

Figure 40: BRVO with previous laser. Cost-effectiveness acceptability curve (CEAC)



Abbreviations: QALY, quality-adjusted life-year

In BRVO patients with previous laser therapy, the CEAC indicates that at a willingness to pay threshold of £20,000 per incremental QALY gained, approximately **94%** of simulations were cost-effective. At a willingness to pay threshold of £30,000 per incremental QALY gained, approximately **97%** of simulations were cost-effective (Figure 40).

6.7.9 Scenario analysis

Scenario analyses were conducted for the following patient groups: all RVO, CRVO, BRVO-macular haemorrhage and BRVO with previous laser. For each patient subgroup a total of 10 scenarios were investigated (Table 140 to Table 143).

Table 140: All RVO. results of scenario analysis.

Scenario	Incremental Cost	Incremental QALYs	ICER
Source of utility estimates/100% BSE patients	-£10,455	0.57	Dominant
Costs of vision loss: High service uptake/High unit cost	-£11,573	0.23	Dominant
Costs of vision loss: Low service uptake/Low unit cost	£5,552	0.23	£24,537
Stabilisation of visual acuity at day 360	£1,291	0.12	£10,764
Not treated extrapolation assumptions	£3,280	0.13	£24,924
Excess mortality of blindness	£1,056	0.18	£5,848
Fellow eye occurrence	£192	0.29	£659
Discounting	£2,573	0.32	£8,029
Constant trial proportion retreated	£4,751	0.25	£19,100
All patients start in ETDRS 39-43 letters	£396	0.25	£1,556
Visual decline of 1.5% per 6 months	1,630	0.21	£7,685
84% FEO results in ME	1,996	0.21	£9,356

Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ETDRS, Early Treatment Diabetic Retinopathy Study.

Two scenario analyses produced ICERs greater than £20,000.

- Assuming low uptake of services associated with vision loss and the lowest unit costs of these services the ICER is **£24,537**
- Applying the transition probabilities of observation patients to all Ozurdex patients who are not retreated with Ozurdex produces an ICER of **£24,924**

Table 141: CRVO. results of scenario analysis.

Scenario	Incremental Cost	Incremental QALYs	ICER
Source of utility estimates/100% BSE patients	-£26,482	0.84	Dominant
Costs of vision loss: High/High	-£16,656	0.31	Dominant
Costs of vision loss: Low/Low	£7,262	0.31	£23,763
Stabilisation of visual acuity at day 360	£621	0.15	£4,252
Not treated extrapolation assumptions	£4,076	0.21	£19,644
Excess mortality of blindness	£966	0.24	£4,015
Fellow eye occurrence	£421	0.37	£1,147
Discounting	£3,009	0.43	£7,028
Constant trial proportion retreated	£4,166	0.36	£11,469
All patients start in ETDRS 39-43 letters	£737	0.32	£2,334
Visual decline of 1.5% per 6 months	1,844	0.29	£6,433
84% FEO results in ME	2,186	0.29	£7,438

Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ETDRS, Early Treatment Diabetic Retinopathy Study.

In CRVO, one scneraio analysis produced an ICER greater than £20,000. Assuming low uptake of services associated with vision loss and the lowest unit cost of these services an ICER of **£23,763** was produced.

Table 142: BRVO - macular haemorrhage. results of scenario analysis.

Scenario	Incremental Cost	Incremental QALYs	ICER
Source of utility estimates/100% BSE patients	-£2,298	0.44	Dominant
Costs of vision loss: High/High	-£9,163	0.19	Dominant
Costs of vision loss: Low/Low	£4,641	0.19	£24,450
Stabilisation of visual acuity at day 360	£1,608	0.11	£14,283
Not treated extrapolation assumptions	£2,812	0.10	£29,045
Excess mortality of blindness	£1,025	0.15	£6,677
Fellow eye occurrence	-£30	0.26	Dominant
Discounting	£2,291	0.27	£8,454
Constant trial proportion retreated	£5,065	0.20	£25,871
All patients start in ETDRS 39-43 letters	£361	0.21	£1,722
Visual decline of 1.5% per 6 months	1,444	0.18	£8,108
84% FEO results in ME	1,833	0.18	£10,419

Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ETDRS, Early Treatment Diabetic Retinopathy Study.

In BRVO-macular haemorrhage patients, there were two scenario analyses which resulted in ICERs greater than £20,000

- Assuming low uptake of services associated with vision loss and the lowest unit cost of these services an ICER of **£24,450** was produced
- Applying the transition probabilities of observation patients to all Ozurdex patients who are not retreated produces an ICER of **£29,045**

Table 143: BRVO with previous laser. results of scenario analysis.

Scenario	Incremental Cost	Incremental QALYs	ICER
Source of utility estimates/100% BSE patients	-£14,507	0.77	Dominant
Costs of vision loss: High/High	-£19,762	0.31	Dominant
Costs of vision loss: Low/Low	£4,223	0.31	£13,482
Stabilisation of visual acuity at day 360	£208	0.20	£1,028
Not treated extrapolation assumptions	£206	0.19	£1,059
Excess mortality of blindness	-£2,074	0.25	Dominant
Fellow eye occurrence	-£3,997	0.41	Dominant
Discounting	£195	0.44	£440
Constant trial proportion retreated	£568	0.41	£1,392
All patients start in ETDRS 39-43 letters	-£5,774	0.46	Dominant
Visual decline of 1.5% per 6 months	-1,282	0.30	Dominant
84% FEO results in ME	-653	0.29	Dominant

Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ETDRS, Early Treatment Diabetic Retinopathy Study.

In Ozurdex in BRVO with previous laser, no scenario was able to produce an ICER which exceeded £20,000.

6.7.10 Summary of main findings from sensitivity analysis

Results were robust to changes in the majority of parameters. The only parameters when varied in univariate sensitivity analysis resulting in ICERs exceeding £20,000 were:

- The cost of residential care in all RVO patients and BRVO patients with macular haemorrhage
- The percentage of patients in whom the WSE is affected in CRVO patients

Other consistently influential parameters included:

- Percentage of patients in the poorest health state receiving residential care
- Discount rate for costs
- Determinants of fellow eye occurrence (Weibull regression parameters)

Probabilistic analysis has shown that in the vast majority of simulations, Ozurdex is associated with increased health benefits for all patient populations. For all RVO, CRVO and BRVO with macular haemorrhage, the mean incremental costs were positive. In BRVO with previous laser, the mean incremental cost was negative, suggesting that Ozurdex is associated with reduced costs when compared to observation.

6.7.11 Key drivers of the cost-effectiveness results

Key drivers of cost-effectiveness are:

- The annual cost of residential care
- The percentage of patients in whom the WSE is affected
- The percentage of patients retreated over time
- The assumptions surrounding Ozurdex patients who do not receive repeat injections i.e. if the transition probabilities for observation (Sham) patients are applied to all patients who are not retreated with Ozurdex, irrespective of whether they were deemed to have resolved (OCT ≤ 250μm) or not
- The total cost of vision loss

6.8 Validation

6.8.1 Model validation

Validation and quality assurance of calculations used within the economic analysis were carried out by the agency responsible for model development. A qualified

person who had not been involved with model programming performed a quality control (QC) check following the agency's standard operating procedure. A comprehensive checklist was used during the QC process and included the following key checkpoints:

- Code review: including review of cell calculations, links between worksheets, macros, visual basic code.
- Logic checks: e.g., changing input parameters to see if corresponding results are expected, including input of out-of-range values.
- Format and layout: including review of labels, titles/footnotes, spelling, version compatibility if applicable.

Quality assurance of reported outcomes was undertaken by the agency responsible for submission drafting. Several 'macros' contained within model modules were used to generate results. In order to QC the results reported, manually generated model outcomes were compared with those automatically produced using macros. Documentation of this process is available upon request.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Rationale for subgroup analysis

The longer the duration of ME following BRVO, the less likely it is to resolve spontaneously. In addition, the longer the duration of ME, the more challenging the treatment (31). Duration of ME at baseline is therefore included in our subgroup analysis.

Duration of RVO was identified in the final scope presented by NICE and is therefore included here (see Section 5.3.7).

6.9.2 Subgroup patient characteristics

- BRVO of duration ≤ 90 days
- BRVO of duration > 90 days

6.9.3 Description of statistical analysis

These subgroups were specified as post-hoc analyses from the GENEVA 008 and 009 clinical trials.

6.9.4 Results of subgroup analysis

Table 144: BRVO ≤ 90 days

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus observation (QALYs)
Observation	£11,486	11.48	-	-	-
Ozurdex	£10,993	11.75	-£493	0.27	Dominant

Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.

Table 145: BRVO > 90 days

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus observation (QALYs)
Observation	£8,771	11.56	-	-	-
Ozurdex	£10,699	11.72	£1,929	0.17	£11,418

Abbreviations: QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.

6.9.5 Relevant subgroups not considered

Interviews with clinical experts and the Final Scope approved by NICE have recognised the presence/absence of ischemia as a relevant subgroup. These patients could not be adequately identified from the GENEVA clinical trial data and are therefore not included.

6.10 Interpretation of economic evidence

6.9.1 Comparison with published economic literature

Section 6.1 identified only one study which considered the cost-effectiveness of an intervention in macular oedema (23). This study did not include Ozurdex.

6.9.2 Relevance of the economic evaluation to all patient groups

The economic evaluation includes all patients populations in whom expert opinion (54) suggests that Ozurdex could routinely be used on the basis that Ozurdex represents the only licensed treatment in these patient populations.

6.9.3 Strengths and weaknesses of the evaluation

Strengths of the analysis

- **The use of patient-level data from two identically designed trials to inform transition probabilities and a considered approach to estimating transition probabilities in the absence of retreatment**

- **The use of robust utility estimates for WSE patients and an explicit recognition that HRQL differs by whether diagnosis is in the BSE or WSE**
  This analysis represents the first analysis, of which the authors are aware, which accounts for the difference in HRQL in patients in whom the BSE and WSE is affected. The inclusion of different utility data for BSE and WSE will provide the most accurate picture of potential health benefits derived from treatment and is the first analysis, of which the authors are aware, which accounts for the potential HRQL gains in patients in whom the WSE is affected.

- **The use of Weibull extrapolation to inform FEO is more conservative than the constant risk assumed in the only other economic evaluation of an intervention macular oedema (23)**
  The use of Weibull extrapolation assumes that the risk of FEO diminishes over time. FEO in the BSE is a driver of excess mortality and cost in patients in the lowest visual acuity health state (≤38 letters). Assuming fewer patients in whom the BSE is affected and consequently fewer of these patients in the lowest visual acuity health state, would therefore be expected to result in more conservative estimates of ICERs compared with Brown et al (2002).

Limitations of this analysis

- **Reliance on clinical expert opinion to inform assumptions for which the published literature was not available. These assumptions included:**

  - **Time to stabilisation of visual acuity**
    Should stabilisation in visual acuity occur beyond the timeframes modelled (2.5 years BRVO; 3 years CRVO (see Extrapolating visual acuity), the weighted average cost of Ozurdex per treated patient would increase. The impact on the ICERs reported is difficult to judge given a lack of long-term data pertaining to changes in visual acuity in patients receiving long-term treatment with Ozurdex. If treatment beyond the timeframes modelled served only to maintain visual acuity, then we would expect the ICERs reported to increase. Expert opinion (54) suggests that only a small minority of patients would not attain stabilisation over the timeframes modelled. This point is considered further in Ozurdex retreatment rates below.

- **Medical resource use associated with routine monitoring**

  As expert opinion suggests that routine medical resource use is likely to be equivalent in patients who are and are not treated with Ozurdex (with the exception of routine monitoring of IOP), the use of expert opinion for this parameter is not expected to influence the applicability of the results presented in this analysis to clinical practice.

- **Ozurdex retreatment rates**
  A scenario analysis is presented in which 78.8% of BRVO patients receives the maximum five treatments and 85.7% of CRVO patients receives six treatments, so that this parameter is appropriately tested through sensitivity analysis. These percentages are the retreatment rates observed at day 180 in GENEVA studies (implementation of clinical data in the model). The model did not include treatment costs beyond year three, however one attendee at the New York Expert Panel felt that treatment might continue beyond year three in a small percentage of patients(54). The effect of extending treatment beyond year three was therefore investigated by applying a discounted cost of Ozurdex treatment and administration to 5% of CRVO patients during year 3 (assuming no additional efficacy associated with treatment). This analysis showed that costs extended to year 4 in CRVO patients had little effect on the ICERs reported (£6,363 vs. £6,088 in the base-case analysis).

- **The absence of sham data for months six to 12 necessitated the use of data from months three to six for extrapolation of visual acuity outcomes in observation patients whilst extrapolation of visual acuity outcomes for Ozurdex treated patients used data for months six to 12.** This analysis sought to use the last available data set for each arm from the GENEVA trials. The use of transition probabilities based on data from months six to 12 for Ozurdex-treated patients may underestimate the benefits of Ozurdex treatment on the basis that the peak effect of Ozurdex is generally observed at month 2-3 post implant. At month six, the treatment response is lower. The ICERs reported would therefore be conservative on this basis. With regards the use of data for months three to six to inform the extrapolation of visual acuity outcomes in observation patients, Markov traces suggest minimal change in visual acuity among observation patients beyond 1 year (Section 6.7.2) and therefore this assumption is unlikely to bias the analysis in favour of Ozurdex.

- **The use of Weibull extrapolation of the risk of FEO from 6 years of data presented in Hayreh et al. to the lifetime perspective is an uncertainty (71).**
  The Weibull extrapolation assumes a diminishing risk of FEO over time. At six years the annual risk is just 1.3%. This increasingly small value would not be expected to have a sizeable impact on the ICERs reported.

- **The lack of efficacy evidence which would allow an indirect comparison with other treatments identified in the NICE final scope**

In clinical practice intravitreal injections of triamcinolone (a corticosteroid) or bevacizumab (a VEGF inhibitor) may be used to treat ME following RVO. However, the safety and efficacy of triamcinolone and bevacizumab as intravitreal injections has yet to be established and these treatments are not currently licensed in the UK for the treatment of ME following BRVO or CRVO. Clinically available formulations for triamcinolone and bevacizumab are not designed for ocular use (as stated by the manufacturers). Genentech/Roche have raised concerns regarding the compounding of bevacizumab into smaller doses for intraocular use as it is not designed, manufactured or approved for such use (11).

Significantly, the prescribing information for the injectable suspension of triamcinolone (Kenalog, manufactured by Bristol Myers Squibb in a formulation for intra-articular injection) states that intraocular injection is contraindicated (12). Adequate studies to demonstrate the safety of Kenalog as intraocular (intravitreal) injections have not been performed and endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances, including vision loss, have been reported with the intravitreal administration of Kenalog (12). In addition, intraocular injection of corticosteroid formulations containing benzyl alcohol, such as Kenalog, is not recommended because of potential toxicity to the eye from the benzyl alcohol (12).

Results of the systematic review within this submission suggest there are currently no published RCTs, which evaluate the efficacy and safety of bevacizumab or triamcinolone (Kenalog formulation or equivalent) (See section 5.7).

Standard care for CRVO in the UK should be considered to be observation based on the results of previous RCTs. In the case of BRVO, some patients are suitable for treatment with laser photocoagulation. However, some patients for example with intra-retinal haemorrhage may not be considered appropriate patients for laser treatment; in this patient population observation could once again be considered standard care.

6.9.4 Further analyses

Further data collection and analyses, which could enhance the robustness of the results presented include:

- Long-term data collection of patients receiving multiple injections of Ozurdex reporting..
    - Percentage of patients receiving repeat injections over time
    - Characteristics of patients requiring injections beyond the time frames modelled (2.5 years BRVO, 3 years CRVO)
    - Changes in visual acuity resulting from multiple injections of Ozurdex
    - Incidence of raised IOP, cataract and retinal tear/detachment

It should be noted that the manufacturer intends to pursue the collection of these additional data through the undertaking of a post approval commitment study.

- Further long-term observational data pertaining to the natural history of patients with ME following RVO to determine mean time to visual acuity stabilisation
- Performing analyses in which FEO in the WSE and recurrence in the same eye are included

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

A large published epidemiology study estimates the 5-year incidence of BRVO as 0.6% and CRVO as 0.2% in people aged over 40 years (2). This equates to a 1-year incidence of BRVO and CRVO of 0.12% and 0.04% respectively[20]. Macular oedema following RVO is estimated to occur in 50% of BRVO patients and 84% of CRVO patients (5, 38).

Applying these incident rates to the general population aged over 40 years in England and Wales (26,746,841) equates to 16,048 incident patients with ME following BRVO and 8,987 incident patients with ME following CRVO (101).

Based on an estimate of 90% of BRVO and 100% of CRVO patients requiring treatment, 14,443 incident patients with ME following BRVO and 8,987 incident patients with ME following CRVO would require treatment.

Table 146: Data, sources and assumptions to determine numbers of incident patients with ME following RVO who require treatment

Parameter	Value	Reference
Population for England and Wales	54,809,100	Office of National Statistics (101)
% population > 40 years	49%	Office of National Statistics (101)
% annual increase in population p.a.	0.67%	Office of National Statistics (101)
5-year incidence of RVO > 40 years	0.6% BRVO 0.2% CRVO	Klein et al., 2008 (2)
1-year incidence of RVO > 40 years	0.12% BRVO 0.04% CRVO	1-EXP(-(-LN(1-five-year incidence)/5))
% patients with ME BRVO	50%	Margolis et al., 2006 (5)
% patients with ME CRVO	84%	Central Vein Occlusion Study Group, 1993 (38)
% pts requiring	90% BRVO	Assumption

[20] Assuming 1-year incidence =1-EXP(-(-LN(1-five-year incidence)/5))

treatment	100% CRVO	
% BRVO pts with macular haemorrhage	62%	GENEVA 008 and 009 (Table 9 of Section 5)
% BRVO Pts having laser treatment	34%	Allergan Data on File (102)
% BRVO pts with previous laser requiring further treatment	35%	1 minus % pts gaining two or more lines of VA at three years follow up The Branch Vein Occlusion Study Group 1984 (7)
Annual risk of requiring further treatment in incident BRVO pts with previous laser (applied each year for three years)	13.4%	1-EXP(-(-LN(1-three-year probability)/3))

Pts: Patients; VA: visual acuity, ME: macular oedema, RVO: retinal vein occlusion; BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion

In GENEVA 008 and GENEVA 009, the presence of macular haemorrhage at baseline was assessed. Five-hundred and fifteen (255 in the Ozurdex treatment group and 260 in the Sham group) of 830 patients with BRVO (62%) had "Definite" presence of macular haemorrhage at the qualification or baseline study visit (Table 9 of Section 5). It should be noted that a proportion of these patients may have been suitable for laser treatment and therefore the estimated number of incident patients based on this proportion represents a maximum that is unlikely to be seen in clinical practice. The estimated maximum number of incident patients with BRVO-MH on this basis is 8,955 in England and Wales.

The incident number of BRVO patients with previous laser was estimated based on the percentage of patients in the Branch Vein Occlusion Study, that were reported to have attained two lines or more in VA at three-years' follow up (65%) (7). If 35% of patients attained fewer than two lines in VA over the three-year period, this equates to an annual probability of attaining fewer than two lines of 13.4% (see Table 146). This probability was applied to the proportion of incident BRVO patients who undergo laser (assumed to be 34% (102)) for a period of three years (for patient numbers see Table 147).

Beyond year 1, it is assumed that there is a constant incidence rate but an annual growth in population size of 0.67% per annum (101).

Table 147: Patients eligible for treatment in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
All RVO	**23,430**	**23,587**	**23,745**	**23,904**	**24,065**
CRVO	8,987	9,047	9,108	9,169	9,230
BRVO	14,443	14,540	14,637	14,736	14,834
BRVO-MH	8,955	9,015	9,075	9,136	9,197
BRVO-previous laser	657	1,230	1,731	1,743	1,755

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Observation is currently the standard clinical management strategy for patients with CRVO and those patients affected by ME following BRVO who are not considered appropriate for immediate laser photocoagulation, such as those with macular haemorrhage or in patients who have previously been treated with laser photocoagulation but have not achieved adequate therapeutic response (Section A 2.6).

Ozurdex is the only licensed pharmacological intervention for the treatment of ME following CRVO or BRVO. [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.3 What assumption(s) were made about market share (when relevant)?

N/A

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The procedure cost to administer Ozurdex was included. This was based on the Office of Population Censuses and Surveys (OPCS) code C89.2 “Insertion of steroid into posterior segment of eye” (92). The administration of Ozurdex was assumed to be as a day case procedure, and the corresponding NHS reference costs were extracted (HRG code BZ23Z, Vitreous Retinal Procedures - category 1 (£648) (93)) (Table 107).

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit cost of Ozurdex is £870 (exc. VAT). Ozurdex is the first licensed pharmacological intervention for the treatment of ME following CRVO or BRVO. Therefore, the costs associated with Ozurdex treatment are not reflected in current NHS reference costs or PbR tariffs. Current NHS reference costs and PbR tariffs are below the cost of an Ozurdex implant and would not adequately cover the cost of the procedure.

The total per-treatment cost of Ozurdex was therefore estimated to be £1,518 (£648 administration and £870 the unit cost of Ozurdex).

Cost estimates per patient assumed incident patients consume on average 6-months of Ozurdex treatment in their first year. Retreatment rates were as presented in Table 149. These were estimated by the New York Clinical Expert Panel (Table 102).

Table 149: Estimated percentage of patients requiring Ozurdex treatment over time

Year	Year 1		Year 2		Year 3	
Injection	**1**	**2**	**3**	**4**	**5**	**6**
BRVO	100%	79%	19%	19%	8%	0%
CRVO	100%	86%	63%	63%	37%	37%

7.6 Were there any estimates of resource savings? If so, what were they?

N/A

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

[redacted]

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Ozurdex is the first licensed pharmacological treatment in patients with CRVO and patients with BRVO who are unsuitable for or who have failed to respond to laser photocoagulation. With the availability of a licensed therapy, clinicians may decrease the use of unlicensed intravitreal triamcinolone acetonide (IVTA; 'Kenalog' formulation or equivalent) and bevacizumab. However, since the Summary of Product Characteristics for these therapies do not include intra-vitreal injection and no independent guidelines are available to inform assumptions surrounding frequency of administration and follow up, the quantities and therefore costs offsets could not be quantified to an adequate degree for inclusion in this analysis.

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9 Appendices

9.1 Appendix 1: SPC/IFU, scientific discussion or drafts.

Appendix 1a: Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in applicator

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One implant contains 700 micrograms of dexamethasone.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravitreal implant in applicator.
Disposable injection device, containing a rod-shaped implant. which is not visible.
The implant is approximately 0.46 mm in diameter and 6 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OZURDEX is indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) (see section 5.1).

4.2 Posology and method of administration

OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Posology
The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk (see section 5.1).

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4).

Special populations
Elderly (≥65 years old)
No dose adjustment is required for elderly patients.

Renal impairment
OZURDEX has not been studied in patients with renal impairment however no special considerations are needed in this population.

Hepatic impairment
OZURDEX has not been studied in patients with hepatic impairment, however no special considerations are needed in this population.

Paediatric population
There is no relevant use of OZURDEX in the paediatric population in macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).

Method of administration
Single-use intravitreal implant in applicator for intravitreal use only.
Each applicator can only be used for the treatment of a single eye.

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent).

A broad spectrum topical antimicrobial should be given prior to and on the day of the injection procedure. Adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage (see section 6.6). Then, in a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately.

Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view.

Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial.

4.3 Contraindications

OZURDEX is contraindicated in

- Hypersensitivity to the active substance or to any of the excipients.
- Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Advanced glaucoma which cannot be adequately controlled by medicinal products alone.

4.4 Special warnings and precautions for use

Monitoring
Any intravitreous injection can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. In addition, patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection.

Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Adverse reactions
Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections.

In clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second injection (see section 4.8) with only 1 patient out of 368 requiring cataract surgery during the first treatment and 3 patients out of 302 during the second treatment.
As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. Of the patients experiencing an increase of IOP of ≥10 mmHg from baseline, the greatest proportion showed this IOP increase at around 60 days following an injection. Patients of less than 45 years of age are more likely to experience increases in IOP. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post-injection as needed.

Other warnings and precautions
Corticosteroids should be used cautiously in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*.

The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.

OZURDEX has not been studied in aphakic patients Therefore OZURDEX should be used with caution in these patients.

OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia. Therefore OZURDEX is not recommended.

Anti-coagulant therapy was used in 1.7% of patients receiving OZURDEX; there were no reports of hemorrhagic adverse events in these patients. Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%). OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Systemic absorption is minimal and no interactions are anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Long-term systemic treatment with glucocorticoids during pregnancy increases the risk for intra-uterine growth retardation and adrenal insufficiency of the newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local, intraocular treatment, OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast feeding
Dexamethasone is excreted in breast milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive and use machines

Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection (see section 4.8). They should not drive or use machines until this has resolved.

4.8 Undesirable effects

a) The clinical safety of OZURDEX has been assessed in two Phase III randomised, double-masked, sham-controlled studies in patients with macular oedema following central retinal vein occlusion or branch retinal vein occlusion. A total of 427 patients were randomised to OZURDEX and 426 to sham in the two Phase III studies. A total of 401 patients (94 %) randomised and treated with OZURDEX completed the initial treatment period (up to day 180).

A total of 47.3 % of patients experienced at least one adverse reaction. The most frequently reported adverse reactions in patients who received OZURDEX were increased intraocular pressure (24.0 %) and conjunctival haemorrhage (14.7 %).

The adverse reaction profile for BRVO patients was similar to that observed for CRVO patients although the overall incidence of adverse reactions was higher for the subgroup of patients with CRVO.

b) The following adverse reactions, considered related to OZURDEX treatment were reported during the two Phase III clinical trials.

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) adverse reactions are presented according to MedDRA System organ class in Table 1. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Frequency	Adverse reaction
Nervous system disorders	uncommon	Headache
Eye disorders	very common	Intraocular pressure increased, conjunctival haemorrhage*
	common	Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*
	uncommon	Retinal tear*, anterior chamber flare*

* Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant

c) Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. During the initial treatment period, 0.7 % (3/421) of the patients who received OZURDEX required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2 % (1/423) with sham.

The adverse reaction profile of 341 patients analysed following a second injection of OZURDEX, was similar to that following the first injection. A total of 54 % of patients experienced at least one adverse reaction. The incidence of increased IOP(24.9 %) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. The overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

4.9 Overdose

If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinflammatory agents, ATC code: S01BA01

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. Vascular Endothelial Growth Factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

The efficacy of OZURDEX was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1,267 patients who received treatment with dexamethasone 350 µg or 700 µg implants or sham (studies 206207-008 and 206207-009). A total of 427 were randomised to OZURDEX, 414 to dexamethasone 350 µg and 426 patients to sham.

Based on the pooled analysis results, treatment with OZURDEX implants showed statistically significantly greater incidence of responders, defined as patients achieving a ≥ 15 letter improvement from baseline in Best Corrected Visual Acuity (BCVA) at 90 days following injection of a single implant, when compared with sham ($p < 0.001$).

The proportion of patients achieving the primary efficacy measure of ≥ 15 letter improvement from baseline in BCVA following injection of a single implant is shown in Table 2. A treatment effect was seen at the first observation time point of day 30. The maximum treatment effect was observed at day 60 and the difference in the incidence of responders was statistically significant favouring OZURDEX compared with sham at all time points to day 90 following injection. There continued to be a numerically greater proportion of responders for a ≥ 15 letter improvement from baseline in BCVA in patients treated with OZURDEX compared with sham at day 180.

Table 2. Proportion of Patients with ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, ITT Population)

Visit	OZURDEX N = 427	Sham N = 426
Day 30	21.3 % [a]	7.5%
Day 60	29.3% [a]	11.3%
Day 90	21.8% [a]	13.1%
Day 180	21.5%	17.6%

[a] Proportion significantly higher with OZURDEX compared to sham ($p < 0.001$)

The mean change from baseline BCVA was significantly greater with OZURDEX compared to sham at all time points.

In each Phase III study and the pooled analysis, the time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response curves were significantly different with OZURDEX compared to sham ($p < 0.001$) with OZURDEX treated patients achieving a 3-line improvement in BCVA earlier than sham treated patients.

OZURDEX was numerically superior to sham in preventing vision loss as shown by a lower of proportion of patients experiencing deterioration of vision of ≥ 15 letters in the OZURDEX group throughout the 6-month assessment period

In each of the phase III studies and the pooled analysis, mean retinal thickness was significantly less, and the mean reduction from baseline was significantly greater, with OZURDEX (-207.9 microns) compared to sham (-95.0 microns) at day 90 ($p < 0.001$, pooled data). The treatment effect as assessed by BCVA at day 90 was thus supported by this anatomical finding. By Day 180 the mean retinal thickness reduction (-119.3 microns) compared with sham was not significant.

Patients who had a BCVA score of <84 OR retinal thickness > 250 microns by optical coherence tomography OCT and in the investigator's opinion treatment would not put the patient at risk; were eligible to receive an OZURDEX treatment in an open label extension. Of the patients who were treated in the open label phase, 93% received an OZURDEX injection between 5 and 7 months after the initial treatment.

As for the initial treatment, peak response was seen at Day 60 in the open label phase. The cumulative response rates were higher throughout the open label phase in those patients receiving two consecutive OZURDEX injections compared with those patients who had not received an OZURDEX injection in the initial phase.

The proportion of responders at each time point was always greater after the second treatment compared with the first treatment. Whereas, delaying treatment for 6 months results in a lower proportion of responders at all time points in the open label phase when compared with those receiving a second OZURDEX injection.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with
OZURDEX in all subsets of the paediatric population for retinal vascular occlusion. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Plasma concentrations were obtained from a subset of 21 patients in the two, 6-month efficacy studies prior to dosing and on day 7, 30, 60, and 90 following the intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent of the plasma dexamethasone concentration values for the 350 µg dose group and 86% for the 700 µg dose group were below the lower limit of quantitation (0.05 ng/ml). The highest plasma concentration value of 0.094 ng/ml was observed in one subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In a 6-month monkey study following a single intravitreal injection of OZURDEX the dexamethasone vitreous humour C_{max} was 100 ng/ml at day 42 post-injection and 5.57 ng/ml at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection. The rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humour > aqueous humour > plasma.

In an *in vitro* metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed. This is consistent with results from rabbit and monkey ocular metabolism studies.

Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine.

The OZURDEX matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at doses considered sufficiently in excess of the maximum dose for human indicating little relevance to clinical use.

No mutagenicity, carcinogenicity, reproductive or developmental toxicity data are available for OZURDEX. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application.

Dexamethasone exposure to the healthy/untreated eye via contralateral diffusion has been observed in rabbits following delivery of the implant to the posterior segment of the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ester terminated 50:50 poly D,L-lactide-co-glycolide.
- Acid terminated 50:50 poly D,L-lactide-co-glycolide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 pack contains:

1 sustained release sterile implantable rod shaped implant containing
700 micrograms of dexamethasone, located in the needle (stainless steel) of a disposable applicator.

The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab.

The applicator containing the implant is packaged in a sealed foil pouch containing

desiccant.

6.6 Special precautions for disposal and other handling

OZURDEX is for single use only.
Each applicator can only be used for the treatment of a single eye.

If the seal of the foil pouch containing the applicator is damaged, do not use. Once the foil pouch is opened the applicator should be used immediately.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Co. Mayo
Westport
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

Appendix 1b: CHMP Assessment report

Evaluation of Medicines for Human Use

CHMP Assessment report

Ozurdex

International Nonproprietary Name: dexamethasone

Procedure No. EMEA/H/C/001140

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

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Allergan Pharmaceuticals Ireland submitted on 24 February 2009 an application for Marketing Authorisation to the European Medicines Agency for Ozurdex, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the Agency/CHMP on 24 April 2008. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The legal basis for this application refers to:

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

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

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

1.1.1 Information on paediatric requirements

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

1.1.1 Licensing status:

A new application was filed in the following countries: United States of America.

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

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

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

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 24 February 2009.
- The procedure started on 25 March 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 June 2009.
- During the meeting on 20-23 July 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2009.
- The summary report of the inspection carried out at the following site Allergan Inc, California, USA between 9-12 November 2009 was issued on 8 December 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2010.
- During the CHMP meeting on 15-18 February 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 9 April 2010.
- During the meeting on 17-20 May 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ozurdex on 20 May 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 May 2010.

2 Scientific discussion

Introduction

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

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

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

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

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

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

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

Ozurdex is a sterile, single-use system intended to deliver one biodegradable implant into the vitreous for the treatment of macular oedema. The rationale of the design is

to overcome ocular drug delivery barriers and prolong the duration of dexamethasone effect in the eye. This biodegradable implant delivers a 700 micrograms total dose of dexamethasone to the vitreous with gradual release over time allowing for sustained levels of dexamethasone in the target areas. Ozurdex may offer a new therapeutic option in the treatment of macular oedema while reducing the potential for side effects typically observed from steroid administration through other routes of delivery (e.g. systemic).

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

2.2. Quality aspects

Introduction

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

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

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

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

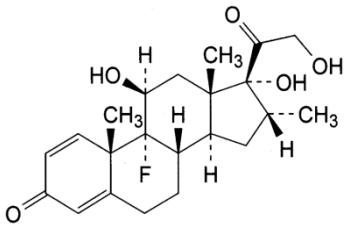
To ensure that air is not introduced into the eye, the applicator has been designed to vent air through a small gap between the implant and the inner needle wall. This allows air to move back through and out of the needle as the implant is being delivered. The small size of this gap prevents fluid from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

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

Active substance

Dexamethasone is chemically designated as pregna-1,4-diene-3,20-dione-9-fluoro-11,17,21-trihydroxy-16-methyl-,(11β,16α) or 9α-Fluoro-11β,17,21-trihydroxy-16β-

methylpregna-1,4-diene-3,20-dione (IUPAC) or (11β, 16α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione (CAS) and has the following structure:



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

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

- ***Manufacture***

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

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

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

- ***Specification***

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

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

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

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

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

- ***Stability***

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

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

Finished Medicinal Product

- ***Pharmaceutical Development***

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

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

The change from a tablet to an extruded filament required:

1. Change of polymers as the extruded implant needed to be mechanically stronger than the tablet (which was surgically inserted). The polymeric matrix was also changed in order to achieve drug release profile for the extruded filament, equivalent to that observed for the tablet. Many different PLA and PLGA polymer combinations were tested and a combination of two PLGA polymers was selected.
2. Evidence that the extrusion and the sterilization process did not adversely affect the safety, quality or performance of the implant. The effects of extrusion on the active substance were studied. The effect of extrusion on the drug substance was studied comparing the crystallinity, melting point, melting enthalpy and IR spectra of dexamethasone in the implant with the same properties of the pure dexamethasone.

   The effects of gamma sterilization were studied in relation to the polymer matrix. Gamma radiation reduces the molecular weight of PLGA polymers by cleaving the backbone chains, and this could potentially result in faster drug release from gamma irradiated implants than from non-irradiated implants. The studies showed that the drug release rate with the gamma radiation dose selected was not affected.
3. Improve dimensional tolerance and content uniformity to facilitate placement of the implant in a 22 gauge needle, the delivery of the implant from the needle

and a guarantee that cut filaments provide a consistent dose of dexamethasone.

The final formulation was established as a combination of two poly D,L-lactide-co-glycolide) polymers to produce a suitable matrix that controls the sustained release of dexamethasone, and ensure a mechanical strength suitable for use in the applicator. This formulation was established in Phase 2b clinical study and has remained unchanged since then.

- ***Adventitious agents***

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

- ***Manufacture of the product***

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

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

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

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

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

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

- ***Product specification***

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

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

Single HPLC method is used for dexamethasone content, content uniformity and related substances. The method is specific for dexamethasone, separates dexamethasone from its impurities, and there is no placebo interference. Satisfactory

validation data, according to ICH validation guidelines, have been provided. Suitability of the method for routine control and stability has been demonstrated.

The dexamethasone release profile from the implant is determined by using a non-standard dissolution apparatus and HPLC method.This method is intended to determine the amount of dexamethasone released from the polymer matrix over a 21 day period for quality control purposes only. Combined with the outer and inner blood-retinal barriers as well as a host of retinal pigmented epithelial drug transport mechanisms this makes an a priori in vitro-in vivo correlation in humans impossible. Therefore, for the intravitreal implant, the quality control drug release method is not intended to fully represent the human in-vivo performance of the drug product, but rather to ensure that the implant manufacturing process is reproducible.

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

- ***Stability of the product***

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

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

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

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

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

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

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

Discussion on chemical, pharmaceutical and biological aspects

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

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

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

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

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

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

The control of excipients is satisfactory.

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

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

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

Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1 Introduction

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

All definitive toxicology studies were carried out in full compliance with Good

Laboratory Practice (GLP) regulations. Investigations undertaken to establish suitable doses for use in the toxicity and pharmacokinetic studies were performed in accordance with the general principles of GLP.

2.3.2. Pharmacology

- ***Primary pharmacodynamic studies***

The applicant provided data from published literature (Nakada, 1987) regarding dexamethasone binding affinity to glucocorticoid receptors in fibroblasts. Data from saturation analysis yielded a K_d of 3.47 ± 0.38 nM and a B_{max} of 50,100 ± 2,200 sites/cell (n=3). The K_d value for [^{3}H] dexamethasone binding correlated very well with the 2.77 nM EC_{50} value for dexamethasone regulation of β-adrenergic receptor subtype. The relevance of these data was initially unclear to the CHMP, but the applicant provided an acceptable justification arguing that the provided references could be extrapolated to the claimed indication as there were no available specific dexamethasone pharmacology data on tissue explants or cell culture models for the blood-retinal barrier at the time of initial submission. In addition, a new reference was submitted by the applicant during the procedure that showed dexamethasone cytokine induction inhibition in human retinal microvascular pericytes in the same range of concentrations (2 nM).

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

- ***Secondary pharmacodynamic studies***

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

- ***Safety pharmacology programme***

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

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

- ***Pharmacodynamic drug interactions***

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

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

2.3.3. Pharmacokinetics

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

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

According to the Draft EMEA Guideline on Validation of Bioanalytical Methods (EMEA/CHMP/EWP/192217/2009) more flexible approaches are admitted when

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

Absorption

The ocular absorption of DEX PS DDS was studied in New Zealand White (NZW) rabbits and cynomolgus monkeys following a single dose administration for different observation periods. Tablet, single and double extruded dosage forms were tested, and two different implantation methods were used, sclerotomy and implantation via Ozurdex applicator. The extruded implants generally released dexamethasone more gradually and with less variability than the tablet implants, and the extruded form showed greater uniformity of dexamethasone release compared to the tablet implant.

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

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

Distribution

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

reflect the potential contralateral exposure in the untreated eye, as observed in rabbits, as a warning for eventual findings in clinical practice.

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

The applicant was requested by the CHMP in the Scientific Advice (EMEA/CHMP/SAWP/340437/2005) to provide in the MAA data on melanin binding (especially intraocular) in a specific study in a pigmented species or from literature. The in vivo results submitted by the applicant instead, adequately reflect the absence of dexamethasone binding to melanin in Dutch-Belted rabbits. In addition, dexamethasone showed rapid clearance from all ocular tissues in NZW rabbits and Cynomolgus monkeys. Dexamethasone is therefore not expected to accumulate in human pigmented ocular tissue.

Metabolism

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

Excretion

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

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

Pharmacokinetic drug interactions

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

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

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

2.3.4. Toxicology

Toxicity studies were conducted to evaluate the ocular and systemic effects of DEX PS DDS following administration in NZW rabbits. Repeat-dose intravitreal ocular toxicity studies were also conducted in NZW rabbits and cynomolgus monkeys using the DEX PS DDS and the Ozurdex applicator system. No new studies were performed to investigate the mutagenicity, carcinogenicity, or reproductive effects due to the well established clinical use of dexamethasone and the low systemic exposure following intravitreal administration. All toxicology studies with the DEX PS DDS were conducted according to Good Laboratory Practice (GLP) guidelines and procedures.

Table 1 - Ozurdex Toxicology Program

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

- ***Single dose toxicity***

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

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

Lymphotoxicity and decreased body weight was observed, this was most evident up to 30 days post-implantation and considered a dexamethasone-related systemic effect. These effects were reduced at two months and disappeared thereafter. The intravitreal dose of dexamethasone administered in each 700 µg DEX PS DDS implant is equivalent to approximately 0.2 mg/kg body weight in rabbits, which is roughly 20 times higher than the expected therapeutic dose for man (assuming 60 kg body weight). In more detail, the safety margins relating to the exposure to dexamethasone range from 3.8 to 17 fold in animal studies with use of the applicator, and from 7 to 100 fold following topical and intravenous dexamethasone.

- ***Repeat dose toxicity***

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

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

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

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

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

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

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

- ***Genotoxicity***

Previous studies to evaluate the mutagenic potential of dexamethasone in bacteria and mammalian cells in vitro have been negative. Given the long history of safe use of dexamethasone and with the low levels of patient exposure, genotoxicity studies have not been performed and this was considered acceptable to the CHMP.

- ***Carcinogenicity***

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

- ***Reproduction Toxicity***

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

- ***Toxicokinetic data***

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

- ***Local Tolerance***

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

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

- ***Other toxicity studies***

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

To evaluate the performance of the DEX PS DDS applicator, a special study in NZW rabbits was conducted. The Ozurdex applicator system was used to implant DEX PS DDS into the posterior segment of rabbit eyes. The study found that the applicator system was easy to use. Traumatic cataracts and other reactions were observed in this study, but these are thought to be likely related to the dimensions of the rabbit eye and not a problem associated with the Ozurdex applicator.

<u>Phototoxicity</u>

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

Studies on impurities

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

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

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

2.3.5. Ecotoxicity/environmental risk assessment

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

2.4. Clinical aspects

2.4.1. Introduction

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

2.4.2. GCP

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

A routine GCP inspection has been performed on the request from the CHMP In the

GCP inspection no critical findings were identified by the GCP inspectors.

Table 2 - Overview of clinical studies

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

2.4.3. Pharmacokinetics

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

The results indicated that exposure is low. No ocular pharmacokinetic evaluations were conducted. In both studies, the majority of plasma dexamethasone concentrations were below the level of quantitation (BLQ). In the pooled studies, plasma dexamethasone concentrations from 10 of 73 samples in the DEX 700 group and from 2 of 42 samples in the DEX 350 group were above the LLOQ, and ranged from 0.0521 ng/mL to 0.0940 ng/mL. There were no apparent correlations between plasma dexamethasone concentration and age, body weight, or sex. The single highest plasma dexamethasone concentration observed in the phase 3 studies was 0.0940 ng/mL which is only 13.4% of that reported following multiple ocular

applications of 1 drop of dexamethasone disodium phosphate (0.1%) to one eye every 1.5 hours.

2.4.4. Pharmacodynamics

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

2.4.5. Clinical efficacy

- ***Dose response study***

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

Study DC103-06

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

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

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

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

- ***Main studies***

This application is based on two pivotal phase III studies to support the efficacy and safety of DEX PS DDS in the treatment of macular oedema: Study 206207-009 and Study 206207-008. The studies which were identical in design, were six-month randomised, sham-controlled studies with a 6-month open label extension, assessing the safety and efficacy of 700 µg and 350 µg dexamethasone posterior segment drug delivery system, in patients with macular oedema due to Branch or Central Retinal Vein Occlusion. Results of the open label extension were provided during the procedure. In the extension phase, patients in all three groups received a second DEX 700 implant and were followed up for a further 6 months (re-treated population). A number of patients who received only one treatment at baseline were followed up to 12 months (single treatment population).

<u>STUDY 206207-009 and STUDY 206207-008</u>

- **Methods**
- **Study Participants**

Inclusion criteria

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

Exclusion criteria

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

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

- **Treatments**

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

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

- **Objectives**

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

Secondary objectives were to evaluate the safety and efficacy of the 700 µg compared with the 350 µg DEX PS DDS applicator systems in patients with macular oedema due to BRVO or CRVO as well as to assess the safety of the 700 µg DEX

PS DDS applicator system for an additional 6 months in patients who qualify for treatment in an open-label extension.

- **Outcomes/endpoints**

Primary efficacy endpoint

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

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

Secondary key endpoints of efficacy

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

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

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

- **Sample size**

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

For this 3-arm study with a 1:1:1 ratio for treatment allocation, a total of 495 patients was needed. Accounting for approximately 10% dropout rate, approximately 550 patients were to be enrolled.

- **Randomisation**

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

- **Blinding (masking)**

Masking was maintained through the use of a treating investigator who performed the study treatment procedure, and a follow-up investigator who did not participate in

study treatment procedures. Individuals collecting efficacy data (BCVA, contrast sensitivity, fluorescein angiography, OCT, and fundus photography) and the central reading facility remained unaware of patient treatment assignments. Patients remained masked from the initial study treatment assignment and for the whole duration of the trial.

- **Statistical methods**

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

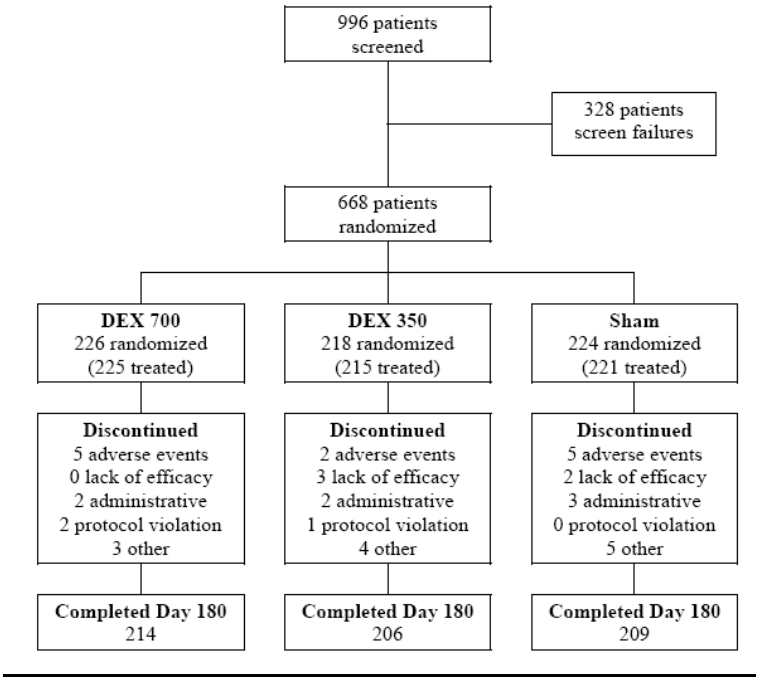
The primary efficacy variable was the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye. This included a comparison between DEX 700 and Sham and a comparison between DEX 350 and Sham at initial treatment day 180 in the ITT population.

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

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

- **Results - Study 206207-009**

Participant flow



- **Recruitment and numbers analysed**

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

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

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

- **Baseline data**

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

Table 3- Demography Study 206207-009

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

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

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

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

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

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

- ophthalmic beta blocking agents (25.7% [58/226] in the DEX 700 group, 21.6% [47/218] in the DEX 350 group, and 2.7% [6/224] in the Sham group),
- sympathomimetics in glaucoma therapy (12.8% [29/226] in the DEX 700 group, 12.8% [28/218] in the DEX 350 group, and 1.3% [3/224] group),
- ophthalmic prostaglandin analogues (9.7% [22/226] in the DEX 700 group, 11.5% [25/218] in the DEX 350 group, and 1.3% [3/224] in the Sham group), and
- other ophthalmologicals (9.7% [22/226] in the DEX 700 group, 11.0% [24/218] in the DEX 350 group, and 9.8% [22/224] in the Sham group).

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

- **Outcomes and estimation**

Primary endpoints

BCVA 15 or More Letters Improvement in ITT Population

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

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

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

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

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

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

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

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

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

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

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

Secondary endpoints

BRVO

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

CRVO

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

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

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

study eye as the ITT population. Excluding patients with acute macular oedema (<90days), the rate of responders in the sham groups decreased leading to statistical, although not clinical, significant differences between DX700 and sham.

Time to 15 or more letters improvement in BCVA

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

Categorical change from baseline BCVA

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

BCVA 10 or more letters improvement in ITT population

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

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

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

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

Mean change from baseline BCVA

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

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

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

Contrast sensitivity

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

Retinal Thickness in ITT population and diagnostic subgroups

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

Retinal volume measured by Optical Coherence Tomography

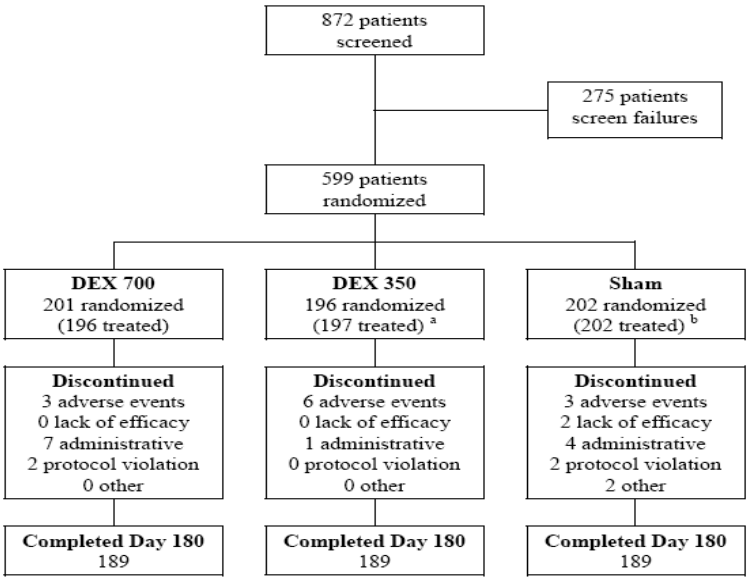
Retinal volume was significantly less with DEX 700 and DEX 350 compared to Sham at day 90 ($p \leq 0.005$), though not at day 180. There were no differences between the 2 doses of DEX.

Fluorescein Leakage

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

- **Results - Study 206207-008**

Participant flow



- **Recruitment and numbers analysed**

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

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

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

- **Baseline data**

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

Table 4 - Demography Study 206207-008

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

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

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

a P-value based on 1-way ANOVA

b P-value based on Pearson's chi-square or Fisher's exact test

c P-value based on Cochran-Mantel-Haenszel method using modified ridit scores

d Asian race category excludes Japanese

e Description of "other" race in Listing 16.2.4-1

f P-value based on Pearson's chi-square or Fisher's exact test comparing Caucasians to non-Caucasians

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

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

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

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

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

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

- **Outcomes and estimation**

Primary endpoints

BCVA 15 or More Letters Improvement in ITT Population

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

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

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

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

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

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

Source: Table 14.2-2.1

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

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

Source: Table 14.2-2.2

Note: baseline is relative to the timepoint of injection

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

Secondary endpoints

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

BRVO

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

CRVO

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

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

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

Time to 15 or more letters improvement in BCVA

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

Categorical change from baseline BCVA

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

BCVA 10 or more letters improvement in ITT population

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

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

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

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

Mean change from baseline BCVA

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

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

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

Contrast sensitivity

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

Retinal Thickness in ITT population and diagnostic subgroups

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

Retinal volume measured by Optical Coherence Tomography

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

Fluorescein Leakage

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

- ***Ancillary analyses***

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- ***Supportive studies***

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

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

2.4.6. Discussion on clinical efficacy

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

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

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

The CHMP initially also had concerns regarding the fact that the 12 month efficacy data do not seam to offer reassurance that patients benefit from a second implant. There was limited evidence that patients benefit from a second or further implants and although at early time-points of 60 and 90 days there was statistically significant

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

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

In a further attempt to identify a patient population that could clearly benefit from the treatment with DEX 700 the CHMP highlighted that despite not being authorised for the claimed indication, these patients are not left untreated and some other therapeutic alternatives are usually tested with some degree of success. The possible place in therapeutic of Ozurdex was therefore somewhat difficult for the CHMP to understand. The CHMP therefore requested the applicant to explore whether there is a subset of patients who could potentially benefit from Ozurdex in the light of the available treatments. The applicant argued that despite the burden of

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

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

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

> *"The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).*
>
> *Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk (see section 5.1).*

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4).”

2.4.7. Conclusions on the clinical efficacy

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

2.4.8. Clinical safety

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

- ***Patient exposure***

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

Table 2.5.5–1 Exposure to DEX PS DDS

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

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

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

- ***Adverse events***

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

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

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

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

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

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

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

Non-ocular adverse events

The most common non-ocular events reported were influenza 9 (2.1%) DEX 700 vs 2 (0.5%) Sham, headache 14 (3.3%) DEX 700 vs 7 (1.7%) Sham and hypertension 17 (4.0%) DEX 700 vs 15 (3.5%) Sham. Thus, so far, for systemic adverse reactions, no specific pattern indicating safety risks with the active treatment was revealed.

Ocular adverse events

Initial treatment

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

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

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

Open-label extension

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

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

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

Deaths

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

Serious adverse events in the phase III studies

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

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

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

- ***Laboratory findings***

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

- ***Safety in special populations***

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

Use in pregnancy and lactation

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

Overdose

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

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

No interaction studies have been performed, however due to the low systemic levels of dexamethasone, drug interactions are not expected. In the analyses of the initial treatment period for the pooled phase 3 studies, there was no evidence of drug-drug interactions. However, specific analyses to identify such interactions were not conducted. As expected, many of the patients in these studies were using multiple concomitant medications, such as proton pump inhibitors, systemic antihypertensives, anti-inflammatory and antirheumatic agents, lipid modifying agents, and analgesics.

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

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

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

- ***Post marketing experience***

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

2.5. Discussion on clinical safety

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

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

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

The safety profile of DEX PS DDS in patients with macular oedema due to CRVO and BRVO did not show any unexpected signal related with the administration technique or the drug. With a few notable exceptions, the occurrence of non-serious ocular adverse events following intravitreal DEX administration does not raise any major concern. One such exception is the appearance of IOP increases reported in nearly 25% of actively treated participants in the pivotal programme. It is emphasised that only a few of these patients were in need of acute medical and surgical intervention and warnings are appropriately included in section 4.4 of the SPC.

2.6. Conclusions on the clinical safety

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

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

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

2.7.2 Risk management plan

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

Table 5 - Summary of the risk management plan

Safety concern	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
Important Identified risks		
Increased intraocular pressure (IOP), Glaucoma and Ocular Hypertension	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011 • Conduct of an observational study to gain experience with repeat administration. This study will recruit patients requiring a 2nd or subsequent implant due to deteriorating visual acuity with the aim of collecting long term outcome and safety data in such patients. The study design will ensure that sufficient patients requiring more than 2 implants are recruited to provide additional useful information on this patient group.	Included in section 4.4 of the SPC : • As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. Of the patients experiencing an increase of IOP of ≥ 10 mm Hg from baseline, the greatest proportion showed this IOP increase at around 60 days following an injection. Patients of less than 45 years of age are more likely to experience increases in IOP. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post injection as needed. Included as “very common” adverse reaction in Section 4.8; Undesirable effects. Educational material to instruct prescribers on the recommended injection technique and important risks associated with OZURDEX. Educational material to instruct patients on important risks including increased intraocular pressure and ocular hypertension associated with OZURDEX.
Cataracts including traumatic cataracts related to injection techniques	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: Long-term safety data studies 206207-010 and 206207-011	Included in section 4.4 of the SPC: • Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections. In clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second injection (see section 4.8) with only 1 patient out of 368 requiring cataract surgery during the first treatment and 3

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

		Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex and not be used in active ocular herpes simplex.
Retinal tear/detachment	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Included as “uncommon” adverse reaction” in section 4.8 of the SPC
Significant vitreous leak or hypotony	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.2: Posology and method of administration of the SPC has clear instruction on the proper injection procedure. • Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous. Educational material to instruct prescribers on the recommended injection technique.
Systemic corticosteroid effects	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of	Bilateral administration could potentially lead to increased systemic absorption of the steroid. Section 4.4 addresses this as follows:

	safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.
Mechanical failure of device and implant misplacement	Routine pharmacovigilance Enhanced pharmacovigilance: added to the Sentinel Event List for intensive follow-up of safety reports Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.2: Posology and method of administration of the SPC has clear instruction on the proper injection procedure. • Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualization is possible in the large majority of cases. In cases in which the implant cannot be visualized, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view. Educational material to instruct prescribers on the recommended injection technique
Missing Information		
Paediatric Use	Routine pharmacovigilance	Section 4.2 Posology and method of administration: There is no relevant use of OZURDEX in the paediatric population in macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).
Pregnancy and lactation	Routine pharmacovigilance	Section 4.6 Pregnancy and lactation: Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Systemic levels of dexamethasone in humans have been shown to be low. OZURDEX is not recommended during pregnancy unless clearly

		necessary. Dexamethasone is excreted in breast milk. However, no effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.
Long-term safety, repeat dosing data	Routine pharmacovigilance Additional activities: • Long-term safety data studies 206207-010 and 206207-011 • Conduct of an observational study to gain experience with repeat administration. This study will recruit patients requiring a 2nd or subsequent implant due to deteriorating visual acuity with the aim of collecting long term outcome and safety data in such patients. The study design will ensure that sufficient patients requiring more than 2 implants are recruited to provide additional useful information on this patient group.	
Concurrent use of anticoagulants	Routine pharmacovigilance Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.4: Anti-coagulant therapy was used in 1.7% of patients receiving OZURDEX; there were no reports of hemorrhagic adverse events in these patients. Anti platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival

		haemorrhage (24%). OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.
Patients with significant retinal ischaemia	Routine pharmacovigilance Additional activities: • Long-term safety data studies 206207-010 and 206207-011	Section 4.4: OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia. Therefore OZURDEX is not recommended.

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

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

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

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

The physician information should contain the following key elements:

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

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

- Patient information leaflet
- How to prepare for OZURDEX treatment

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

- **User consultation**

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

2.7.3. Benefit-risk balance

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

- **Benefits**

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

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

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

Beneficial effects

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

Uncertainty in the knowledge about the beneficial effects.

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

- **Risks**

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

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

Unfavourable effects

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

Uncertainty in the knowledge about the unfavourable effects

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

- **Benefit-risk balance**

Importance of favourable and unfavourable effects

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

Benefit-risk balance

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

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

The provided data indicate that there is a maintained effect up to 6 month, but not thereafter, with regards to visual acuity and prevention of visual loss in treatment with Ozurdex in adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO). These efficacy results were replicated following a second implant. Furthermore, increase in IOP was easily managed and there was no evidence of accumulation. The implant is administered through a needle with minimal trauma to the eye and slowly releases dexamethasone into the vitreous with effects lasting up to 6 months, preventing the need for frequent intravitreal injections which can increase the risk for complications.

- **Risk management plan**

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

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

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

- Physician information
- Intravitreal injection procedure video

- Intravitreal injection procedure pictogram
- Patient information pack

The physician information should contain the following key elements:

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

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

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

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

2.7.4. Recommendation

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

9.2 Appendix 2: Search strategy for section 5.1

The following information should be provided.

9.2.1 Databases searched

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library

9.2.2 The date on which the search was conducted.

The searches were conducted between the 13th and 15th July 2010

9.2.3 The date span of the search.

No date restriction was applied to the searches

9.2.4 Search strategy

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (13/07/2010)		
1	(macular edema or macula oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4761
2	exp Macular Edema/	2870
3	exp Edema/	30215
4	exp Macula Lutea/	8428
5	(macula adj3 oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	38
6	(macula adj3 edema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
7	or/1-6	42083
8	exp Retinal Vein/	1612
9	exp Retinal Vein Occlusion/	2253
10	central retinal vein occlusion.mp.	1095
11	branch retinal vein occlusion.mp.	592
12	CRVO.mp.	486
13	BRVO.mp.	284
14	((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7364
15	or/8-14	7380
16	7 and 15	899
17	exp Dexamethasone/ or dexamethasone intravitreal implant.mp.	39473
18	ozurdex.mp.	2
19	exp Triamcinolone Acetonide/ or Triamcinolone acetate.mp.	4286
20	bevacizumab.mp.	3925
21	avastin.mp.	654
22	ranibizumab.mp.	553
23	lucentis.mp.	115
24	or/17-23	47668
25	16 and 24	267
26	Randomized controlled trials as Topic/	68165

27	Randomized controlled trial/	295049
28	Random allocation/	69084
29	Double blind method/	107498
30	Single blind method/	14183
31	Clinical trial/	463576
32	exp Clinical Trials as Topic/	230746
33	or/26-32	746998
34	(clinic$ adj trial$1).tw.	150646
35	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	106922
36	Placebos/	29078
37	Placebo$.tw.	127857
38	Randomly allocated.tw.	12516
39	(allocated adj2 random).tw.	658
40	or/34-39	319491
41	33 or 40	848222
42	Case report.tw.	158646
43	Letter/	698027
44	Historical article/	266063
45	or/42-44	1113386
46	41 not 45	824309
47	25 and 46	57

EMBASE 1980 to 2010 Week 27 (13/07/2010)		
1	(macular edema or macula oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	3203
2	exp retina macula edema/	4884
3	exp eye edema/ or exp retina macula cystoid edema/	1687
4	exp retina macula lutea/	2157
5	(macula$ adj3 oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	650
6	(macula adj3 edema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	4248
7	or/1-6	7368
8	exp retina vein/	2259
9	exp retina vein occlusion/	2427
10	exp central retina vein occlusion/	1198
11	exp branch retinal vein occlusion/	593
12	CRVO.mp.	421
13	BRVO.mp.	263
14	((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	5624
15	or/8-14	5632
16	exp dexamethasone/ or dexamethasone intravitreal implant.mp.	45562
17	ozurdex.mp.	8
18	Triamcinolone acetate.mp. or exp triamcinolone acetate/	202
19	exp bevacizumab/	11764
20	avastin.mp.	4179
21	ranibizumab.mp. or exp ranibizumab/	1314
22	lucentis.mp.	724
23	or/16-22	57465
24	7 and 15 and 23	204
25	Clinical trial/	511038
26	Randomized controlled trial/	161579

27	Randomization/	26505
28	Single blind procedure/	8659
29	Double blind procedure/	59391
30	Crossover procedure/	19196
31	Placebo/	105648
32	Randomi?ed controlled trial$.tw.	38265
33	Rct.tw.	3453
34	Random allocation.tw.	455
35	Randomly allocated.tw.	7754
36	Allocated randomly.tw.	831
37	(allocated adj2 random).tw.	169
38	Single blind$.tw.	5280
39	Double blind$.tw.	54600
40	((treble or triple) adj blind$).tw.	111
41	Placebo$.tw.	79634
42	Prospective study/	89032
43	or/25-42	637397
44	Case study/	5209
45	Case report.tw.	90799
46	Abstract report/ or letter/	350140
47	or/44-46	443754
48	43 not 47	615972
49	24 and 48	88

COCHRANE LIBRARY SEARCH (15/07/2010)		
1	MeSH descriptor Macular Edema explode all trees	269
2	MeSH descriptor Edema explode all trees	891
3	macula* near/3 oedema	133
4	macula* near/3 edema	691
5	CMO or CME	262
6	(#1 OR #2 OR #3 OR #4 OR #5)	1786
7	MeSH descriptor Retinal Vein Occlusion explode all trees	97
8	MeSH descriptor Retinal Vein explode all trees	39
9	retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)	332
10	central retinal vein occlusion	205
11	branch retinal vein occlusion	85
12	CRVO	55
13	BRVO	43
14	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	345
15	MeSH descriptor Dexamethasone explode all trees	1962
16	dexamethasone	3606
17	Triamcinolone acetate	68
18	Bevacizumab	344
19	Avastin	67
20	ranibizumab	130
21	lucentis	40
22	(#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR 21)	69346
23	(#6 AND #14 AND #22)	30

9.2.5 Additional searches

No additional searches were performed; the clinical trial programme and associated unpublished data (e.g. CSRs) were provided by the manufacturer (Allergan).

9.2.6 Inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- Randomised controlled trials evaluating the efficacy and safety of dexamethasone in eyes with vision loss due to macular oedema associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) compared with one or more of the following interventions: sham treatment/placebo, triamcinolone acetonide, bevacizumab, ranibizumab.
- Outcomes of interest included:
    - 15-letter gain from baseline in best corrected visual acuity (BCVA)
    - 15-letter loss from baseline in BCVA
    - mean change from baseline in retinal thickness (micrometres)

Exclusion criteria
The following studies were excluded from the review:

- Non-systematic reviews, letters, commentaries, case reports/series/surveys
- Studies conducted in paediatric and child (<17 years) populations
- Studies that are not investigating macular oedema associated with BRVO or CRVO
- Studies that do not include the treatments and/or comparators as detailed in the inclusion criteria
- Studies that do not report relevant outcome data on efficacy and safety of dexamethasone with any of the comparators
- Systematic reviews and/or meta analyses
- Duplicate record

Non-randomised evidence identified in this search (e.g. observational data, retrospective studies, single arm studies) were excluded from the RCT search, but were labelled at exclusion phase for subsequent interrogation.

9.2.7 Data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data was extracted from eligible publications into a pre-defined Microsoft Excel® spreadsheet by a reviewer.

9.3 Appendix 3: Quality assessment of RCT(s)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

A quality assessment of the included RCTs is provided in Table 18 of Section 5.4

9.4 Appendix 4: Search strategy for section 5.7

The “master” clinical search described in Section 5.1 and Section 9.2 was designed to identify any eligible studies for indirect comparisons.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7

There were no relevant studies identified to carry out an indirect and/or mixed treatment comparisons.

9.6 Appendix 6: Search strategy for section 5.8

The “master” clinical search described in Section 5.1 and Section 9.2 was designed to identify any eligible non-RCT studies using DEX.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8

There were no relevant non-RCT studies identified in dexamethasone.

9.8 Appendix 8: Search strategy for section 5.9

The “master” clinical search described in Section 5.1 and Section 9.2 was designed to identify any eligible studies for adverse events associated with DEX.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9

There were no relevant studies designed primarily to assess the safety of dexamethasone.

9.10 Appendix 10: Search strategy for cost-effectiveness studies

9.10.1 Databases searched

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library (NHS EED)
- EconLIT

9.10.2 The date on which the search was conducted.

The searches were conducted between 13th July and 3rd August 2010

9.10.3 The date span of the search.

No date restriction was applied to the searches.

9.10.4 Search strategy

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (13/07/2010)		
1	Quality-Adjusted Life Years/	4455
2	exp Models, Economic/	7264
3	exp Markov Chains/	6490
4	exp Monte Carlo Method/	14104
5	exp Decision Trees/	7301
6	(pharmacoeconomic? or (pharmaco adj economic?)).tw.	2408
7	"quality adjusted life year?".tw.	3555
8	qaly?.tw.	3031
9	cba.tw.	8011

10	cea.tw.	13723
11	cua.tw.	669
12	markov$.tw.	8895
13	(monte adj carlo).tw.	20038
14	(decision adj2 (tree? or analys$)).tw.	5959
15	exp Cost-Benefit Analysis/	48708
16	((cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	137411
17	(cost adj2 qaly$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	704
18	or/1-17	204144
19	(macular edema or macula oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4761
20	exp Macular Edema/	2870
21	exp Edema/	30215
22	exp Macula Lutea/	8428
23	(macula$ adj3 oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	895
24	(macula adj3 edema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
25	or/19-24	42456
26	18 and 25	141

EMBASE 1980 to 2010 Week 27 (13/07/2010)		
1	(macular edema or macula oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	4052
2	exp retina macula edema/	5843
3	exp eye edema/ or exp retina macula cystoid edema/	2196
4	exp retina macula lutea/	2914
5	(macula$ adj3 oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	805
6	(macula adj3 edema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	5218
7	or/1-6	9393
8	exp quality adjusted life year/	5185
9	"cost benefit analysis"/ or "cost effectivenss analysis"/ or "cost minimization analysis"/	35130
10	exp Monte Carlo method/	9356
11	"decision tree"/	532
12	(pharmacoeconomic? or (pharmaco adj economic?)).tw.	3373
13	"quality adjusted life year?".tw.	3284
14	qaly?.tw.	2826
15	cba.tw.	5842
16	cea.tw.	11673
17	cua.tw.	427
18	markov$.tw.	6269
19	(monte adj carlo).tw.	13745
20	(decision adj2 (tree? or analys$)).tw.	5150
21	((cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	154149
22	(cost adj2 qaly$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	661
23	health economics/ or economic evaluation/ or pharmacoecomics/	16321

24	or/8-23	205468
25	7 and 24	150

COCHRANE LIBRARY/NHS EED (15/07/2010)		
1	MeSH descriptor **Eye** explode all trees	4655
2	MeSH descriptor **Eye Diseases** explode all trees	9595
3	MeSH descriptor **Retina** explode all trees	892
4	MeSH descriptor **Retinal Diseases** explode all trees	2156
5	MeSH descriptor **Edema** explode all trees	891
6	MeSH descriptor **Macula Lutea** explode all trees	233
7	macula* near/3 oedema	133
8	macula* near/3 edema	691
9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	12433
10	MeSH descriptor **Quality-Adjusted Life Years** explode all trees	2661
11	MeSH descriptor **Models, Economic** explode all trees	2278
12	MeSH descriptor **Markov Chains** explode all trees	1198
13	MeSH descriptor **Monte Carlo Method** explode all trees	401
14	MeSH descriptor **Decision Trees** explode all trees	808
15	pharmacoeconomic*	2687
16	qaly	2257
17	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	8579
18	(#9 AND #17)	187
19	(#9 AND #17) (NHS EED)	152

Econlit (03/08/2010)		
1	macular edema.mp. [mp=heading words, abstract, title, country as subject]	0
2	macular oedema.mp. [mp=heading words, abstract, title, country as subject]	0
3	retinal disease.mp. [mp=heading words, abstract, title, country as subject]	0
4	retinal vein occlusion.mp. [mp=heading words, abstract, title, country as subject]	0
5	visual aquity.mp. [mp=heading words, abstract, title, country as subject]	0
6	vision loss.mp. [mp=heading words, abstract, title, country as subject]	3
7	1 or 2 or 3 or 4 or 5 or 6	3

9.10.5 Additional searches

No additional searches were performed.

9.10.6 The inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- Cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility studies involving patients with retinal vein occlusion.

Exclusion criteria
The following studies were excluded from the review:

- Did not investigate branch retinal vein occlusion
- Not a cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility study

9.10.7 The data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data was extracted from eligible publications into a pre-defined Microsoft Excel® spreadsheet by a reviewer.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies

	Brown et al (2002) Incremental cost-effectiveness of laser therapy for visual loss secondary to branch retinal vein occlusion	
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	The aim of the study was to compare the incremental cost-effectiveness of laser therapy versus no treatment for macular oedema occurring secondary to branch retinal vein occlusion
2. Was the economic importance of the research question stated?	Yes	To the author's knowledge, a cost effectiveness analysis has not been previously performed for the treatment of visual loss associated with branch retinal vein occlusion
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	The model perspective was that of the U.S.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	The alternative treatment was no treatment.
6. Was the form of economic evaluation stated?	Yes	This was a cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The cost-utility analysis was used to compare incremental cost effectiveness
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Effectiveness data for laser photocoagulation therapy was obtained by the Branch Vein Occlusion Study Group.
9. Were details of the design and results of the effectiveness study given (if based on a single	Yes	Branch Vein Occlusion Study Group enrolled 139 eligible eyes with branch retinal vein occlusion assigned randomly to either a treatment group or untreated control group. Eligible eyes had a visual acuity ranging from

study)?		20/40 to 20/200 and vision was decreased primarily due to macular oedema associated with the branch vein occlusion. The mean follow-up for this study was 3.1 years and mean age of patients was 66 years.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	The primary outcome was the cost per quality-adjusted life-year ($/QALY gained)
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	Control group: A visual acuity of 20/70 has been shown to correlate with a utility value of 0.74, a visual acuity of 20/45 has been shown to correlate with a utility value of 0.785 Branch retinal vein occlusion: utility value of 0.92 was assigned to all patients in the analysis, treated or untreated, who had better vision on the fellow eye than in the eye with branch retinal vein occlusion
14. Were productivity changes (if included) reported separately?	No	Not reported
15. Was the relevance of productivity changes to the study question discussed?	NA	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice	No	

of model used and the key parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Not clear	
23. Was the discount rate stated?	Yes	Costs were discounted at 3%
24. Was the choice of rate justified?	Yes	Reference was given to previous studies
25. Was an explanation given if cost or benefits were not discounted?	No	Only costs were discounted
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Two-way sensitivity analysis was performed, varying both the discount rate employed for costs, and the yearly recurrent risk of developing a retinal venous occlusion in the contralateral eye in patients who initially had good vision ion the contralateral eye.
28. Was the choice of variables for sensitivity analysis justified?	Not clear	
29. Were the ranges over which the parameters were varied stated?	Yes	The ranges around the discount rate and yearly recurrent risk were provided.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Photocoagulation therapy was compared with no treatment
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

9.12 Appendix 12: Search strategy for section 6.4

A search was conducted by Covance between the 12th and 13th of December 2009 using Medline, Embase and Cochrane Library databases. An update of these searches with these databases was conducted on 16th of July 2010. A search was not conducted on EconLIT by Covance, and a search on this database was conducted on 3rd August 2010.

Covance Search

9.12.1 Databases searched

The following databases were searched:

- Ovid MEDLINE(R) 1966 to Present
- EMBASE 1974 to Present
- The Cochrane Library

9.12.2 The date on which the search was conducted.

The searches were conducted between the 12th and 13th December 2009

9.12.3 The date span of the search.

No date restriction was applied to the searches

9.12.4 Search strategy

1. Embase.com (Medline and Embase databases)

No.	Query	Results
#1	'eye disease'/mj OR 'eye'/exp/mj OR eye:ti	208899
#2	'vision'/exp/mj OR vision:ti	73923
#3	'visual impairment'/exp/mj OR 'visual impairment':ti	22212
#4	'visual acuity'/exp/mj OR 'visual acuity':ti	8904
#5	'retina disease'/exp/mj OR 'retina'/exp/mj OR retina:ti	150063
#6	'macular edema'/exp/mj OR 'macular edema':ti	3120
#7	'retinal vein occlusion'/exp/mj OR 'retinal vein occlusion':ti	2936
#8	'macular degeneration'/exp/mj OR 'macular degeneration':ti	8335
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	374903
#10	'standard gamble':ab,ti OR sg:ab,ti	4710

No.	Query	Results
#11	'time tradeoff':ab,ti OR tto:ab,ti	576
#12	'sf 6d':ab,ti OR 'eq-5d':ab,ti OR euroqol:ab,ti	2153
#13	'quality of life'/exp AND ('rating scale'/exp OR 'scoring system'/exp OR 'questionnaire'/exp)	32296
#14	'quality of life'/exp/mj	29918
#15	qwb:ab,ti OR 'quality of well being':ab,ti	266
#16	'quality adjusted life year'/exp OR 'qaly':ab,ti OR 'quality adjusted life years':ab,ti	7054
#17	utilit*:de,ab,ti OR preference:de,ab,ti AND (value*:de,ab,ti OR weight*:de,ab,ti OR scor*:de,ab,ti OR index*:de,ab,ti)	39587
#18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	97614
#19	#9 AND #18	1044
#20	#19 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim	561

2. Cochrane Library 2009, issue 4

#1	MeSH descriptor **Eye** explode all trees	4450
#2	MeSH descriptor **Eye Diseases**, this term only	304
#3	MeSH descriptor **Vision, Ocular** explode all trees	290
#4	MeSH descriptor **Vision Disorders** explode all trees	879
#5	MeSH descriptor **Retina** explode all trees	844
#6	MeSH descriptor **Retinal Diseases** explode all trees	2017
#7	(eye or vision or retina):ti	2675
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)	8771
#9	(standard gamble or sg):ti,ab,kw	267
#10	(time tradeoff OR tto):ti,ab,kw	75
#11	(sf 6d OR eq-5d OR euroqol):ti,ab,kw	490

#12	(qwb OR quality of well being):ti,ab,kw	5315
#13	(qaly OR quality adjusted life year*):ti,ab,kw	2871
#14	(utilit* OR preference AND (value* OR weight* OR scor*)):ti,ab,kw	5009
#15	(quality of life AND (rating OR scoring OR questionnaire)):ti,ab,kw	9597
#16	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	19605
#17	(#8 AND #16)	265
#18	(aged or adult):kw	320853
#19	(#17 AND #18)	168

9.12.5 Additional searches

No additional searches were performed.

9.12.6 Inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- Studies associated with vision loss
- Studies containing preference-based utility measures or QoL for vision loss
- Studies in which health states represent health states in the economic evaluation
- Studies reporting the primary utility data
- Studies in which results were reported by visual acuity

Exclusion criteria
The following studies were excluded from the review:

- Studies not associated with vision loss
- Studies which did not contain preference-based utility measures or QoL for vision loss (includes case study/series and general review/commentary)
- Studies in which health states did not represent health states in the economic evaluation (e.g. children and studies where vision loss is secondary to systemic disease)
- QoL studies which did not report the primary utility data or which were an economic evaluation
- Studies in which results were not reported by visual acuity (e.g. self-reported acuity)

- Duplicate studies

9.12.7 Data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria.

Updated search

9.12.1 Databases searched

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library (NHS EED)
- EconLIT

9.12.3 The date span of the search.

No date restriction was applied to the searches.

9.12.4 Search strategy

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (16/07/2010)		
1	eye disease/ or eye/ or eye:ti.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	52952
2	vision/ or vision.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	95441
3	visual impairment/ or visual impairment.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4388
4	visula acuity/ or visual acuity.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	54889
5	retina disease/ or retina/ or retina.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	76493
6	macular edema/ or macula edema.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2939
7	retinal vein occlusion/ or retinal vein occlusion.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2845
8	macular degeneration/ or macular degeneration.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	11299
9	or/1-8	246099
10	(standard gamble or sg).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4550
11	(time tradeoff or tto).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	540
12	(sf 6d or eq-5d or euroqol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2070
13	quality of life/ and (rating scale/ or scoring system/ or questionnaire/)	20899
14	quality of life/	84524
15	(qwb or quality of well being).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	285
16	quality adjusted life year/ or qaly.mp. or quality adjusted life years.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	6125

17	(value* or weight* or scor* or index*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2462049
18	(value* or weight* or scor* or index*).m_titl.	222509
19	9 and 18	1642
20	limit 19 to (humans and ("adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") and last year)	56

EMBASE 1980 to 2010 Week 27 (16/07/2010)		
1	'eye disease'/ or 'eye'/ or eye:ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	52507
2	'vision'/ or vision:ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	52626
3	"visual impairment'/ or 'visual impairment':ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	25234
4	'visual acuity'/ or 'visual acuity':ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	54362
5	'retina disease'/ or 'retina'/ or retina:ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	46936
6	'macular edema'/ or 'macular edema':ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	3595
7	'retinal vein occlusion'/ or 'retinal vein occlusion':ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	2450
8	'macular degeneration'/ or 'macular degeneration':ti.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	5797
9	or/1-8	213032
10	('standard gamble' or sg).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	5182
11	('time tradeoff' or tto).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	621
12	('sf 6d' or 'eq-5d' or euroqol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	2567
13	'quality of life'/ and ('rating scale'/ or 'scoring system'/ or 'questionnaire'/)	35069
14	'quality of life'/	148587
15	(qwb or 'quality of well being').mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	309
16	'quality adjusted life year'/ or qaly.mp. or 'quality adjusted life years'.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	7920
17	((utilit* or preference) and (value* or weight* or scor* or index*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	42599
18	or/10-17	198623
19	9 and 18	2615
20	limit 19 to (human and yr="2009 -Current" and (adult <18 to 64 years> or aged <65+ years>))	144

COCHRANE LIBRARY/NHS EED 16/07/2010		
1	MeSH descriptor **Eye** explode all trees	4655

2	MeSH descriptor **Eye Diseases** explode all trees	9595
3	MeSH descriptor **Vision, Ocular** explode all trees	305
4	MeSH descriptor **Vision Disorders** explode all trees	925
5	MeSH descriptor **Retina** explode all trees	892
6	MeSH descriptor **Retinal Diseases** explode all trees	2156
7	(eye or vision or retina):ti	2880
8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)	13198
9	(standard gamble):ti,ab,kw	98
10	(time tradeoff OR tto):ti,ab,kw	80
11	(sf 6d OR eq-5d OR euroqol):ti,ab,kw	574
12	(qwb OR quality of well being):ti,ab,kw	5715
13	(qaly OR quality adjusted life year*):ti,ab,kw	3167
14	(utilit* OR preference AND (value* OR weight* OR scor*)):ti,ab,kw	5363
15	(quality of life AND (rating OR scoring OR questionnaire)):ti,ab,kw	10503
16	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	21090
17	(#8 AND #16)	424
18	(aged or adult):kw	331912
19	(#17 AND #18)	280
20	(#19), from 2009 to 2010	32

Econlit (03/08/2010)		
1	macular edema.mp. [mp=heading words, abstract, title, country as subject]	0
2	macular oedema.mp. [mp=heading words, abstract, title, country as subject]	0
3	retinal disease.mp. [mp=heading words, abstract, title, country as subject]	0
4	retinal vein occlusion.mp. [mp=heading words, abstract, title, country as subject]	0
5	visual aquity.mp. [mp=heading words, abstract, title, country as subject]	0
6	vision loss.mp. [mp=heading words, abstract, title, country as subject]	3
7	1 or 2 or 3 or 4 or 5 or 6	3

9.12.5 Additional searches

No additional searches were performed.

9.12.6 The inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- A preference based measure of quality of life, either generic or valued in a separate study with appropriate methods (i.e. Standard gamble or time trade off) or
- One of the following non-preference quality of life measures: SF-12 or SF-36

Exclusion criteria
The following studies were excluded from the review:

- Did not investigate vision loss
- No quality of life data

9.12.7 The data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data were extracted from eligible publications by a reviewer.

9.13 Appendix 13: Resource identification, measurement and valuation

The following information should be provided.

9.13.1 Databases searched

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library

9.13.2 The date on which the search was conducted.

The searches were conducted between 3rd August and 6th August 2010

9.13.3 The date span of the search.

No date restriction was applied to the searches.

9.13.4 Search strategy

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (6/08/2010)		
1	(Cost* or (cost* and (healthcare or health care)) or (fiscal or funding or financial or finance) or (cost* and estimate*) or (cost* and variable) or (cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*) or (unit* and cost*) or (economic* or pharmacoeconomic* or price* or pricing) or (high and cost*) or (low and cost*) or (resource and use*) or (length and stay) or hospitali* or (bed and day*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	702009
2	(macular edema or macula oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4801
3	exp Macular Edema/	2902
4	exp Edema/	30281
5	exp Macula Lutea/	8460
6	(macula$ adj3 oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	906
7	(macula adj3 edema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
8	2 or 3 or 4 or 5 or 6 or 7	42589
9	exp Retinal Vein/	1621
10	exp Retinal Vein Occlusion/	2265
11	central retinal vein occlusion.mp.	1100
12	branch retinal vein occlusion.mp.	602
13	CRVO.mp.	488
14	BRVO.mp.	288
15	((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7395
16	9 or 10 or 11 or 12 or 13 or 14 or 15	7411
17	1 and 8 and 16	16

EMBASE 1980 to 2010 Week 30 (6/08/2010)		
1	(Cost* or (cost* and (healthcare or health care)) or (fiscal or funding or	1047977

	financial or finance) or (cost* and estimate*) or (cost* and variable) or (cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*) or (unit* and cost*) or (economic* or pharmacoeconomic* or price* or pricing) or (high and cost*) or (low and cost*) or (resource and use*) or (length and stay) or hospitali* or (bed and day*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	
2	(macular edema or macula oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	4876
3	exp retina macula edema/	6558
4	exp eye edema/ or exp retina macula cystoid edema/	2682
5	exp retina macula lutea/	5696
6	(macula$ adj3 oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	962
7	(macula adj3 edema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	5928
8	2 or 3 or 4 or 5 or 6 or 7	13159
9	exp retina vein/	1161
10	exp retina vein occlusion/	3733
11	exp central retina vein occlusion/	1330
12	exp branch retinal vein occlusion/	150
13	CRVO.mp.	588
14	BRVO.mp.	355
15	((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	10513
16	9 or 10 or 11 or 12 or 13 or 14 or 15	10530
17	1 and 8 and 16	62

COCHRANE LIBRARY/NHS EED 6/08/2010		
1	MeSH descriptor **Macular Edema** explode all trees	269
2	MeSH descriptor **Edema** explode all trees	891
3	macula* near/3 oedema	133
4	macula* near/3 edema	691
5	CMO or CME	262
6	(#1 OR #2 OR #3 OR #4 OR #5)	1786
7	MeSH descriptor **Retinal Vein Occlusion** explode all trees	97
8	MeSH descriptor **Retinal Vein** explode all trees	39
9	retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)	332
10	central retinal vein occlusion	205
11	branch retinal vein occlusion	85
12	CRVO	55
13	BRVO	43
14	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	345
15	(#6 AND #14)	94

Econlit (03/08/2010)		
1	macular edema.mp. [mp=heading words, abstract, title, country as subject]	0
2	macular oedema.mp. [mp=heading words, abstract, title, country as subject]	0
3	retinal disease.mp. [mp=heading words, abstract, title, country as subject]	0
4	retinal vein occlusion.mp. [mp=heading words, abstract, title, country as subject]	0
5	visual aquity.mp. [mp=heading words, abstract, title, country as subject]	0
6	vision loss.mp. [mp=heading words, abstract, title, country as subject]	3
7	1 or 2 or 3 or 4 or 5 or 6	3

9.13.5 Additional searches

No additional searches were performed.

9.13.6 The inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- UK resource use for people with vision loss

Exclusion criteria
The following studies were excluded from the review:

- Did not investigate vision loss
- Not UK related.

9.13.7 The data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data was extracted from eligible publications by a reviewer.

9.14 Appendix 14: Non-RCT search of comparators

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library

9.14.2 The date on which the search was conducted.

The searches were conducted between 3rd August and 6th August 2010

9.14.3 The date span of the search.

No date restriction was applied to the searches.

9.14.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (3/08/2010)		
1	(macular edema or macula oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	4782
2	exp retina macula edema/	0
3	exp eye edema/ or exp retina macula cystoid edema/	0
4	exp retina macula lutea/	0
5	(macula$ adj3 oedema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	902
6	(macula adj3 edema).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
7	or/1-6	5298
8	retinal vein.mp. or exp retina vein/	4326
9	retinal vein occlusion.mp. or exp retina vein occlusion/	2833

10	central retinal vein occlusion.mp. or exp central retina vein occlusion/	1097
11	branch retinal vein occlusion.mp. or exp branch retinal vein occlusion/	596
12	CRVO.mp.	487
13	BRVO.mp.	286
14	((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	7379
15	or/8-14	7395
16	exp dexamethasone/ or dexamethasone intravitreal implant.mp.	39515
17	ozurdex.mp.	2
18	Triamcinolone acetate.mp. or exp triamcinolone acetate/	44
19	exp bevacizumab/	0
20	avastin.mp.	664
21	ranibizumab.mp. or exp ranibizumab/	564
22	lucentis.mp.	115
23	or/16-22	40735
24	7 and 15 and 23	56
25	Case study/	1473142
26	Case report.tw.	159199
27	Abstract report/ or letter/	699896
28	or/25-27	2050599
29	24 not 28	44
30	exp case control studies/	473996
31	exp cohort studies/	773846
32	Case control.tw.	53823
33	(cohort adj (study or studies)).tw.	50002
34	Cohort analy$.tw.	2366
35	(Follow up adj (study or studies)).tw.	31248
36	(observational adj (study or studies)).tw.	25174
37	Longitudinal.tw.	99775
38	Retrospective.tw.	188151
39	Cross sectional.tw.	105627
40	Cross-sectional studies/	113722
41	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	1400799
42	29 and 41	28

EMBASE 1980 to 2010 Week 30 (3/08/2010)		
1	(macular edema or macula oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	4876
2	exp retina macula edema/	6558
3	exp eye edema/ or exp retina macula cystoid edema/	2682
4	exp retina macula lutea/	5696
5	(macula$ adj3 oedema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	962
6	(macula adj3 edema).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	5928
7	or/1-6	13159
8	retinal vein.mp. or exp retina vein/	4222
9	retinal vein occlusion.mp. or exp retina vein occlusion/	4075
10	central retinal vein occlusion.mp. or exp central retina vein occlusion/	1825
11	branch retinal vein occlusion.mp. or exp branch retinal vein occlusion/	850
12	CRVO.mp.	588
13	BRVO.mp.	355
14	((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	10513

15	or/8-14	10530
16	exp dexamethasone/ or dexamethasone intravitreal implant.mp.	81526
17	ozurdex.mp.	10
18	Triamcinolone acetate.mp. or exp triamcinolone acetate/	265
19	exp bevacizumab/	13034
20	avastin.mp.	4433
21	ranibizumab.mp. or exp ranibizumab/	1451
22	lucentis.mp.	755
23	or/16-22	94845
24	7 and 15 and 23	229
25	Case study/	9738
26	Case report.tw.	188909
27	Abstract report/ or letter/	747109
28	or/25-27	942300
29	24 not 28	198
30	exp case control studies/	50109
31	exp cohort studies/	85385
32	Case control.tw.	57261
33	(cohort adj (study or studies)).tw.	54119
34	Cohort analy$.tw.	2445
35	(Follow up adj (study or studies)).tw.	33379
36	(observational adj (study or studies)).tw.	29045
37	Longitudinal.tw.	105069
38	Retrospective.tw.	214362
39	Cross sectional.tw.	113403
40	Cross-sectional studies/	42628
41	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	636001
42	29 and 41	36

COCHRANE LIBRARY SEARCH (3/08/2010)		
1	MeSH descriptor Macular Edema explode all trees	269
2	MeSH descriptor Edema explode all trees	891
3	macula* near/3 oedema	133
4	macula* near/3 edema	691
5	CMO or CME	262
6	(#1 OR #2 OR #3 OR #4 OR #5)	1786
7	MeSH descriptor Retinal Vein Occlusion explode all trees	97
8	MeSH descriptor Retinal Vein explode all trees	39
9	retina* near/3 (vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)	332
10	central retinal vein occlusion	205
11	branch retinal vein occlusion	85
12	CRVO	55
13	BRVO	43
14	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	345
15	MeSH descriptor Dexamethasone explode all trees	1962
16	DEXAMETHASONE	3606
17	triamcinolone acetate	68
18	bevacizumab	344
19	avastin	67
20	ranibizumab	130
21	lucentis	40
22	(#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)	4117
23	(#6 AND #14 AND #22)	19

9.14.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were carried out.

9.14.6 The inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- Non – randomised controlled trials, retrospective or observational studies evaluating the efficacy and safety of triamcinolone acetonide and/or bevacizumab in eyes with vision loss due to macular oedema associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- Outcomes of interest included:
    - 15-letter gain from baseline in best corrected visual acuity (BCVA)
    - 15-letter loss from baseline in BCVA
    - mean change from baseline in retinal thickness (micrometres)

Exclusion criteria
The following studies were excluded from the review:

- Non-systematic reviews, letters, commentaries, case reports/series/surveys
- Studies conducted in paediatric and child (<17 years) populations
- Studies that are not investigating macular oedema associated with BRVO or CRVO
- Studies that do not include the treatments and/or comparators as detailed in the inclusion criteria
- Studies that do not report relevant outcome data on efficacy and safety Systematic reviews and/or meta analyses
- Duplicate record

9.14.7 The data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data was extracted from eligible publications into a pre-defined Microsoft Excel® spreadsheet by a reviewer.

9.15 Appendix 15: Mortality of vision loss data search

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library

9.15.2 The date on which the search was conducted.

A search was conducted between the 12th and 13th of December 2009 using Medline, Embase and Cochrane Library databases. An update of these searches with these databases was conducted on 16th of July 2010.

9.15.3 The date span of the search.

No date restriction was applied to the searches.

9.15.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (14/07/2010)		
1	visual impairment.mp. or exp visual impairment/	4347
2	visual acuity.mp. or exp visual acuity/	59235
3	vision loss.mp.	2260
4	exp Retinal Diseases/	82335
5	or/1-4	129624
6	mortality.mp. or exp Mortality/	490320
7	('mortality risk' or 'survival rate').mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	136270
8	6 or 7	518286
9	5 and 8	1694
10	limit 9 to (humans and yr="2010 -Current" and ("young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))	21

EMBASE 1980 to 2010 Week 27 (14/07/2010)		
1	visual impairment.mp. or exp visual impairment/	40570
2	visual acuity.mp. or exp visual acuity/	48516
3	vision loss.mp.	2035
4	exp retina disease/	97926
5	or/1-4	155553
6	exp mortality/ or mortality.mp.	391525
7	('mortality risk' or 'survival rate').mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	95039
8	6 or 7	457408
9	5 and 8	4280
10	limit 9 to (human and yr="2010 -Current" and (adult <18 to 64 years> or aged <65+ years>))	58

COCHRANE LIBRARY SEARCH (15/07/2010)		
1	MeSH descriptor **Vision Disorders** explode all trees	925
2	vision impairment	465
3	vision loss	958
4	MeSH descriptor **Visual Acuity** explode all trees	2752
5	MeSH descriptor **Retinal Diseases** explode all trees	2156
6	(#1 OR #2 OR #3 OR #4 OR #5)	5357
7	MeSH descriptor **Mortality** explode all trees	8790
8	mortality	35169
9	survival rate or mortality risk	31144
10	(#7 OR #8 OR #9)	44821
11	(#6 AND #10)	318
12	aged or adult	374843
13	(#11 AND #12)	290
14	(#13), in 2010	48

9.15.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were carried out.

9.15.6 The inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- The risk of mortality due to vision loss.

Exclusion criteria
The following studies were excluded from the review:

- Did not investigate vision loss or mortality

9.15.7 The data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data was extracted from eligible publications by a reviewer.

9.16 Appendix 16: Cost of vision loss search

The following information should be provided.

9.16.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *NHS EED*
- *EconLIT*

The following databases were searched:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2010 Week 27
- The Cochrane Library

9.16.2 The date on which the search was conducted.

The searches were conducted on 10th August 2010.

9.16.3 The date span of the search.

No date restriction was applied to the searches.

9.16.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) 1950 TO PRESENT (10/08/2010)	
((Cost* or ((healthcare or health care) and cost)) and (blindness or "low vision" or "visual impairment" or "vision loss") and (UK or England or Wales or Scotland)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	27

EMBASE 1980 to 2010 Week 31 (10/08/2010)

((Cost* or ((healthcare or health care) and cost)) and (blindness or "low vision" or "visual impairment" or "vision loss") and (UK or England or Wales or Scotland)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]	60

COCHRANE LIBRARY/NHS EED (10/08/2010)	
((Cost* or ((healthcare or health care) and cost)) and (blindness or "low vision" or "visual impairment" or "vision loss") and (UK or England or Wales or Scotland))	34

Econlit (10/08/2010)	
((Cost* or ((healthcare or health care) and cost)) and (blindness or "low vision" or "visual impairment" or "vision loss") and (UK or England or Wales or Scotland)).mp. [mp=heading words, abstract, title, country as subject]	2

9.16.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were carried out.

9.16.6 The inclusion and exclusion criteria.

Inclusion criteria
The following studies were included in the review:

- UK cost of blindness

Exclusion criteria
The following studies were excluded from the review:

- Did not investigate cost of blindness.
- Not UK related.

9.16.7 The data abstraction strategy.

Identified studies were assessed in order to ascertain they met the pre-defined inclusion/exclusion criteria. Data was extracted from eligible publications by a reviewer.

9.17 Appendix 17: Results of literature review for excess mortality risk associated with blindness

Summary of results –(search conducted between the 12th and 13th of December 2009)

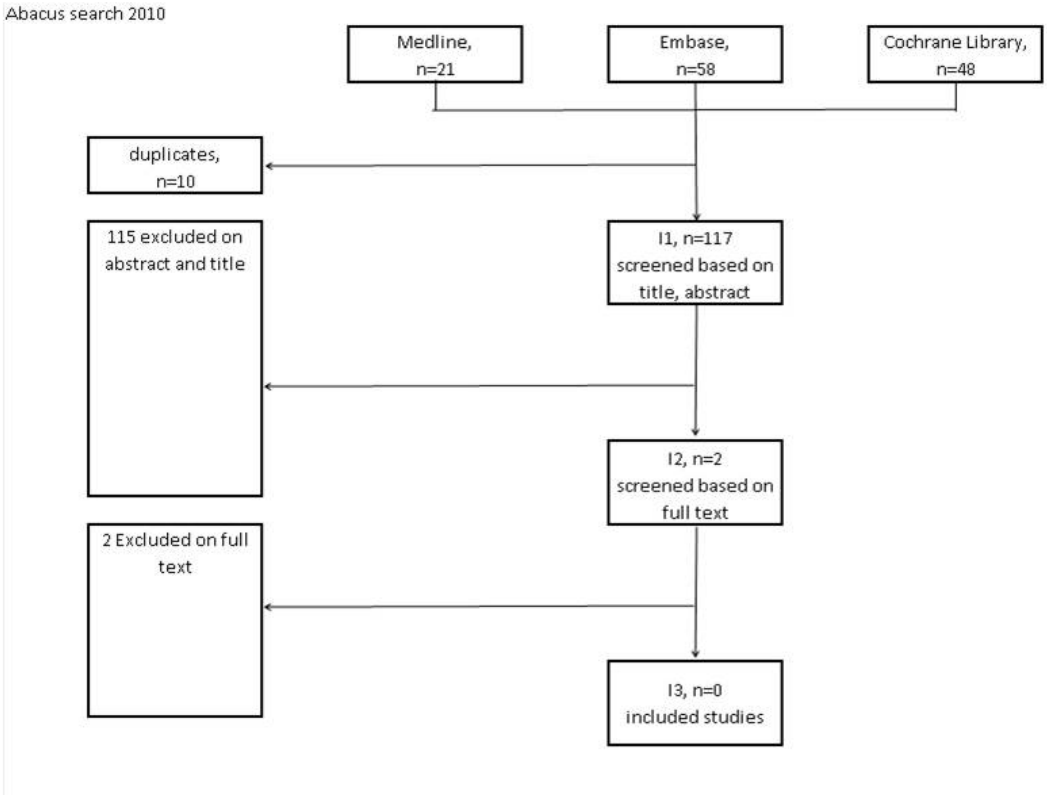
Study Name, Location (citation)	**visual acuity category**	**Measure (95% Confidence Interval)**	**Multivariate controls**
Campania Geriatric Observational Study, Italy (Cacciatore 2004)	Blindness (self-reported)	Not reported (but reported to be non-significant)	Age, sex, comorbidity, diabetes, hypertension.
Quebec study, Canada (Tournier 2008)	Blindness/Severe Vision Impairment (per ICD-9 coding)	HR: 1.52 (1.37, 1.68)	Age and gender
		HR: 1.34 (1.21, 1.48)	Gender, year of entry in the cohort, chronic disease score, depression, fracture and diabetes.
Melbourne Visual Impairment Project (VIP), Australia (McCarty 2001)	BCVA <20/200	OR: 1.41 (0.13, 15.34)	Age, sex, country of birth, smoking, hypertension, arthritis.
Analysis of Medicare claims, USA (Zhou 2006)	Wet AMD patients with blindness (per ICD-9 codes)	RR: 1.5 (NR, but stated to be significant)	Age, gender and race.
National Health Interview Survey (NHIS), United States. (Lee 2002) (Christ 2008)	Blind in both eyes (self reported) (NHIS 1986-1994 with mortality linkage to 1997)	Males: HR: 1.82 (1.31, 2.54) Females: HR: 2.89 (2.22, 3.77)	Sample design, age and reported eye diseases (includes cataract, glaucoma, retinopathy, and 2 or more of these eye diseases)
		Males: HR: 1.33 (0.96, 1.84) Females: HR: 2.21 (1.61, 3.02)	Sample design, age, reported eye diseases (includes cataract, glaucoma, retinopathy, and 2 or more of these eye diseases) as well as race, marital status, educational level, and reported health status
	Blind in both eyes (self reported) (NHIS 1986-1996 with mortality linkage to 2002)	HR: 1.28 (1.07, 1.53)	Age, sex, racial identity, marital status, education level, and number of nonocular health conditions
		HR: 1.54 (1.28, 1.86)	Structural Equation Modelling: Total HR including direct and indirect (covariates include disability and self-rated health)

Study Name, Location (citation)	visual acuity category	Measure (95% Confidence Interval)	Multivariate controls
French national longitudinal study, France (Berdeaux 2007)	Blind in both eyes (self reported)	OR: 2.262 (0.851, 6.024), p=ns	Activities of daily living (ADL), age, sex, and geographical region

AMD: age-related macular degeneration; BCVA: Best corrected visual acuity; HR: Hazard ratio; ICD-9: International Classification of Diseases, Ninth Revision; OR: Odds ratio; RR: Relative risk.

The update conducted on July 16th 2010, did not identify additional studies (see consort flow diagram, Figure 41)

Figure 41: Results of updated search July 16th 2010



9.18 Appendix 18: Suitability of HRQL studies identified

Table 151: HRQL search 1 (November 2009)

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>1.</td><td>Aballea 2007</td><td>Preference valuation method: TTO

Scale anchors:
TTO Version 1: death vs perfect health
TTO Version 2: death vs present health (converted to perfect health by equation)

Sample size:
Version 1: n= 24
Version 2: n= 14

Study population: community members (wearing simulation spectacles reflecting mild visual impairment (VI), moderate VI and post-</td><td>Eye conditions (% of subjects):
• Severe VI: 13%

Demographics:
• Age (yrs), mean (SD): NR
• Gender, female %: NR</td><td>TTO (binocular vision)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)

TTO Version 1

TTO Version 2</th></tr><tr><td>NR</td><td>Mild VI

v1 (24)

v2 (14)</td><td>

0.57

0.76</td></tr><tr><td>NR</td><td>Severe VI

v1 (24)

v2 (14)</td><td>

0.32

0.50</td></tr></table>
Note: Utility values were also reported by age group (18–39, 40–59, 60+ years).</td><td>Not reported.</td><td>Utility values elicited directly from patients</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>operative vision)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>2.</td><td>Aspinall 2007</td><td>Preference valuation method: TTO (conjoint analysis also performed)

Scale anchors:

TTO: existing condition vs perfect vision

Sample size: 122

Study population: Hospital patients (with AMD)</td><td>Eye conditions (% of patients):

• AMD: 100%

Demographics:

• Age (yrs), mean (SD): 77 (6.7)
• Gender, female %: 58</td><td>TTO (binocular vision)

<table><tr><th>Model State #</th><th>Study VA Category (logMAR) (n)</th><th>Utility (CI: 95%)</th></tr><tr><td>0</td><td>≤0.1</td><td>0.93 (0.86 to 0.99)</td></tr><tr><td>0-1[a]</td><td>0.12–0.40</td><td>0.86 (0.78 to 0.93)</td></tr><tr><td>1-3[a]</td><td>0.42–0.70</td><td>0.74 (0.64 to 0.83)</td></tr><tr><td>3-5[a]</td><td>0.72–1.30</td><td>0.68 (0.57 to 0.79</td></tr><tr><td>5</td><td>>1.30</td><td>0.76 (0.3 t 1.15)</td></tr><tr><td>NA</td><td>all pts (115)</td><td>0.805 (0.56-1.05)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td>Not reported.</td><td>Utility values elicited directly from patients. Scale anchors are existing condition vs. perfect vision (as opposed to death vs. perfect health)</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>3.</td><td>Bansback 2007</td><td>Preference valuation method: TTO, Visual Function Index VF-14, HUI3, HUI3-V, EQ-5D and SF-6D

Scale anchors:

TTO: death vs perfect health

Sample size: n= 209

Study population: hospital patients</td><td>Eye conditions (% of patients):

• AMD: 100% unilateral or bilateral (21.1% diffuse or dry)

Demographics:

• Age (yrs), mean (SD): 79.6 (7.5)
• Age (yrs), (range): 43-96
• Gender, female %: 57.9

Baseline Characteristic

Visual

• BSE VA (distant, LogMAR), Mean (SD; range): 1.01 (0.67, -0.08–2.86)
• WSE VA (distant, LogMAR), Mean (SD; range): 1.68 (0.75; 0.10–2.86)
• Binocular near VA (LogMAR), Mean (SD; range): 0.46 (0.88; 1.90–1.36)</td><td>TTO

<table><tr><th>Model State #</th><th>Study VA Category (Distant) LogMAR* (n)</th><th>Utility (SD)(range)</th></tr><tr><td>NR</td><td>All pts (204)</td><td>0.63 (0.31) (0 to 1)</td></tr></table>
HUI3

<table><tr><th>Model State #</th><th>Study VA Category (Distant) LogMAR* (n)</th><th>Utility (SD)(range)</th></tr><tr><td>NR</td><td>All pts (206)</td><td>0.34 (0.28)(-0.24 to 1.00)</td></tr></table>*Best corrected

Results of VA not reported.</td><td>Not reported.</td><td>Yes: HQRL reported directly from patients which is based on a choice method (TTO, EQ-5D, SF-6D and HU13)</td></tr>
<tr><td>4.</td><td>Bass 2004</td><td>Preference valuation method: vision preference</td><td>Eye conditions (% of subjects):

• Subfoveal CNV:</td><td>Preference values (Vision in BSE)</td><td>Preference values (Vision in WSE)

<table><tr><th>Model</th><th>Study VA</th><th>Utility</th></tr></table></td><td>Vision preference scale is not choice-</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>value scale

Scale anchors:

death vs perfect health (conversion equation used)

Sample size: n= 792

Study population: patients (with subfoveal CNV due to AMD, ocular histoplasmosis syndrome or unknown cause)</td><td>100%

Demographics:

• Age (yrs), median (range): 75 (nr)
• Gender, female %: 53</td><td>
<table>
<tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>≥20/40 (482)</td><td>0.69</td></tr>
<tr><td>1-4</td><td>20/50–20/160 (226)</td><td>0.58</td></tr>
<tr><td>5</td><td>≤20/200 (84)</td><td>0. 3</td></tr>
</table>
Preference values (Vision in both eyes)
<table>
<tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>≥20/40 and 20/50–160 (233)</td><td>0.71</td></tr>
<tr><td>0</td><td>≥20/40 and ≤20/200 (249)</td><td>0.67</td></tr>
</table>
</td><td>
<table>
<tr><th>State #</th><th>Category (n)</th><th>(SD)</th></tr>
<tr><td>1-4</td><td>20/50–20/160 (284)</td><td>0.68</td></tr>
<tr><td>5</td><td>≤20/200 (508)</td><td>0.62</td></tr>
</table>
Note: p<0.001 for comparison of Model State 1-4 with Model State 5.
</td><td>based</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>1</td><td>20/50–20/160 Both eyes

(51)</td><td>0.56</td></tr>
<tr><td>1-4</td><td>20/50–20/160 and ≤20/200

(175)</td><td>0.59</td></tr>
<tr><td>5</td><td>≤20/200 Both eyes

(84)</td><td>0.53</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>5.</td><td>Bass 2008</td><td>Preference valuation method: vision preference value scale (VPVS)

Scale anchors: blindness vs perfect vision (converted to death vs perfect health by equation)

Sample size: n= 170</td><td>Eye conditions (% of subjects):

• Subfoveal CNV: 100%

Demographics:

Observation group: (n=81)

• Age (yrs), median: 49
• Gender, female %: 57%</td><td>Not reported.</td><td>Preference values (Vision in study eye)[a]:
<table>
<tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr>
<tr><td>0-3[b]</td><td>VA 20/100 or better

(98)[c]</td><td>Baseline

Observation: 0.70

Surgery: 0.69</td></tr>
</table>
</td><td>VPVS, SF-36, HADS, NEI-VFQ. Vision preference value scale is not choice-based</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Study population: patients (with subfoveal CNV due to ocular histoplasmosis syndrome or unknown cause).

Note: RCT comprised two treatment groups: observation group and surgery group. Trial protocol required BCVA of 20/50 to 20/800 inclusive in at least 1 eye (the study eye) and LP or better in the other eye.</td><td>Surgery group: (n=89)

• Age (yrs), median (range): 48 (nr)
• Gender, female %: 62%</td><td></td><td><table><tr><td>3-5[b]</td><td>VA worse than 20/100

(72)[c]</td><td>Baseline

Observation: 0.68

Surgery: 0.65</td></tr></table>
[a] Only study eye VA reported, other eye VA was LP or better (per inclusion criteria).

[b] VA scores do not fit into one defined model state, but cross model states as identified.

[c] Baseline study VA 20/50 to 20/100.

[d] Baseline study VA 20/125 to 20/800.

Note: Follow-up VPVS scores also reported at 6, 12, 24 and 36 months.</td><td></td></tr>
<tr><td>6.</td><td>Brown 1998</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs disease-free state</td><td>Eye conditions (% of patients):

Study Group:

• AMD: 37%
• Diabetic retinopathy: 26%
• Retinal detachment: 11%
• RVO: 10%</td><td>TTO: Study Group (asked to score their utility based on assuming vision in both eyes was as poor as their WSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (CI: 95%)</th></tr><tr><td>0-1[a]</td><td>20/40-20/50 (12)</td><td>0.71 (0.61-0.81)</td></tr><tr><td>1-3[a]</td><td>20/60-20/100 (29)</td><td>0.68 (0.60-0.76)</td></tr><tr><td>5</td><td>20/200-20/400</td><td>0.58 (0.50-0.66)</td></tr></table></td><td>Not reported.</td><td>TTO used to obtain utility values directly from patients. Scale anchors are existing condition vs. disease-free state</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Sample size: n=306 (133 who were asked to assume that the VA in both of their eyes was as poor as the VA in their WSE measured against 173 patients with known utility values who had similar bilateral visual loss)

Study population: patients</td><td>• Cataract: 2%
• Others: 14%

Control Group:

• AMD: 40%
• Diabetic retinopathy: 38%
• Retinal detachment: 5%
• RVO: 6%
• Cataract: 5%
• Others: 6%

Demographics:

Study Group:

• Age (yrs), mean: 69
• Age (yrs), median (range): 71 (47-89)
• Gender, female %: 61

Control Group:

• Age (yrs), mean: 67
• Age (yrs), median (range): 70 (37-85)
• Gender, female %:64</td><td><table><tr><td></td><td>(33)</td><td></td></tr><tr><td>5</td><td>CF-LP (59)</td><td>0.47 (0.28-0.66)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.

TTO: Control Group

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (CI: 95%)</th></tr><tr><td>0-1[a]</td><td>20/40-20/50 (75)</td><td>0.77 (0.72-0.82)</td></tr><tr><td>1-3[a]</td><td>20/60-20/100 (54)</td><td>0.71 (0.65-0.77)</td></tr><tr><td>5</td><td>20/200-20/400 (31)</td><td>0.60 (1.53-0.67)</td></tr><tr><td>5</td><td>CF-LP (13)</td><td>0.45 (0.42-0.52)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td></td><td></td></tr>
<tr><td>7.</td><td>Brown 1999a</td><td>Preference valuation method: TTO and SG, VF-</td><td>Eye conditions (% of patients):</td><td>TTO and SG utilities (BSE)

<table><tr><th>Model</th><th>Study VA</th><th>Utility (SD; CI: 95%)</th></tr></table></td><td>TTO and SG utilities (WSE)

<table><tr><th>Model</th><th>Study</th><th>Utility (SD;</th></tr></table></td><td>Utility values were obtained using TTO and</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>14

Scale anchors:

TTO: existing condition vs perfect vision (according to questionnaire in Appendix p.507)

SG: perfect vision (according to questionnaire in Appendix p.507) vs immediate death

Sample size: 325

Study population: hospital patients (with visual loss to a minimum of 20/40 or greater in ≥1 eye)</td><td>• AMD: 33%
• Diabetic retinopathy: 33%
• Retinal detachment: 7%
• RVO: 7%
• Cataract: 7%
• Others: 13%

Demographics:

• Age (yrs), mean: 67.5
• Age (yrs), median (range): 70 (28-87)
• Gender, female %: 63</td><td>
<table>
<tr><th>State #</th><th>Category (n)</th><th>TTO

SG</th></tr>
<tr><td>0</td><td>20/20 (32)</td><td>0.92 (0.13; 0.87-0.97)
0.96 (0.06; 0.94-0.98)</td></tr>
<tr><td>0</td><td>20/25 (50)</td><td>0.87 (0.19; 0.82-0.92)
0.92 (0.15; 0.88-0.96)</td></tr>
<tr><td>0</td><td>20/30 (44)</td><td>0.84 (0.19; 0.79-0.89)
0.91 (0.18; 0.86-0.96)</td></tr>
<tr><td>0</td><td>20/40 (54)</td><td>0.80 (0.22; 0.74-0.86)
0.89 (0.17; 0.84-0.94)</td></tr>
<tr><td>1</td><td>20/50 (31)</td><td>0.77 (0.20; 0.70-0.84)
0.83 (0.15; 0.75-0.91)</td></tr>
<tr><td>≈2[a]</td><td>20/70 (40)</td><td>0.74 (0.21; 0.67-0.81)
0.80 (0.25; 0.72-0.88)</td></tr>
<tr><td>3</td><td>20/100 (18)</td><td>0.67 (0.21; 0.57-0.77)
0.82 (0.22; 0.72-0.82)</td></tr>
<tr><td>5</td><td>20/200 (16)</td><td>0.66 (0.23; 0.55-0.77)
0.80 (0.21; 0.70-0.90)</td></tr>
<tr><td>5</td><td>20/300 (13)</td><td>0.63 (0.16; 0.54-0.72)
0.78 (0.21; 0.67-0.89)</td></tr>
<tr><td>5</td><td>20/400 (9)</td><td>0.54 (0.17; 0.43-0.65)
0.59 (0.19; 0.47-0.71</td></tr>
<tr><td>5</td><td>CF (12)</td><td>0.52 (0.29; 0.36-0.68)
0.65 (0.26; 0.50-0.80)</td></tr>
<tr><td>5</td><td>HM-NLP (6)</td><td>0.35 (0.29; 0.10-0.60)
0.49 (0.37; 0.17-0.81)</td></tr>
<tr><td>NA</td><td>All Pts (325)</td><td>0.77 (0.23; 0.75-0.79)
0.85 (0.21; 0.83-0.87)</td></tr>
</table>
[a]VA scores do not fit into one defined model state, but cross model states as identified.
</td><td>
<table>
<tr><th>State #</th><th>VA Category (n)</th><th>CI: 95%)
TTO
SG</th></tr>
<tr><td>0-1[a]</td><td>20/40-20/50 (18)</td><td>0.86 (0.18; 0.78-0.94)
0.93 (0.13; 0.87-0.99)</td></tr>
<tr><td>2-3[a]</td><td>20/70-20/100 (12)</td><td>0.90 (0.16; 0.83-0.97)
0.96 (0.05; 0.93-0.99)</td></tr>
<tr><td>5</td><td>20/200-20/400 (13)</td><td>0.95 (0.12; 0.88-1.00)
0.94 (0.13; 0.87-1.00)</td></tr>
<tr><td>5</td><td>CF-LP (28)</td><td>0.88 (0.18; 0.81-0.95)
0.92 (0.14; 0.87-0.97)</td></tr>
<tr><td>5</td><td>NLP (7)</td><td>0.81(0.19; 0.67-0.95)
0.95 (0.08; 0.89-1.00)</td></tr>
</table>
[a]VA scores do not fit into one defined model state, but cross model states as identified.
</td><td>SG measured directly from patients. Scores are anchored at existing condition and perfect vision</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Note: article also reports utility values from different disease states and different age groups.</td><td></td><td></td></tr>
<tr><td>8.</td><td>Brown 1999b</td><td>Preference valuation method: TTO and SG

Scale anchors:

TTO: existing condition vs perfect vision

SG: perfect vision vs immediate death

Sample size: n=95

Study population: patients with diabetic retinopathy with BCVA decreased to 20/40 or worse in at least one eye</td><td>Eye conditions (% of patients):

• Diabetic retinopathy: 100%

Causes of vision loss

(from 190 eyes):

• Macular edema: 84%
• Retinal capillary nonperfusion: 9%
• Retinal detachment: 5%
• Vitreous hemorrhage:2%

Demographics:

• Age (yrs), mean (SD): 63 (11.0)
• Age (yrs), median (range): 64 (28-87)
• Gender, female %: 61</td><td>TTO and SG utilities (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)
TTO
SG</th></tr><tr><td>NA</td><td>Overall (95)</td><td>0.77 (0.21; 0.73-0.81)
0.88 (0.20; 0.84-0.92)</td></tr><tr><td>0</td><td>20/20-20/25 (15)</td><td>0.85 (0.19; 0.75-0.95)
0.90 (0.14; 0.83-0.97)</td></tr><tr><td>0-1[a]</td><td>20/30-20/50 (48)</td><td>0.78 (0.20; 0.72-0.84)
0.92 (0.2; 0.88-0.96)</td></tr><tr><td>1-3[a]</td><td>20/60-20/100 (21)</td><td>0.78 (0.19; 0.70-0.86)
0.84 (0.22; 0.72-0.96)</td></tr><tr><td>5</td><td>20/200-20/400 (7)</td><td>0.64 (0.15; 0.53-0.75)
0.71 (0.18; 0.58-0.84)</td></tr><tr><td>5</td><td>CF-HM (4)</td><td>0.59 (0.37; 0.23-0.95)
0.70 (0.42; 0.29-1.11)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td>Not reported.</td><td>TTO and SG used to obtain utility values and HRQL changes are reported directly from patients. Scale anchors are existing condition vs. perfect health/immediate death</td></tr>
<tr><td>9.</td><td>Brown 2000a</td><td>Preference valuation method: TTO + SG</td><td>Eye conditions (% of patients):</td><td>Patients

<table><tr><th>Model</th><th>Study VA</th><th>Utility</th></tr></table></td><td>Not reported</td><td>TTO and SG used to obtain utility values and</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Scale anchors:

TTO: existing condition vs perfect health

SG: perfect vision vs immediate death

Sample size: n=103

Patients with AMD = 72

Physicians = 46

Study population: Patients and Physicians</td><td>Patients

• AMD: 100%
Physicians with normal vision

Demographics:

Patients

• Age (yrs), mean (SD): 74
• Age (yrs), median (range): 56-85
• Gender, female %: NR
Physicians

• Age (yrs), mean (SD):34.8
• Age (yrs), median (range): 30 (27-69)
• Gender, female %: 31</td><td>
<table>
<tr><th>State #</th><th>Category (n=72)</th><th>TTO
SG</th></tr>
<tr><td>0</td><td>20/20-20/25
21</td><td>0.89
0.96</td></tr>
<tr><td>0-1</td><td>20/30-20/50
23</td><td>0.81
0.88</td></tr>
<tr><td>1-3</td><td>20/60-20/100
11</td><td>0.57
0.69</td></tr>
<tr><td>5</td><td>20/200-20/400
12</td><td>0.52
0.71</td></tr>
<tr><td>5</td><td>CF-HM
5</td><td>0.40
0.55</td></tr>
</table>
Physicians
<table>
<tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>20/20-20/25</td><td>0.99
0.99</td></tr>
<tr><td>0-1</td><td>20/30-20/50</td><td>0.97
0.99</td></tr>
<tr><td>1-3</td><td>20/60-
20/100</td><td>0.89
0.96</td></tr>
<tr><td>5</td><td>20/200-
20/400</td><td>0.77
0.88</td></tr>
<tr><td>5</td><td>CF-HM</td><td>0.67
0.77</td></tr>
</table>
</td><td></td><td>HRQL changes are reported directly from patients. Scale anchors are existing condition vs. perfect health/immediate death</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>10.</td><td>Brown 2000b</td><td>Preference valuation method: TTO and SG

Scale anchors:

TTO: existing condition vs perfect vision

SG: perfect vision vs immediate death

Sample size: n=72

Study population: patients with unilateral or bilateral AMD, and vision loss to a minimum of the 20/40 level in at least one eye.</td><td>Eye conditions (% of patients):

• AMD: 100%

Demographics:

• Age (yrs), mean (SD): 74.4
• Age (yrs), range: 56-85
• Gender, female %: 67</td><td>TTO and SG utilities (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (CI: 95%)
TTO
SG</th></tr><tr><td>NA</td><td>20/20-LP (72)</td><td>0.72 (0.66-0.78)
0.81 (0.76-0.86</td></tr><tr><td>0</td><td>20/20-20/25 (21)</td><td>0.89 (0.82-0.96)
0.96 (0.92-1.00)</td></tr><tr><td>0-1[a]</td><td>20/30-20/50 (23)</td><td>0.81 (0.73-0.89)
0.88 (0.83-0.93)</td></tr><tr><td>1-3[a]</td><td>20/60-20/100 (11)</td><td>0.57 (0.47-0.67)
0.69 (0.52-0.86)</td></tr><tr><td>5</td><td>20/200-20/400 (12)</td><td>0.52 (0.38-0.66)
0.71 (0.57-0.85)</td></tr><tr><td>5</td><td>CF-LP (5)</td><td>0.40 (0.29-0.50)
0.55 (0.36-0.74)</td></tr></table>[a]VA scores do not fit into one defined model state, but cross model states as identified.</td><td>Not reported.</td><td>TTO and SG used to obtain utility values and HRQL changes are reported directly from patients. Scale anchors are existing condition vs. perfect vision/immediate death</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>11.</td><td>Brown 2001a</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect vision

Sample size: n= 125

Study population: patients enrolled for a test-retest study</td><td>Eye conditions (% of patients):

• AMD: 43%
• Diabetic retinopathy: 26%
• Retinal detachment: 7%
• RVO: 5%
• Cataract: 10%
• Others: 9%

Demographics:

• Age (yrs), mean: 65.6
• Age (yrs), median (range): 68 (37-82)
• Gender, female %: 64</td><td>TTO utility score (BSE at initial examination)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>0</td><td>20/40 (n=125)</td><td>0.76 (0.21; 0.73-0.80)</td></tr></table>
TTO utility score (BSE at follow-up examination)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>0</td><td>20/40 (125)</td><td>0.76 (0.22; 0.72-0.80)</td></tr></table></td><td>Not reported.</td><td>TTO used to obtain utility values and HRQL changes are reported directly from patients. Scale anchors are existing condition vs. perfect vision</td></tr>
<tr><td>12.</td><td>Brown 2001b</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect vision</td><td>Eye conditions (% of patients):

• AMD: 23%
• Diabetic retinopathy: 18%
• Retinal detachment: 20%
• RVO: 9%
• Cataract: 16%
• Others: 14%</td><td>TTO utility score (both eyes)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>0</td><td>Good vision in both eyes (20/20-20/25 in both eyes) (66)</td><td>0.97 (0.05; 0.96-.98)</td></tr><tr><td>0</td><td>Good vision</td><td>0.89 (0.17;</td></tr></table></td><td>TTO utility scores (WSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>0-1[a]</td><td>20/40-20/50 (24)</td><td>0.87 (0.16; 0.81-0.93)</td></tr><tr><td>2-3[a]</td><td>20/70-</td><td>0.90 (0.16;</td></tr></table></td><td>TTO used to obtain utility values and HRQL changes are reported directly from patients. Scale anchors are existing condition vs.</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Sample size: n= 147 (66 with good vision in both eyes and 81 with good vision in one eye)

Study population:
Specialist practice patients divided into 2 groups – one group with good vision in both eyes (defined as 20/20-20/25 in both eyes) and one group with good vision in one eye only (defined as 20/40 or less in the second eye).</td><td>Demographics:

Good vision in both eyes:

• Age (yrs), mean (SD): 60 (10.0)
• Age (yrs), median (range): 61 (27-84)
• Gender, female %: 57.6

Good vision in one eye:

• Age (yrs), mean (SD): 66 (11.0)
• Age (yrs), median (range): 67 (37-89)
• Gender, female %: 59.3</td><td><table><tr><td></td><td>in one eye (20/20-20/25 in one eye and ≤20/40 in other eye) (81)</td><td>0.85-.93)</td></tr></table></td><td><table><tr><td></td><td>20/100 (12)</td><td>0.81-0.99)</td></tr><tr><td>5</td><td>20/200-20/400 (14)</td><td>0.94 (0.13; 0.81-1.00)</td></tr><tr><td>5</td><td>CF-LP (25)</td><td>0.88 (0.18; 0.81-0.95)</td></tr><tr><td>5</td><td>NLP (6)</td><td>0.81 (0.16; 0.65-0.97)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td>perfect vision</td></tr>
<tr><td>13.</td><td>Brown 2001c</td><td>Preference valuation method: TTO and SG

Scale anchors:

TTO: existing condition vs perfect vision

SG: perfect vision vs immediate death</td><td>Eye conditions (% of patients):

NLP group (n=15)

• AMD: 13%
• Diabetic retinopathy: 33%
• Retinal detachment: 33%
• Other 14%
• Not reported 7%</td><td>TTO and SG utilities (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)
TTO
SG</th></tr><tr><td>5</td><td>20/200-20/400 (33)</td><td>0.65 (0.21; 0.58-0.72)
0.80 (0.21; 0.73-0.87)</td></tr><tr><td>5</td><td>LP-CF (17)</td><td>0.47 (0.29; 0.33-0.61)
0.60 (0.29; 0.46-0.74)</td></tr></table></td><td>TTO and SG utilities (WSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)
TTO
SG</th></tr><tr><td>5</td><td>NLP[a] (15)</td><td>0.62 (0.25; 0.49-0.75)
0.73 (0.31; 0.57-0.89)</td></tr></table>[a] The NLP group was asked to give a utility score assuming complete blindness in both eyes.</td><td>TTO and SG used to obtain utility values and HRQL changes are reported directly from patients. Scale anchors are existing condition vs. perfect vision/immediate death</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
		Sample size: n=65 3 different levels of blindness; 15 pts with NLP 17 pts with LP-CF 33 pts with 20/200-20/400 **Study population:** patients (with varying degrees of legal blindness). Note 3 study groups: (1) NLP group: complete absence of vision (NLP) in ≥1 eye who were asked to assume a scenario of no NLP in the second eye as well. (2) CF group: patients with LP to CF in the better seeing eye.	LP-CF group (n=17) • AMD: 47% • Diabetic retinopathy: 29% • Retinal detachment: 6% • RVO: 12% • Other 6% 20/200-20/400 group (n=33) • AMD: 42% • Diabetic retinopathy: 40% • Retinal detachment: 3% • RVO: 9% • Other 6% **Demographics:** NLP group: • Age (yrs), mean (SD): 61 • Age (yrs), median (range): 37-84 • Gender, female %: 60 CF group:	5 | NLP (15) | 0.26 (0.08; 0.19-0.33) 0.32 (0.24; 0.20-0.44)		

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>(3) 20/200–20/400 group: patients with 20/200–20/400 vision in the better seeing eye.</td><td>• Age (yrs), mean (SD): 72
• Age (yrs), median (range): 46-81
• Gender, female %: NR

20/200-20/400 group:

• Age (yrs), mean (SD): 69
• Age (yrs), median (range): 37-84
• Gender, female %: NR</td><td></td><td></td><td></td></tr>
<tr><td>14.</td><td>Brown 2001d</td><td>Preference valuation method: TTO and SG

Scale anchors:

TTO: existing condition vs perfect vision

SG: perfect vision vs immediate death

Sample size: n=325

Study population: patients</td><td>Eye conditions (% of patients):

• AMD: 33%
• Diabetic retinopathy: 33%
• Retinal detachment: 8%
• RVO: 8%
• Cataract: 7%
• Others: 11%

Demographics:

• Age (yrs), mean (SD): 67.5
• Age (yrs), median (range): 70
• Gender, female %: 63</td><td>TTO and SG utilities

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (range)
TTO
SG</th></tr><tr><td>NA</td><td>All pts (325)</td><td>0.77 (0.05 to 1.00)
0.85 (0.01 to 1.00)</td></tr></table>
A correlation of TTO utility values is available for better-seeing and worse-seeing eye.

For TTO the Spearman correlation coefficient was 0.455 (p<0.001) for vision in the better seeing eye and 0.25 (p<0.001) for vision in the poorer seeing eye.</td><td>Not reported.</td><td>TTO and SG used to obtain utility values and HRQL changes are reported directly from patients. Scale anchors are existing condition vs. perfect vision/immediate death</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>with vision loss 20/40 or less in at least one eye with predominantly vitreoretinal pathology.</td><td></td><td>For SG the Spearman correlation coefficient was 0.37 (p<0.001) for vision in the better seeing eye and 0.25 (p<0.001) for vision in the poorer seeing eye.</td><td></td><td></td></tr>
<tr><td>15.</td><td>Brown 2002a</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect vision

Sample size: n=390

250 with comorbidities

140 without comorbidities

Study population: patients from two specialist practices.</td><td>Eye conditions (% of patients):

• Not reported
Comorbidities:

• Diabetes mellitus (69%)
• Cardiac disease (40%)
• Cancer (21%)
• Previous cerebral accident (17%)
• Renal disease requiring dialysis (5%)

Demographics:

• Age (yrs), mean (SD): 66 (12.4)
• Age (yrs), median (range): 27-89
• Gender, female %: 62.3</td><td>TTO utility scores

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>NA</td><td>Pts with co-morbidities</td><td>0.77 (0.23; 0.74-0.80)</td></tr><tr><td>NA</td><td>Pts without co-morbidities</td><td>0.87 (0.19; 0.84-0.90)</td></tr></table></td><td>Not reported.</td><td>TTO used to obtain utility values directly from patients. Scale anchors are existing condition vs. perfect vision.</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>16.</td><td>Brown 2002b</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect vision

Sample size: n=579

Study population: patients with either AMD or diabetic retinopathy.</td><td>Eye conditions (% of patients):

• AMD: 42%
• Diabetic retinopathy: 58%

Demographics:

AMD group

• Age (yrs), mean (SD): 73.2 (9.8)
• Age (yrs), median (range): 74
• Gender, female %: 66

Diabetic retinopathy group

• Age (yrs), mean (SD): 62.2 (11.8)
• Age (yrs), median (range): 65
• Gender, female %: 56</td><td>TTO utility scores (BSE) - DR group

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>NA</td><td>Overall (333)</td><td>0.79 (0.20; 0.77-0.81)</td></tr><tr><td>0</td><td>20/20-20/25 (72)</td><td>0.86 (0.17; 0.82-0.90)</td></tr><tr><td>0</td><td>20/30-20/40 (130)</td><td>0.80 (0.19; 0.77-0.83)</td></tr><tr><td>1-3[a]</td><td>20/50-20/100 (95)</td><td>0.77 (0.18; 0.73-0.81)</td></tr><tr><td>5</td><td>≤20/200 (36)</td><td>0.60 (0.19; 0.54-0.66)</td></tr></table>[a]VA scores do not fit into one defined model state, but cross model states as identified.

TTO utility scores (BSE) - AMD group

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>NA</td><td>Overall (246)</td><td>0.74 (0.23; 0.71-0.77)</td></tr><tr><td>0</td><td>20/20-20/25 (60)</td><td>0.84 (0.21; 0.82-0.86)</td></tr><tr><td>0</td><td>20/30-20/40 (130)</td><td>0.80 (0.19; 0.75-0.85)</td></tr><tr><td>1-3[a]</td><td>20/50-20/100 (95)</td><td>0.71 (0.22; 0.65-0.77)</td></tr><tr><td>5</td><td>≤20/200 (36)</td><td>0.59 (0.22; 0.53-0.65)</td></tr></table>[a]VA scores do not fit into one defined model state, but cross model states as identified.</td><td>Not reported.</td><td>TTO used to obtain utility values directly from patients. Scale anchors are existing condition vs. perfect vision</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>17.</td><td>Brown 2003</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect health (Including perfect vision)

Sample size: n=500

Study population: patients (with ocular diseases)</td><td>Eye conditions (% of patients):

• AMD: 29%
• Diabetic retinopathy: 34%
• Retinal detachment: 7%
• RVO: 11%
• Cataract: 9%
• Others: 10%

Demographics:

• Age (yrs), mean (SD): 67.5 (12.2)
• Age (yrs), median (range): 70 (23-90)
• Gender, female %: 60.6</td><td>TTO utility scores (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>0</td><td>20/20-20/25 (127)</td><td>0.88 (0.15; 0.85-.91)</td></tr><tr><td>0-1[a]</td><td>20/30-20/50 (218)</td><td>0.81 (0.21; 0.78-.84)</td></tr><tr><td>1-3[a]</td><td>20/60-20/100 (83)</td><td>0.72 (0.21; 0.67-.77)</td></tr><tr><td>5</td><td>20/200-NLP (72)</td><td>0.61 (0.19; 0.57-.65)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td>Not reported.</td><td>TTO used to obtain utility values directly from patients.</td></tr>
<tr><td>18.</td><td>Chang 2007</td><td>Preference valuation method: Vision Preference Value Scale (VPVS). Enthusiasm for treatment modalities (observation only, laser photocoagulation and intravitreal triamcinolone) also reported.

Scale anchors: death vs</td><td>Eye conditions (% of patients):

• BVO: 55%
• CVO: 45%

Demographics:

• Age (yrs), mean (SD): 68.6 (12.3)
• Gender, female %: 53</td><td>Not reported.</td><td>Preference values (based on RVO category)[ab]

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>NA</td><td>BVO</td><td>0.65 (0.20)</td></tr><tr><td>NA</td><td>CVO</td><td>0.65 (0.19)</td></tr></table>[a] Mean logMAR VA (SD) of study eye at last visit: 0.86 (1.30).

[b] Mean logMAR VA (SD) of fellow eye at last visit: -0.21 (2.25)</td><td>Vision preference scale is not choice-based</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
		perfect health **Sample size:** n= 153 **Study population:** patients (with RVO). Duration of RVO (yrs), mean (SD) = 2.22 (1.15).	Note: previous treatment for RVO also reported (43% of BVO patients and 35% of CVO patients had received treatment).		Note: preference values also reported for: Subjects with RVO > 1 year vs those with RVO ≤1 year, also subjects with RVO > 2 years vs those with RVO ≤ 2 years. Note: In multivariate regression models adjusting for potential confounders, only duration of vein occlusion (duration of >2 or ≤2 years) (p=0.03) and the last-recorded logMAR VA in the study eye (p=0.02) appeared to be related to preference value.	

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>19.</td><td>Clarke 2006</td><td>Preference valuation method: SF-36.

Scale anchors:

Utility values derived via algorithm (lowest possible value is 0.296 and full health is 1.0)

Sample size: n= 4, 051

Study population: patients with type 2 diabetes</td><td>Eye conditions (% of patients):

• NR

Demographics:

• Age (yrs), mean (SD): 61.6 (8.6)
• Gender, female %: 35</td><td>SF-36 Utility score

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>NA</td><td>all patients</td><td>0.76 (0.11)</td></tr></table>
Change in SF-36 Utility score

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>5</td><td>Legally blind[a]</td><td>-0.054

(95% CI; 0.034-0.074) compared with patients with normal or above normal VA (logMAR score ≤0.0)</td></tr></table>
[a] defined as 20/200 or worse (Snellen acuity) in BSE</td><td>Not reported.</td><td>Yes – SF-36 was used as a measure of HRQL in order to obtain utility values</td></tr>
<tr><td>20.</td><td>Czoski-Murray

2009</td><td>Preference valuation method: TTO and HUI3 (however HUI3 results not reported by VA category)

Scale anchors:</td><td>Eye conditions (% of patients):

• AMD simulated with contact lenses in both eyes</td><td>Note: BSE acuity measured whilst subjects were wearing study contact lenses.

TTO utility scores (by VA of BSE whilst wearing a pair of lenses Type 1 (Reading limit)</td><td>Not reported.</td><td>Yes – generic preference based measures were used in order to obtain utility values HUI3, TTO VF-14 and EQ-5D which is NICEs'</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>TTO: existing condition vs perfect health

Sample size: n=108

Study population: community members using different types of contact lenses (in both eyes) to simulate three different states of AMD

Lenses as follows:

Lens 1 (20/80) = Mild AMD (Reading limit)

Lens 2 (20/200)= Moderate AMD (Legal blindness)

Lens 3 (20/500) = Severe AMD (Untreated AMD)</td><td>Demographics:

• Age (yrs), mean (SD): 32 (12.5)
• Age (yrs), median (range): oldest was 68
• Gender, female %: NR</td><td>
<table>
<tr><th>Model State #</th><th>Study VA Category (n=104)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>≤0.30 (≥20/40) (18)</td><td>0.78 (0.71-0.85)</td></tr>
<tr><td>0-2[a]</td><td>0.31-0.60 (20/40-20/80) (40)</td><td>0.73 (0.66-0.80)</td></tr>
<tr><td>2-5[a]</td><td>0.61-1.30 (20/80-20/400) (46)</td><td>0.65 (0.56-0.74)</td></tr>
<tr><td>5</td><td>≥1.31 (≤20/400) (0)</td><td>--</td></tr>
</table>
[a] VA scores do not fit into one defined model state, but cross model states as identified.

TTO utility scores (by VA of BSE whilst wearing a pair of lenses Type 2 (Legal blindness)

<table>
<tr><th>Model State #</th><th>Study VA Category (n=104)</th><th>Utility (CI: 95%)</th></tr>
<tr><td>0</td><td>≤0.30 (≥20/40) (23)</td><td>0.65 (0.53-0.77)</td></tr>
<tr><td>0-2[a]</td><td>0.31-0.60 (20/40-20/80) (40)</td><td>0.65 (0.56-0.74)</td></tr>
</table>
</td><td></td><td>preferred measure of HRQL directly from the participants themselves</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
				2-5[a] | 0.61-1.30 (20/80-20/400) (41) | 0.49 (0.39-0.58) 5 | ≥1.31 (≤20/400) (0) | -- [a] VA scores do not fit into one defined model state, but cross model states as identified. TTO utility scores (by VA of BSE whilst wearing a pair of lenses Type 3 (Untreated AMD) **Model State #** | **Study VA Category (n=103)** | **Utility (SD)** 0 | ≤0.30 (≥20/40) (0) | -- 0-2[a] | 0.31-0.60 (20/40-20/80) (9) | 0.60 (0.30-0.91) 2-5[a] | 0.61-1.30 (20/80-20/400) (38) | 0.37 (0.25-0.49) 5 | ≥1.31 (≤20/400) (56) | 0.31 (0.22-0.41) [a] VA scores do not fit into one defined model state, but cross model states as identified.		

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>21.</td><td>Espallargues 2005</td><td>Preference valuation method: TTO, HUI3, EQ-5D, SF-6D, VF-14

Scale anchors:

TTO: existing condition vs perfect health (including perfect vision)

Sample size: n=209

Study population: patients with unilateral or bilateral AMD</td><td>Eye conditions (% of patients):

• AMD: 100%

Demographics:

• Age (yrs), mean (SD): 79.6 (7.5)
• Age (yrs), median (range): 43-96
• Gender, female %: 57.9</td><td>EQ-5D utility scores (BSE)

<table>
<tr><th>Model State #</th><th>Study VA Category (distant, logMAR) (decimal) (n=207)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>≤0.30 (≥0.5)</td><td>0.75 (0.27)</td></tr>
<tr><td>0-2[a]</td><td>0.31 to 0.60 (0.25–0.4)</td><td>0.70 (0.20)</td></tr>
<tr><td>2-5[a]</td><td>0.61 to 1.30 (0.05–0.24)</td><td>0.75 (0.20)</td></tr>
<tr><td>5</td><td>1.31 to 2.00 (0.01–0.04)</td><td>0.71 (0.21)</td></tr>
<tr><td>5</td><td>>2.00 (<0.01)</td><td>0.63 (0.22)</td></tr>
<tr><td></td><td>Eta[2]</td><td>0.02</td></tr>
</table>

SF-6D utility scores (BSE)

<table>
<tr><th>Model State #</th><th>Study VA Category (distant, logMAR) (decimal) (n=204)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>≤0.30 (≤0.5)</td><td>0.70 (0.18)</td></tr>
<tr><td>0-2[a]</td><td>0.31 to 0.60 (0.25–0.4)</td><td>0.67 (0.14)</td></tr>
<tr><td>2-5[a]</td><td>0.61 to 1.30 (0.05–0.24)</td><td>0.66 (0.14)</td></tr>
<tr><td>5</td><td>1.31 to 2.00 (0.01–0.04)</td><td>0.65 (0.11)</td></tr>
</table>
</td><td>Not reported.</td><td>Yes – SF-6D, HUI3, VAS, VF-14 and TTO used as HRQL preference based methods in order to obtain utility information including EQ-5D and were obtained from the patients themselves</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>5</td><td>>2.00 (<0.01)</td><td>0.63 (0.10)</td></tr>
<tr><td></td><td>Eta^2</td><td>0.02</td></tr>
</table>

HUI3 utility scores (BSE)
<table>
<tr><th>Model State #</th><th>Study VA Category (distant, logMAR) (n=206)</th><th>Utility (SD)</th></tr>
<tr><td>0</td><td>≤0.30 (≤0.5)</td><td>0.50 (0.35)</td></tr>
<tr><td>0-2[a]</td><td>0.31 to 0.60 (0.25–0.4)</td><td>0.38 (0.25)</td></tr>
<tr><td>2-5[a]</td><td>0.61 to 1.30 (0.05–0.24)</td><td>0.36 (0.25)</td></tr>
<tr><td>5</td><td>1.31 to 2.00 (0.01–0.04)</td><td>0.27 (0.24)</td></tr>
<tr><td>5</td><td>>2.00 (<0.01 decimal)</td><td>0.10 (0.18)</td></tr>
<tr><td></td><td>Eta^2</td><td>0.13*†</td></tr>
</table>

TTO utility scores (BSE)
<table>
<tr><th>Model</th><th>Study VA</th><th>Utility (SD)</th></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td>Espallargues 2005 (continued)</td><td></td><td></td><td>
<table>
<tr><th>State #</th><th>Category (distant, logMAR) (n=204)</th><th></th></tr>
<tr><td>0</td><td>≤0.30 (≤0.5)</td><td>0.73 (0.30)</td></tr>
<tr><td>0-2[a]</td><td>0.31 to 0.60 (0.25–0.4)</td><td>0.67 (0.31)</td></tr>
<tr><td>2-5[a]</td><td>0.61 to 1.30 (0.05–0.24)</td><td>0.64 (0.30)</td></tr>
<tr><td>5</td><td>1.31 to 2.00 (0.01–0.04)</td><td>0.60 (0.33)</td></tr>
<tr><td>5</td><td>>2.00 (<0.01 decimal)</td><td>0.47 (0.31)</td></tr>
<tr><td></td><td>Eta^2</td><td>0.04†</td></tr>
</table>
Eta^2, variability in health status score explained by either VA, contrast sensitivity of VF-14 index and calculated as the sum of squares between groups divided by the total sum of squares from ANOVA results.

* P < 0.05 in ANOVA F test between groups.

† P < 0.05 in ANOVA F test for linear trend.

[a] VA scores do not fit into one defined model state, but cross model states as identified.
</td><td></td><td></td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
	Espallargues 2005 (continued)					
22.	Kempen 2003	**Preference valuation method:** VAS, EQ-5D	**Eye conditions (% of patients):**	Utility values according to CMV category:	Not reported.	Yes –EQ-5D used as a measure of HRQL in order to

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Scale anchors:

VAS: death vs perfect health

Sample size: n= 709

Study population: patients (with AIDS)</td><td>AIDS and:

• No CMV retinitis: 73%
• Long-standing CMV retinitis: 22%
• Newly diagnosed CMV retinitis: 5%

Demographics:

No CMV retinitis: (n=709)

• Age (yrs), mean (SD): 42
• Gender, female %: 20

Long-standing CMV retinitis: (n=212)

• Age (yrs), mean (SD): 42
• Gender, female %: 16

Newly diagnosed CMV retinitis: (n=50)

• Age (yrs), mean (SD): 37
• Gender, female %: 33</td><td><table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)
VAS
EQ-5D</th></tr><tr><td>NA</td><td>No CMV retinitis[a] (709)</td><td>0.725
0.71</td></tr><tr><td>NA</td><td>Long-standing CMV retinitis[b] (212)</td><td>0.723
0.73</td></tr><tr><td>NA</td><td>Newly diagnosed CMV retinitis[c] (50)</td><td>0.639
0.75</td></tr></table>[a] VA (median, standard letters): Better eye: 91; Worse eye: 88.

[a] VA (median, standard letters): Better eye: 88; Worse eye: 76.

[a] VA (median, standard letters): Better eye: 88; Worse eye: 81.</td><td></td><td>obtain utility values and were obtained directly from the patients themselves</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>23.</td><td>Lee 2008</td><td>Preference valuation method: multiple SGs performed (8 performed however only 4 reported)

Scale anchors:

SG 1: death vs perfect health (assuming current health state is own current heath)

SG 2: unilateral blindness vs perfect vision (assuming current health state is own current vision)

SG 3: death vs perfect vision (assuming current health state is binocular blindness)

SG 4: death vs perfect vision (assuming current health state is monocular blindness)</td><td>Eye conditions (% of patients):

• Diabetic retinopathy: 13%
• Glaucoma: 23%
• AMD: 10%
• Cataract: 29%
• Refractive error: 25%

Demographics:

All patients (n=434)

• Age (yrs), mean (SD): 60.9 (15.6)
• Gender, female %: 58.

AMD patients only (n=44)

• Age (yrs), mean (SD): 75.4 (6.2)
• Gender, female %: 50.

Note: demographics also reported separately for each condition and condition severity.</td><td>SG mean utilities (both eyes) – all patients

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>NA</td><td>All pts[a] (434)</td><td>SG 1: 0.90 (0.19)

SG 2: 0.83 (0.25)</td></tr><tr><td>5</td><td>Bilateral blindness (hypothetically)

(434)</td><td>SG 3: 0.40 (0.37)</td></tr><tr><td>NA</td><td>Unilateral blindness (hypothetically)

(434)</td><td>SG 4: 0.78 (0.28)</td></tr></table>[a] Mean BSE VA, logMAR (SD): 0.12 (0.24)

SG mean utilities (both eyes) - AMD patients only

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr></table></td><td>Not reported.</td><td>Utility estimates directly from patients. Anchored on perfect vision</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
		Sample size: n= 434 **Study population:** patients (with 5 common ophthalmic conditions namely: DR, glaucoma, AMD, cataract, and refractive error). Note: SG 3 and SG 4 use hypothetical health states (binocular or monocular blindness), rather than patients' own health/vision.		<table><tr><td>NA</td><td>All AMD pts[a] (44)</td><td>SG 1: 0.83 (0.27) SG 2: 0.63 (0.38)</td></tr><tr><td>0-3[a]</td><td>Mild AMD (CVA ≥20/40 in BSE) to Moderate (CVA 20/50 to 20/100 in BSE) (23)</td><td>SG 1: 0.89 (0.23) SG 2: 0.86 (0.24)</td></tr><tr><td>5</td><td>Severe AMD (VA ≤20/200 in BSE) (21)</td><td>SG 1: 0.76 (0.30) SG 2: 0.39 (0.37)</td></tr></table> [a] Mean BSE VA, logMAR (SD): 0.40 (0.41) [b] Note: SG utility values adjusted for age and comorbidity also reported. Note: SG utilities also reported separately for DR, Glaucoma, Cataract and refractive error.		
24.	Lloyd 2008	**Preference valuation method:** SG, EQ-5D, HUI3, NEI-VFQ 25	**Eye conditions (% of patients):** • Diabetic retinopathy: 38% (n=122)	SG mean utility scores (BSE) – VA categories reported in Snellan Equivalent (metres)		Yes – HUI-3, NEI-VFQ 25 and SG have been used to obtain HRQL utility scores including

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Scale anchors:

SG: perfect health state vs immediate death

Sample size: 321

Study population: patients and community. Two patient groups and one community group as follows:

1. Diabetic retinopathy: n=122

2. Diabetes, no DR: n=49

3. Community: n=150

Note: all subjects completed SG for health states associated with different levels of VA.</td><td>Demographics:

Diabetic retinopathy:

• Age (yrs), mean (SD): 62.2 (12.6)
• Gender, female %: 34

Diabetes, no DR:

• Age (yrs), mean (SD): 52.6 (15.2)
• Gender, female %: 44

Community:

• Age (yrs), mean (SD): 44.4 (15.9)
• Gender, female %: 65</td><td>
<table>
<tr><th>State #</th><th>Study VA Category</th><th>DR

Utility (SD)

(N = 48)</th><th>Diabetes without DR

Utility (SD)

(N = 47)</th><th>General public

Utility (SD)

(N = 150)</th><th>Estimated means (SE)*</th></tr>
<tr><td>0</td><td>6/6–6/9</td><td>0.81 (0.20)</td><td>0.77 (0.28)</td><td>0.83 (0.16)</td><td>0.814 (0.016)</td></tr>
<tr><td>0-1[a]</td><td>6/12–6/18</td><td>0.69 (0.27)</td><td>0.66 (0.28)</td><td>0.75 (0.20)</td><td>0.728 (0.018)</td></tr>
<tr><td>2-3[a]</td><td>6/24–6/36</td><td>0.70 (0.26)</td><td>0.61 (0.30)</td><td>0.68 (0.23)</td><td>0.674 (0.019)</td></tr>
<tr><td>5</td><td>6/60–6/120</td><td>0.67 (0.26)</td><td>0.57 (0.32)</td><td>0.63 (0.23)</td><td>0.629 (0.019)</td></tr>
<tr><td>5</td><td>CF–hand motion</td><td>0.58 (0.31)</td><td>0.53 (0.32)</td><td>0.58 (0.26)</td><td>0.570 (0.021)</td></tr>
</table>
[a] VA scores do not fit into one defined model state, but cross model states as identified.

SG mean utility scores (BSE) – VA categories reported in Snellan Equivalent (metres)</td><td></td><td>the preferred method of measure, the EQ-5D. The scores were obtained directly from the patients themselves</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Mean utility values from MAUIs (EQ-5D or HUI-3) or VFQ-25 - Diabetes patients with and without retinopathy (VA of BSE)

<table>
<tr><th>Model State #</th><th>Study VA Category (n)</th><th>EQ-5D single index (SD)</th><th>HUI-3 (SD)</th><th>VFQ-25 total score (SD)</th></tr>
<tr><td>NR</td><td>Diabetic no retinopathy (49)</td><td>0.83 (0.20)</td><td>0.81 (0.20)</td><td>90.6 (13.1)</td></tr>
<tr><td>0</td><td>6/6–6/9 (68)</td><td>0.75 (0.23)</td><td>0.78 (0.22)</td><td>86.3 (13.6)</td></tr>
<tr><td>0-1[a]</td><td>6/12–6/18 (13)</td><td>0.50 (0.30)</td><td>0.30 (0.38)</td><td>61.5 (25.4)</td></tr>
<tr><td>2-3[a]</td><td>6/24–6/36 (10)</td><td>0.68 (0.29)</td><td>0.61 (0.35)</td><td>61.1 (22.6)</td></tr>
<tr><td>5</td><td>6/60–6/120 (7)</td><td>0.53 (0.47)</td><td>0.52 (0.50)</td><td>39.5 (24.3)</td></tr>
<tr><td>5</td><td>CF hand motion (3)</td><td>0.34 (0.36)</td><td>0.37 (0.00)</td><td>29.2 (16.1)</td></tr>
</table>
[a] VA scores do not fit into one defined model state, but cross</td><td></td><td></td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>model states as identified.</td><td></td><td></td></tr>
<tr><td>25.</td><td>Sahel 2007</td><td>Preference valuation method: HUI3

Scale anchors: NA

Sample size: n=360

Study population: patients (with AMD)</td><td>Eye conditions (% of patients):

• AMD: 100%

Demographics:

• Age (yrs), mean (SD): 77, (8.0)
• Age (yrs), median (range): 78 (51 – 96)
• Gender, female %: 59.6</td><td>HUI3 utility scores (both eyes)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>0</td><td>BSE≥20/40, WSE≥20/200 (98)</td><td>0.62 (0.28)</td></tr><tr><td>0</td><td>BSE≥20/40, WSE,<20/200 (46)</td><td>0.60 (NR)</td></tr><tr><td>1+</td><td>BSE<20/40, WSE≥20/200</td><td>0.40 (NR)</td></tr><tr><td>1+</td><td>BSE<20/40, (46) WSE<20/200 (92)</td><td>0.39 (0.25)</td></tr></table></td><td>See data for both eyes. Indicates, minimal utility impacted for change in VA of WSE.</td><td>Yes – HUI3 and NEI-VFQ 25 were used to obtain HRQL utility scores excluding the preferred method of measure, the EQ-5D. The scores were obtained directly from the patients themselves</td></tr>
<tr><td>26.</td><td>Shah 2004</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect health

Sample size: n=136</td><td>Eye conditions (% of patients):

• AMD: 35.3%
• Diabetic retinopathy: 64.7%

Demographics:

• Age (yrs), mean (SD): 67.5
• Age (yrs), median (range): 25-92
• Gender, female %: 66.2</td><td>TTO utilities (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n=136)</th><th>Utility (SD; CI: 95%)</th></tr><tr><td>0</td><td>20/20-20/40 (71)</td><td>0.88 (0.19; 0.87-1.00)</td></tr><tr><td>1-3[a]</td><td>20/50-20/100 (43)</td><td>0.90 (0.14; 0.85-1.00)</td></tr><tr><td>5</td><td>20/200-NLP (22)</td><td>0.76 (0.23; 0.73-0.87)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross</td><td>Not reported.</td><td>Utility scores directly from the patients.</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Study population: patients (with DR or AMD)</td><td></td><td>model states as identified.</td><td></td><td></td></tr>
<tr><td>27.</td><td>Sharma 2000</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect health

Sample size: n=237

Study population: patients with ocular diseases.

Note: the intention of the study was to develop a mathematical method for converting VA to utility value.</td><td>Eye conditions (% of patients):

• AMD: 33.8%
• Diabetic retinopathy: 39.2%
• RVO: 9.3%
• Cataract: 5.1%
• Others: 12.6%

Demographics:

• Age (yrs), mean: 68.4
• Gender, female %: 64</td><td>Actual TTO utility results from the study population were not reported. It was found that utility values from patients with ocular disease were strongly associated with VA in the BSE and could be estimated mathematically. Two equations were proposed and a set of calculated utility values based on hypothetical VA in BSE were reported as shown below.

Utility values based on the equations:

<table><tr><th>Model State #</th><th>VA</th><th>Utility, equation 1[a]</th><th>Utility, equation 2[b]</th></tr><tr><td>0</td><td>20/40</td><td>0.701</td><td>0.650</td></tr><tr><td>1</td><td>20/60</td><td>0.638</td><td>0.590</td></tr><tr><td>2</td><td>20/80</td><td>0.607</td><td>0.560</td></tr><tr><td>3</td><td>20/100</td><td>0.588</td><td>0.542</td></tr><tr><td>5</td><td>20/200</td><td>0.551</td><td>0.505</td></tr></table>
[a] Equation 1: Univariate equation (R^2 =0.173; F =69.1. P< 0.001) U =(0.374)(VA in BSE) + 0.514</td><td>Not reported</td><td>Utility scores were measured using TTO but the scores were obtained directly from the patients themselves</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>[b] Equation 2: Bivariate equation (R^2 =0.258; F=13.2. P< 0.001). U = (0.362)(VA in BSE) + (0.0346)(duration of visual loss) + 0.4</td><td></td><td></td></tr>
<tr><td>28.</td><td>Sharma 2002</td><td>Preference valuation method: TTO, SG

Scale anchors:

TTO: existing condition vs normal vision

SG: perfect vision vs immediate death

Sample size: n=323

Study population: patients</td><td>Eye conditions (% of patients):

• AMD: 33.1%
• Diabetic retinopathy: 32.5%
• Others: 34.4%

Demographics:

• Age (yrs), mean (SD): 67.5 (11.9)
• Gender, female %: 63.5</td><td>TTO and SG utility scores (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (Snellan Equivalent, metres) (n=323)</th><th>Utility (CI: 95%)
TTO
SG</th></tr><tr><td>0</td><td>6/7.5 or better (75)</td><td>0.908 (0.875 to 0.942)
0.948 (0.924 to 0.972)</td></tr><tr><td>0-1[a]</td><td>6/9 to 6/15 (136)</td><td>0.797 (0.762 to 0.833)
0.897 (0.869 to 0.925)</td></tr><tr><td>1-3[a]</td><td>6/18 to 6/30 (58)</td><td>0.708 (0.653 to 0.764)
0.769 (0.696 to 0.842)</td></tr><tr><td>5</td><td>6/60 to 6/120 (37)</td><td>0.621 (0.555 to 0.687)
0.742 (0.672 to 0.812)</td></tr><tr><td>5</td><td>CF to NLP (17)</td><td>0.473 (0.323 to 0.624)
0.603 (0.451 to 0.754)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td>Not reported.</td><td>Utility scores were measured using TTO but the scores were obtained directly from the patients themselves</td></tr>
<tr><td>29.</td><td>Sharma 2003</td><td>Preference valuation method: TTO</td><td>Eye conditions (% of patients):

• Diabetic retinopathy: 100</td><td>TTO utility scores (BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n=221)</th><th>Utility (SD)</th></tr></table></td><td>Not reported.</td><td>Utility scores were measured using TTO but the scores were obtained directly from the patients</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td>Scale anchors:

TTO: existing condition vs normal vision

Sample size: n=186 (221 were enrolled and 186 completed the TTO) demographic data reported for 221 participants.

Study population: patients with diabetic retinopathy</td><td>Demographics:

• Age (yrs), mean (SD): 63.5 (12.5)
• Age (yrs), median (range): 67.0
• Gender, female %: 51.6</td><td><table><tr><td>0</td><td>6/7.5 or better (68)</td><td>0.88 (0.19)</td></tr><tr><td>0-1[a]</td><td>6/9-6/15 (99)</td><td>0.79 (0.22)</td></tr><tr><td>1-3[a]</td><td>6/18-6/30 (33)</td><td>0.72 (0.26)</td></tr><tr><td>5</td><td>6/60-6/120 (18)</td><td>0.73 (0.22)</td></tr><tr><td>5</td><td>CF-NLP (3)</td><td>0.48 (0.47)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td></td><td>themselves</td></tr>
<tr><td>30.</td><td>Sharma 2006 (report to Allergan)</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs perfect vision

Sample size: n= 100

Study population:</td><td>Demographics:

• Age (yrs), mean (range): 60 (22-89)
• Gender, female %: 55</td><td>TTO utility scores (both eyes):

<table><tr><th>Model State # (BSE & WSE) (n)</th><th>VA BSE</th><th>VA WSE</th><th>Utility (SD, 95% CI)</th></tr><tr><td>1 & 1 (50)</td><td>20/60</td><td>20/60</td><td>0.858 (0.1636, 0.811-0.904)</td></tr><tr><td>2 & 5 (25)</td><td>20/80</td><td>20/200</td><td>0.864 (0.1886, 0.787-0.942)</td></tr></table></td><td>TTO utility scores (WSE)[a]

<table><tr><th>Model State #</th><th>VA WSE (n)</th><th>Utility (SD, 95% CI)</th></tr><tr><td>0</td><td>20/25 (100)</td><td>0.992 (0.0438, 0.983-1.000)</td></tr><tr><td>0</td><td>20/40 (36)</td><td>0.957 (0.1141, 0.918-0.996)</td></tr><tr><td>1</td><td>20/50</td><td>0.969 (0.1042, 0.929-</td></tr></table></td><td>Yes – utility scores were measured using TTO but the EQ-5D was not used. The weights were obtained from the public.</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
		Community participants with 20/25 or better vision who underwent simulation of different VA states through lens fogging.		<table><tr><td>5 & 5 (27)</td><td>20/200</td><td>20/200</td><td>0.836 (0.1986, 0.757-0.914)</td></tr><tr><td>5 & 5 (100)</td><td>NLP (black blind)</td><td>NLP (black blind)</td><td>0.648 (0.2533, 0.597-0.698)</td></tr></table>	<table><tr><td></td><td>(28)</td><td>1.000)</td></tr><tr><td>1</td><td>20/60 (36)</td><td>0.963 (0.0785, 0.937-0.990)</td></tr><tr><td>3</td><td>20/100 (27)</td><td>0.989 (0.0487, 0.970-1.000)</td></tr><tr><td>5</td><td>20/200 (25)</td><td>0.905 (0.1880, 0.828-0.983)</td></tr><tr><td>5</td><td>20/400 (46)</td><td>0.958 (0.1037, 0.927-0.989)</td></tr></table> [a] VA in BSE was 20/25 for these patients. Conclusion: WSE does not impact on utility if BSE VA is 20/25.	

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td>31.</td><td>Smith 2008</td><td>Preference valuation method: EQ-5D

Scale anchors:

NA

Sample size: n=2074

Study population: community</td><td>Eye conditions (% of patients):

• Diabetic retinopathy: 100%

Demographics:

• Age (yrs), mean (SD): 65.6
• Gender, female %: 50.5</td><td>EQ-5D utility scores (Best corrected VA in BSE)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>0</td><td>≥20/20 (1324)</td><td>0.82 (0.17)</td></tr><tr><td>0</td><td>20/25 (409)</td><td>0.78 (0.19)</td></tr><tr><td>0</td><td>20/30 (187)</td><td>0.79 (0.17)</td></tr><tr><td>0</td><td>20/40 (87)</td><td>0.75 (0.19)</td></tr><tr><td>1</td><td>20/50 (33)</td><td>0.72 (0.23)</td></tr><tr><td>1</td><td>20/60 (11)</td><td>0.75 (0.15)</td></tr><tr><td>2</td><td>20/70 (8)</td><td>0.60 (0.26)</td></tr><tr><td>2+</td><td>≤20/80 15</td><td>0.71 (0.25)</td></tr></table></td><td>Not reported.</td><td>Yes – utility scores were measured using the preferred HRQL measure, the EQ-5D. The scores were obtained directly from the patients themselves</td></tr>
<tr><td>32.</td><td>Stein 2003</td><td>Preference valuation method: TTO

Scale anchors:

TTO: existing condition vs free of AMD</td><td>Eye conditions (% of patients):

• AMD: 100%
i. Mild AMD %:29.6[a]
ii. Mod AMD %:40.9[a]
iii. Severe AMD %:32.2[a]
[a]Article reports the above</td><td>TTO utility scores (BCVA – binocular vision) - Patients

<table><tr><th>Model State #</th><th>Study VA Category (n=118*)</th><th>Utility (SD)</th></tr><tr><td>0</td><td>Mild AMD 20/30 (34[b])</td><td>0.832 (0.762, 0.901)</td></tr><tr><td>0-3[a]</td><td>Moderate AMD</td><td>0.732 (0.669, 0.795)</td></tr></table></td><td>Not reported.</td><td>Yes – TTO used to obtain utility values from public</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Suitability with NICE reference Case
		Sample size: n=324 **Study population:** Patients: 115 (118[a]) General public[b]: 142 Clinicians[b]: 62 [a] Within group totals equal 118 patients [b] General public and clinicians asked to assume they had each severity of AMD.	*values but when added together, total = 102.7%. When based on 118 patients total = 100%;* *i. Mild AMD %:* *ii. Mod AMD %:* *iii. Severe AMD %:* **Demographics:** Patients • Age (yrs), mean (SD): 75.1 (7.92) • Gender, female %: 64.7 General public • Age (yrs), mean (SD): 29 (7.32) • Gender, female %: 42.1	<table><tr><td></td><td>20/40-20/100 (47 [b])</td><td></td></tr><tr><td>5</td><td>Severe AMD ≥20/200 (37 [b])</td><td>0.566 (0.487, 0.645)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified. [b]*article states 115 in this group but then give within group values totalling 118 patients.* TTO utility scores (BCVA – binocular vision) – General Public <table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (CI: 95%))</th></tr><tr><td>0</td><td>20/30</td><td>0.960 (0.950, 0.970)</td></tr><tr><td>0-3[a]</td><td>20/40-20/100</td><td>0.918 (0.902, 0.934)</td></tr><tr><td>5</td><td>≥20/200</td><td>0.857 (0.834, 0.879)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified. TTO utility scores (BCVA – binocular vision) – Clinicians		

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td>Clinicians

• Age (yrs), mean (SD): 44.3 (13.32)
• Gender, female %: 57.7</td><td><table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>0</td><td>20/30</td><td>0.929 (0.904, 0.954)</td></tr><tr><td>0-3[a]</td><td>20/40-20/100</td><td>0.877 (0.846, 0.909)</td></tr><tr><td>5</td><td>≥20/200</td><td>0.821 (0.785, 0.857)</td></tr></table>[a] VA scores do not fit into one defined model state, but cross model states as identified.</td><td></td><td></td></tr>
<tr><td>33.</td><td>Tung 2005</td><td>Preference valuation method: TTO

Scale anchors:

TTO: death vs perfect health

Sample size: n= 406

Study population: patients (with type 2 diabetes)</td><td>Eye conditions (% of subjects):

Diabetic retinopathy and:

• No DR: 77%
• NPDR: 18%
• PDR: 3%
• Legal blindness: 2%

Demographics:

• Age (yrs), median: in range 60-69.
• Gender, female %: 61</td><td>TTO (according to DR category)

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>NA</td><td>No DR: (286)</td><td>0.94 (0.11)
(95% CI; 0.93-0.95)</td></tr><tr><td>NA</td><td>NPDR: (65)</td><td>0.87 (0.14)
(95% CI; 0.84-0.90)</td></tr><tr><td>NA</td><td>PDR: (12)</td><td>0.83 (0.08)
(95% CI; 0.78-0.88)</td></tr><tr><td>5</td><td>Legal blindness[a]: (9)</td><td>0.81 (0.08)
(95% CI; 0.76-0.86)</td></tr><tr><td>NA</td><td>All pts[b] (372)</td><td>0.92 (0.12)
(95% CI; 0.91-0.93)</td></tr><tr><td>NA</td><td>Traders only[c] (156)</td><td>0.80 (0.11)
(95% CI; 0.78-0.82)</td></tr></table>[a] defined as best corrected acuity of 0.1 (20/200) or worse in</td><td>Not reported.</td><td>TTO used to obtain utility values directly from patients</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Suitability with NICE reference Case</th></tr>
<tr><td></td><td></td><td></td><td></td><td>the better eye.

[b] 34 patients unable to answer.

[c] Includes only patients willing to trade life years for perfect health.</td><td></td><td></td></tr>
<tr><td>34.</td><td>Williams 1998</td><td>Preference valuation method: Quality of Well-being Scale (QWB).

Scale anchors:

The QWB uses a continuum scale of 0 = death to 1.0 = optimum functioning with no symptoms. This scale uses quality estimates (scoring system) obtained from an independent panel of judges.

Sample size: n=86

18 legally blind in both eyes

68 legally blind in one eye.

Study population: patients</td><td>Eye conditions (% of patients):

• AMD: 100%

Demographics:

• Age (yrs), mean (SD): 78.7 (6.3)
• Gender, female %: 51.2</td><td>QWB score

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>5</td><td>Legally blind in one eye

(20/200 or worse in one eye)</td><td>0.584 (0.08)</td></tr></table>
Conclusion

Results show that people with one legally blind eye have a lower quality of life compared to people with two legally blind eyes. This includes distress and anxiety of losing vision in the better seeing eye. A fear not reported in the other group.</td><td>QWB scores

<table><tr><th>Model State #</th><th>Study VA Category (n)</th><th>Utility (SD)</th></tr><tr><td>5</td><td>Legally blind in both eyes

(20/200 or worse in both eyes)</td><td>0.580 (0.07)</td></tr></table></td><td>Yes – QWB used to obtain scores from patients</td></tr>
</table>

Table 152: HRQL updated search (July 2010)

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Meets NICE reference case</th></tr>
<tr><td>1.</td><td>Awdeh 2009</td><td>Observational, cross-sectional, interviewer administered study

Sample size: n= 46</td><td>Eye conditions (% of subjects):

Unilateral BRVO (100%)

Demographics:

• Age (yrs): mean 67.8 (SD 7.9)
• Gender, female %: 50</td><td><table><tr><th>NEI VFQ-25 subscale</th><th>All BRVO patients (SD)</th></tr><tr><td>General health</td><td>61.4 (20.9)</td></tr><tr><td>General vision</td><td>67.8 (15.5)</td></tr><tr><td>Near vision</td><td>72.8 (18.9)</td></tr><tr><td>Distance vision</td><td>77.2 (18.8)</td></tr><tr><td>Driving</td><td>75.3 (23.6)</td></tr><tr><td>Peripheral vision</td><td>83.2 (20.4)</td></tr><tr><td>Colour vision</td><td>96.7 (12.5)</td></tr><tr><td>Ocular pain</td><td>76.6 (20.2)</td></tr><tr><td>Role difficulties</td><td>75.0 (27.0)</td></tr><tr><td>Dependency</td><td>91.7 (19.1)</td></tr><tr><td>Social functioning</td><td>94.0 (12.8)</td></tr><tr><td>Mental health</td><td>73.8 (20.9)</td></tr></table></td><td>N/A</td><td>Utility weights not reported</td></tr>
<tr><td>2.</td><td>Elliott 2009</td><td>Administration of:

• Nursing Home Vision-Targeted Health-Related Quality of Life Questionnaire
• VF-14
• SF-36
In a nursing home population

Sample size: n= 382</td><td>Eye conditions (% of subjects): 38.5% had both cognitive and vision impairments. 13.4% had vision impairments alone.

Demographics: Age; 74.1% in 70s or 80s</td><td><table><tr><th></th><th colspan="2">Vision impairment</th></tr><tr><th>Variable</th><th>No cognitive impairment</th><th>Cognitive impairment</th></tr><tr><td>VF-14, mean</td><td>75.0</td><td>73.6</td></tr><tr><td>SF-36, mean</td><td></td><td></td></tr><tr><td>MCS</td><td>55.3</td><td>51.2</td></tr><tr><td>PCS</td><td>33.9</td><td>34.9</td></tr></table></td><td>N/A</td><td>Utility weights not reported</td></tr>
</table>

<table>
<tr><th></th><th>Study ID</th><th>Study design</th><th>Patient population</th><th>Results (BSE or both eyes)</th><th>Results (WSE or affected/study eye only)</th><th>Meets NICE reference case</th></tr>
<tr><td>3.</td><td>Hirneiss 2010</td><td>Cross-sectional study of employees of large enterprises in Germany

Administration of VFQ-25 (German translation)

Sample size: n= 619</td><td>Eye conditions (% of subjects):
No abnormality (82.6%)
Dry eye disease (9.0%)
Keratoconus (0.6%)
Amblyopia (1.9%)
Strabismus (1.1%)
Allergic conjunctivitis (1.6%)
Retinal/vitreous (2.1%)
Ocular trauma (0.3%)
Uveitis (0.5%)
Glaucoma (0.2%)

Demographics:
Age (yrs); 42 (SD 9)
Gender, female %; 58</td><td><table><tr><th>NEI VFQ-25 subscale</th><th>All patients (SD)</th></tr><tr><td>General health</td><td>73.0 (18.1)</td></tr><tr><td>General vision</td><td>78.6 (15.7)</td></tr><tr><td>Ocular pain</td><td>85.4 (16.6)</td></tr><tr><td>Near vision</td><td>91.9 (13.1)</td></tr><tr><td>Distance vision</td><td>91.8 (11.3)</td></tr><tr><td>Social functioning</td><td>97.9 (9.0)</td></tr><tr><td>Mental health</td><td>87.4 (10.5)</td></tr><tr><td>Role difficulties</td><td>92.8 (13.8)</td></tr><tr><td>Dependency</td><td>98.4 (5.6)</td></tr><tr><td>Driving difficulties</td><td>88.7 (10.6)</td></tr><tr><td>Colour vision</td><td>97.9 (9.3)</td></tr><tr><td>Peripheral vision</td><td>93.3 (15.0)</td></tr><tr><td>Composite score</td><td>91.1 (7.4)</td></tr></table></td><td>N/A</td><td>Utility weights not reported</td></tr>
<tr><td>4.</td><td>Swamy 2009</td><td>Cross-sectional study of surviving participant of the Blue Mountains Eye Study

Administration of NEI-VFQ and SF-36

Sample size: n= 1952 (complete data available for n=1436)</td><td>Eye conditions (% of subjects): Bilateral visual impairment (2.8%), unilateral visual impairment (10.9%)

Demographics:

• Age (yrs); mean 73.8
• Gender, female %: 59</td><td>VFQ-25 composite score: mean 90.7 (9.0)</td><td>N/A</td><td>Utility weights not reported</td></tr>
<tr><td>5.</td><td>van Nispen 2009</td><td>Observational study

Administration of EQ-5D at baseline and month 5

Sample size: 296 (50</td><td>Respondents only:

Eye conditions (% of subjects):

AMD (53.1%)
Diabetic retinopathy (13.2%)
Glaucoma (5.8%)</td><td>At five months, visual acuity, musculoskeletal conditions, COPD/asthma and stroke predicted a decline in QOL (R^2=0.20). At baseline, the visually impaired older people more often reported moderate or severe problems on most EQ-5D dimensions than the two reference groups.</td><td>N/A</td><td>EQ-5D meets reference case.</td></tr>
</table>

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Meets NICE reference case
		lost to follow-up)	Cataract (5.3%) Occluded vein (5.3%) Other (17.3%) **Demographics:** Age (yrs); mean 78.0 (8.9) Gender, female %: 62.6			
6.	van Nispen 2010	Nonrandomised longitudinal study. Administration of five-dimensional Low Vision Quality of Life Questionnaire (LVQOL) at four time points **Sample size:** n= 296	Total: **Eye conditions (% of subjects):** AMD (52.6%) Diabetic retinopathy (13.3%) Glaucoma (6.1%) Cataract (5.5%) Other (22.5%) **Demographics:** Age (yrs); mean 78.4 (8.8) Gender, female %: 61.8 Baseline EQ-5D; 0.67 (0.25)	Results of estimate group-by-time-specific fixed mean regression coefficients available in paper.	N/A	LVQOL not preference-based. EQ-5D reported at baseline only.
7.	Rahi 2009	Population-based cross-sectional study Administration of Vision-related Quality of Life Core Measure 1 (VCM1) **Sample size:** n= 9330	**Eye conditions (% of subjects):** Precluded driving (1.3%) Blind (0.15%) **Demographics:** Age (yrs); All participants 44/45 years-old	Vision-related-quality of life impairment was associated with impaired visual function as measured by any parameter. Vision-related quality of life was strongly associated with being unable to work owing to permanent illness (odds ratio, 5.90; 95% CI, 3.63 -13.22)	N/A	VCM1 not preference-based measure.

	Study ID	Study design	Patient population	Results (BSE or both eyes)	Results (WSE or affected/study eye only)	Meets NICE reference case
8.	Lee 2009	Random sample of patients receiving medical care from an independent association of 48 physician groups. Administration of SF-36 **Sample size:** n= 5,021 reported complete data	**Eye conditions (% of subjects):** Cataract and glaucoma (1%) Cataract and macular degeneration (1%) Glaucoma and macular degeneration (1%) Blurred vision reported by 8%, and 13% reported trouble seeing. **Demographics:** Age (yrs); 18 - 29 (13%, 30 – 39 (24%), 40 – 49 (21%), 50 – 59 (14%), 60 – 69 (14%), 70+ (14%) Gender, female %: 64	"Trouble seeing" had a significant negative association with SF-36 physical (-1.07) and mental (-2.69) health summary score. Whilst ocular symptoms were significantly associated with SF-36 scores, having an eye disease was not after adjusting for other variables in the model.	N/A	Utility weights not reported

9.19 Appendix 19: KOL questions relating to resource use associated with routine monitoring

Approximately what percentage of secondary care consultations associated with the routine monitoring of patients with macular oedema following retinal vein occlusion occur in the following settings?

Day case _____%

Outpatient _____%

Please define typical follow up of patients with macular oedema following retinal vein occlusion. Please define typical resource use per six-month period.

Typically how many units of the following resources are required within the first six months following macular oedema?

	BRVO	CRVO
Ophthalmologist consultation		
Optical coherence tomography (OCT)		
Fluorescein angiography		
Ophthalmoscopy		

Typically how many units of the following resources are required per six-month-period (>6 months and <=3 years following macular oedema)?

	BRVO	CRVO
Ophthalmologist consultation		
Optical coherence tomography (OCT)		
Fluorescein angiography		
Ophthalmoscopy		

Typically how many total units of the following resources are required per six-month-period (>3 years following macular oedema)

	BRVO	CRVO
Ophthalmologist consultation		
Optical coherence tomography (OCT)		
Fluorescein angiography		
Ophthalmoscopy		

Treatment with an intravitreal injection of a sustained-release device into the posterior segment of the eye

Would you expect the administration of such an intravitreal injection to be performed as an outpatient or day case procedure?

Outpatient / day case (please state the % in outpatient)

Which diagnostic tests would typically be performed in association with this procedure, which are above those required in routine monitoring of patients with macular oedema following RVO?

Questionnaire responses

	Patient monitoring	
	Day case	Outpatient
1	0%	100%
2	5%	95%
3	0%	100%
4	0%	100%
Mean	**1%**	**99%**
Lower CI	-2%	95%
Upper CI	5%	102%

	Monitoring - ≤ 6 months							
	CRVO				BRVO			
	Op cont	OCT	Fluores	O'moscopy	Op cont	OCT	Fluores	O'moscopy
1	3	3	1	0	3	3	1	0
2	2	2	1	2	2	2	1	2
3	4	2	1	4	4	2	1	4
4	4	0	0	4	3	1	1	3
Mean	**3**	**2**	**1**	**3**	**3**	**2**	**1**	**2**
Lower CI	2	1	0	1	2	1		1
Upper CI	4	3	1	4	4	3		4

	Monitoring - >6 months and ≤ 3 years							
	CRVO				BRVO			
	Op cont	OCT	Fluores	O'moscopy	Op cont	OCT	Fluores	O'moscopy
1	3	3	0	3	3	3	0	3
2	2	1	0	2	2	1	0	2
3	3	0	0	3	3	0	0	3
4	1	0	0	1	1	1	0.25	1
Mean	**2**	**1**	**0**	**2**	**2**	**1**	**0**	**2**
Lower CI	1	0		1	1	0	0	1
Upper CI	3	2		3	3	2	0	3

	Monitoring - > 3 years							
	CRVO				BRVO			
	Op cont	OCT	Fluores	O'moscopy	Op cont	OCT	Fluores	O'moscopy
1	0	0	0	0	0	0	0	0
2*	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

* Only in pts with complications

	Where will an intravitreal injection be administered?		
	OP	DC	Mix
1	100%		
2		100%	
3		100%	
4	No reponse		
	Additional diagnostic tests associated with intravitreal injection		
1	None		
2	None		
3	None		
4	No reponse		

9.20 Appendix 20: Measures of visual acuity

Figure 42: Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and Snellen Chart

ETDRS chart

Snellen chart

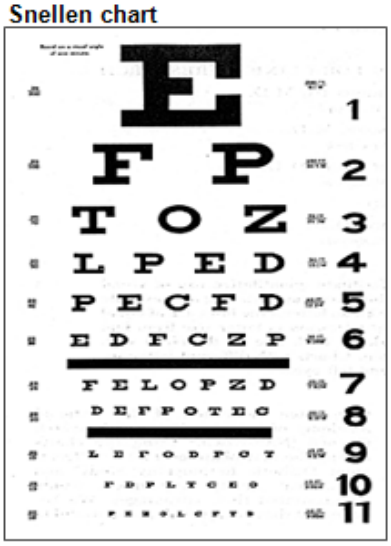


Figure 43: Letter score (ETDRS) versus Snellen equivalent

	Approximate Snellen visual acuities					
Expected score	1 metre	4 metres	6 metres	20 feet	Decimal fraction	LogMAR
34-38	1/10	4/40	6/60	20/200	0.10	+1.0
39.43	118	4/32	6/48	20/160	0.125	+0.9
44-48	1/6.25	4/25	6/38	20/125	0.16	+0.8
49-53	1/5	4 20	6/30	20 100	0.20	+0.7
54-58	1/4	4 16	6/24	20/80	0.25	+0.6
59-63	1/3.15	4 12.6	6/20	20/62.5	0.32	+0.5
64-68	1/2.5	4 10	6/15	20/50	0.40	+0.4
69-73	1/2	4/8	6/12	20/40	0.50	+0.3
74-78	1/1.6	4/6.4	6/10	20/32	0.625	+0.2
79-83	1/1.25	4/5	6/7.5	20/25	0.80	+0.1
84-88	1/1	4/4	6/6	20/20	1.00	0.0
89-93	1/0.8	4/3.2	6/5	20 16	1.25-	0.1
94-98	1/0.625	4/2.5	6/3.75	20/12.5	1.60	-0.2

9.21 Appendix 21: Parameter table

Table 153: Parameter table

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Affected eye (% WSE)	90%	Allergan data on file.	68%	100%	+/- 25%	None				
Fellow eye involvement (annual %)	3.00%	Brown GC, et al. Ophthalmic Epidemiol. 2002 Feb;9(1):1-10.	1.00%	5.00%	Range used in Brown GC, et al. Ophthalmic Epidemiol. 2002 Feb;9(1):1-10.	None				
Fellow eye involvement Weibull: ln(lambda)	-3.91	Parametric Weibull regression based on Hayreh SS, Zimmerman MB, Podhajsky P. Am J Ophthalmol. 1994 Apr 15;117(4):429-41.	-4.248	-3.564	95% CI. Weibull regression	Normal	0.17			
Fellow eye involvement Weibull: ln(gamma)	-0.73	Parametric Weibull regression based on Hayreh SS, Zimmerman MB, Podhajsky P. Am J Ophthalmol. 1994 Apr 15;117(4):429-41.	-0.879	-0.578	95% CI. Weibull regression	Normal	0.08			

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
% CRVO	34.5%	GENEVA 008 & 009	31.9%	37.1%	95% CI. binomial	Beta	0.01	1,267	437	828
CRVO: AE uplift % for treatment 3	15%	Assumption	11%	19%	+/- 25%	None				
CRVO: AE uplift % for treatment 4	40%	Assumption	30%	50%	+/- 25%	None				
CRVO: AE uplift % for treatment 5	40%	Assumption	30%	50%	+/- 25%	None				
CRVO: AE uplift % for treatment 6	40%	Assumption	30%	50%	+/- 25%	None				
BRVO: AE uplift % for treatment 3	15%	Assumption	11%	19%	+/- 25%	None				
BRVO: AE uplift % for treatment 4	40%	Assumption	30%	50%	+/- 25%	None				
BRVO: AE uplift % for treatment 5	40%	Assumption	30%	50%	+/- 25%	None				
BRVO: AE uplift % for treatment 6	40%	Assumption	30%	50%	+/- 25%	None				
Mean VA for HS 0	75.00	GENEVA 008 & 009	69	81	Assumption	Normal	3.06			

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Mean VA for HS 1	63.50	GENEVA 008 & 009	59	68	Assumption	Normal	2.30			
Mean VA for HS 2	56.00	GENEVA 008 & 009	54	58	Assumption	Normal	1.02			
Mean VA for HS 3	48.50	GENEVA 008 & 009	44	53	Assumption	Normal	2.30			
Mean VA for HS 4	41.00	GENEVA 008 & 009	39	43	Assumption	Normal	1.02			
Mean VA for HS 5	33.00	GENEVA 008 & 009	28	38	Assumption	Normal	2.55			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Entry age (years)	64.5	GENEVA 008 & 009	63.9	65.1	95% CI. Normal distribution	Normal	0.33	1,267		
% male	53.4%	GENEVA 008 & 009	51%	56%	95% CI binomial	Beta	0.01	1,267	677	590
Legally blind death rate multiplier	1.54	Christ SL, et al. Invest Ophthalmol Vis Sci. 2008 Aug;49(8):3318-23.	1.28	1.86	95% CI	Normal	0.15			
Discount rate for benefits	3.5%	NICE methods guide	0.0%	6.0%	Arbitrary	None				

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Discount rate for costs	3.5%	NICE methods guide	0.0%	6.0%	Arbitrary	None				
OZURDEX implant cost	£870	Allergan Europe	£653	£1,088	+/- 25%	None				
Intravitreal injection procedure cost	£648	National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures - category 1 (Day case assumed)	£391	£824	Lower/upper quartile unit cost (weighted by activity). SE is approximation base on IQR.	Normal	2.03			
Phakic patients at baseline	87.4%	GENEVA 008 & 009	83.9%	90.4%	95% CI binomial	Beta	0.02	421	368	53
Risk with first OZURDEX treatment	0.27%	GENEVA 008 & 009	0.0%	1.5%	95% CI binomial	Beta	0.00	368	1	367
Risk with second OZURDEX treatment	0.99%	GENEVA 008 & 009	0.2%	2.9%	95% CI binomial	Beta	0.01	302	3	299
Multiplier for risk with each extra treatment	2	Assumption	1	3	Arbitrary	None				
Disutility (for one month)	0.00	Assumed to be included in changes in visual	0.00	0.10	Arbitrary	None				

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
		acuity.								
After first treatment - additional office visits with eye exam for IOP	1	Expert opinion. Estimate of 1 additional consultation per administration.	1.0	3.0	Arbitrary	Gamma	0.51		4	0
After re-treatment - additional office visits with eye exam for IOP	1	Expert opinion. Estimate of 1 additional consultation per administration.	1.00	3.00	Arbitrary	Gamma	0.51		4	0
Beta-blocker unit cost	£1.55	Timolol: Timolol Eye Dps 0.25%. BNF 60	£1.16	£1.94	+/- 25%	None				
Prostaglandins unit cost	£12.48	Latanoprost: Xalatan Eye Dps 50mcg/ml. BNF 60	£9.36	£15.60	+/- 25%	None				
CA Inhibitors unit cost	£6.56	Brinzolamide : Azopt Eye Dps 10mg/ml. BNF 60	£4.92	£8.20	+/- 25%	None				
Combination unit cost	£10.05	Dorzolamide & Timolol: Cosopt Ocumeter Plus Eye Dps. BNF 60	£7.54	£12.56	+/- 25%	None				
Brimonidine unit cost	£6.85	Brimonidine Tartrate: Brimonidine Tart Eye Dps 0.2%. BNF 60	£5.14	£8.56	+/- 25%	None				

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Trabeculoplasty unit cost	£571	National Schedule of Reference Costs 2008-09 for NHS Trusts: Glaucoma - category 1. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)	£343	£712	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.03	305		
Sclerectomy unit cost	£1,278	National Schedule of Reference Costs 2008-09 for NHS Trusts: Glaucoma - category 3. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)	£813	£1,859	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.05	172		
Aqueous shunt unit cost	£1,278	National Schedule of Reference Costs 2008-09 for NHS Trusts: Glaucoma - category 3. Weighted by activity	£813	£1,859	Lower/upper quartile unit cost (weighted by activity). SE	Log	0.05	172		

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
		across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)			is approximation based on IQR.					
Cryotherapy unit cost	£1,061	National Schedule of Reference Costs 2008-09 for NHS Trusts: Glaucoma - category 2. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)	£786	£1,351	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.02	342		
Iridectomy unit cost	£1,061	National Schedule of Reference Costs 2008-09 for NHS Trusts: Glaucoma - category 2. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)	£813	£1,859	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.05	172		

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Scleral reinforcement unit cost	£689	National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures - category 1. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)	£418	£874	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.02	846		
Ophthalmology contact cost	£73	National Schedule of Reference Costs 2008-09 for NHS Trusts: Follow-up Ophthalmology (non-admitted face to face contact).	£59	£90	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.03	140		
OCT/FA/ophthalmoscopy cost	£184	National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures - category 2 (outpatient procedures).	£103	£215	Lower/upper quartile unit cost (weighted by activity). SE is	Log	0.07	66		

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
					approximation based on IQR.					
OCT/ophthalmoscopy cost	£150	National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures - category 1 (outpatient procedures).	£90	£184	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.05	95		
ophthalmoscopy cost	£150	National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures - category 1 (outpatient procedures).	£90	£184	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.05	95		
CRVO: month 0-6: Ophthalmology contact (observation)	3	Clinical expert opinion	2.25	3.75	+/- 25%	Gamma	0.38		61	0

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
CRVO: month 0-6. OCT & FA & ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 0-6. OCT & ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 0-6. ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 6-stabilisation. Ophthalmology contact (observation)	2	Clinical expert opinion	1.5	2.5	+/- 25%	Gamma	0.26		61	0
CRVO: month 6-stabilisation. OCT & FA & ophthalmoscopy (observation)	0	Clinical expert opinion	0	1	Arbitrary	None				
CRVO: month 6-stabilisation. OCT & ophthalmoscopy cost (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 6-stabilisation. ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
CRVO: month 0-6. Ophthalmology contact (Ozurdex pts.)	3	Clinical expert opinion	2.25	3.75	+/- 25%	Gamma	0.38		61	0
CRVO: month 0-6. OCT & FA & ophthalmoscopy	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 0-6. OCT & ophthalmoscopy	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 0-6. ophthalmoscopy	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 6-stabilisation. Ophthalmology contact (Ozurdex pts.)	2	Clinical expert opinion	1.5	2.5	+/- 25%	Gamma	0.26		61	0
CRVO: month 6-stabilisation. OCT & FA & ophthalmoscopy (Ozurdex pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
CRVO: month 6-stabilisation. OCT & ophthalmoscopy (Ozurdex pts.)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 6-stabilisation. ophthalmoscopy (Ozurdex pts.)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
CRVO: month 6-stabilisation. Ophthalmology contact (Ozurdex pts. NOT retreated)	2	Clinical expert opinion	1.5	2.5	+/- 25%	Gamma	0.26		61	0
CRVO: month 6-stabilisation. OCT & FA & ophthalmoscopy (Ozurdex pts. NOT retreated)	0	Clinical expert opinion	0	1	Arbitrary	None				
CRVO: month 6-stabilisation. OCT & ophthalmoscopy (Ozurdex pts. NOT retreated)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: month 6-stabilisation. ophthalmoscopy (Ozurdex pts. NOT retreated)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
CRVO: > month stabilisation. Ophthalmology contact (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
CRVO: > month stabilisation.OCT & FA & ophthalmoscopy (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
CRVO: > month stabilisation. OCT & ophthalmoscopy (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
CRVO: > month stabilisation. ophthalmoscopy (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: month 0-6: Ophthalmology contact (observation)	3	Clinical expert opinion	2.25	3.75	+/- 25%	Gamma	0.38		61	0
BRVO: month 0-6. OCT & FA & ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 0-6. OCT & ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 0-6. ophthalmoscopy (observation)	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: month 6-stabilisation. Ophthalmology contact (observation)	2	Clinical expert opinion	1.5	2.5	+/- 25%	Gamma	0.26		61	0
BRVO: month 6-stabilisation. OCT & FA & ophthalmoscopy (observation)	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: month 6-stabilisation.	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
OCT & ophthalmoscopy cost (observation)										
BRVO: month 6-stabilisation. ophthalmoscopy (observation)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 0-6. Ophthalmology contact (Ozurdex pts.)	3	Clinical expert opinion	2.25	3.75	+/- 25%	Gamma	0.38		61	0
BRVO: month 0-6. OCT & FA & ophthalmoscopy	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 0-6. OCT & ophthalmoscopy	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 0-6. ophthalmoscopy	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: month 6-stabilisation. Ophthalmology contact (Ozurdex pts.)	2	Clinical expert opinion	1.5	2.5	+/- 25%	Gamma	0.26		61	0
BRVO: month 6-stabilisation. OCT & FA & ophthalmoscopy (Ozurdex pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
BRVO: month 6-stabilisation. OCT & ophthalmoscopy (Ozurdex pts.)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 6-stabilisation. ophthalmoscopy (Ozurdex pts.)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 6-stabilisation. Ophthalmology contact (Ozurdex pts. NOT retreated)	2	Clinical expert opinion	1.5	2.5	+/- 25%	Gamma	0.26		61	0
BRVO: month 6-stabilisation. OCT & FA & ophthalmoscopy (Ozurdex pts. NOT retreated)	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: month 6-stabilisation. OCT & ophthalmoscopy (Ozurdex pts. NOT retreated)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: month 6-stabilisation. ophthalmoscopy (Ozurdex pts. NOT retreated)	1	Clinical expert opinion	0.75	1.25	+/- 25%	Gamma	0.13		61	0
BRVO: > month stabilisation. Ophthalmology contact (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
BRVO: > month stabilisation.OCT & FA & ophthalmoscopy (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: > month stabilisation. OCT & ophthalmoscopy (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
BRVO: > month stabilisation. ophthalmoscopy (all pts.)	0	Clinical expert opinion	0	1	Arbitrary	None				
CRVO D180 % treated	85.7%	GENEVA 008 & 009	0.786	0.912	95% CI binomial	Beta	0.03	133	114	19
CRVO D360 % treated	63.0%	Clinical experts panel	0.436	0.824	95% CI normal	Beta	0.10	23	14	8
CRVO D540 % treated	63.0%	Clinical experts panel	0.436	0.824	95% CI normal	Beta	0.10	23	14	8
CRVO D720 % treated	36.5%	Clinical experts panel	0.240	0.492	95% CI normal	Beta	0.06	55	20	35
CRVO D900 % treated	36.5%	Clinical experts panel	0.240	0.492	95% CI normal	Beta	0.06	55	20	35
BRVO D180 % treated	78.8%	GENEVA 008 & 009	74%	83%	95% CI binomial	Beta	0.02	287	227	61

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
BRVO D360 % treated	18.5%	Clinical experts panel	4.2%	33.0%	95% CI normal	Beta	0.07	27	5	22
BRVO D540 % treated	18.5%	Clinical experts panel	4.2%	33.0%	95% CI normal	Beta	0.07	27	5	22
BRVO D720 % treated	8.0%	Clinical experts panel	2.4%	13.6%	95%CI normal	Beta	0.03	91	7	83
Dirichlet sampling for transition matrices (2=yes, 0=no)	0.00	If this value is equal to 2, transition probabilities are drawn from a Dirichlet distribution.	0	0	In PSA, this value is set to 2	None				
Tx 1: Beta-blockers % on meds	14.3%	GENEVA 008 & 009	11%	18%	95% CI binomial	Beta	0.02	395	56	338
Tx 1: Prostaglandins % on meds	8.8%	GENEVA 008 & 009	6%	12%	95% CI binomial	Beta	0.01	392	35	358
Tx 1: CA Inhibitors % on meds	5.0%	GENEVA 008 & 009	3%	8%	95% CI binomial	Beta	0.01	376	19	357
Tx 1: Combination % on meds	10.2%	GENEVA 008 & 009	8%	14%	95% CI binomial	Beta	0.02	390	40	350
Tx 1: Brimonidine % on meds	10.0%	GENEVA 008 & 009	7%	13%	95% CI binomial	Beta	0.02	396	40	357

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Tx 1: Beta-blockers days on meds	92.3	GENEVA 008 & 009	77.8	106.8	95% CI normal	Gamma	7.40		156	1
Tx 1: Prostaglandins days on meds	103.4	GENEVA 008 & 009	92.5	114.3	95% CI normal	Gamma	5.56		346	0
Tx 1: CA inhibitors days on meds	80.4	GENEVA 008 & 009	53.6	107.2	95% CI normal	Gamma	13.67		35	2
Tx 1: Combination days on meds	115.2	GENEVA 008 & 009	100.9	129.5	95% CI normal	Gamma	7.30		249	0
Tx 1: Brimonidine days on meds	90	GENEVA 008 & 009	75.1	104.9	95% CI normal	Gamma	7.60		140	1
Tx > 1: Beta-blockers % on meds	16.7%	GENEVA 008 & 009	13%	21%	95% CI binomial	Beta	0.02	317	53	264
Tx > 1: Prostaglandins % on meds	11.7%	GENEVA 008 & 009	9%	16%	95% CI binomial	Beta	0.02	314	37	277
Tx > 1: CA Inhibitors % on meds	4.7%	GENEVA 008 & 009	3%	8%	95% CI binomial	Beta	0.01	298	14	284
Tx > 1: Combination % on meds	12.9%	GENEVA 008 & 009	10%	17%	95% CI binomial	Beta	0.02	314	41	274
Tx > 1: Brimonidine % on	10.6%	GENEVA 008 & 009	8%	14%	95% CI	Beta	0.02	314	33	281

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
meds					binomial					
Tx > 1: Beta-blockers days on meds	127.3	GENEVA 008 & 009	111.9	142.7	95% CI normal	Gamma	7.86		262	0
Tx > 1: Prostaglandins days on meds	113.6	GENEVA 008 & 009	94.1	133.1	95% CI normal	Gamma	9.95		130	1
Tx > 1: CA inhibitors days on meds	105.3	GENEVA 008 & 009	72.4	138.2	95% CI normal	Gamma	16.79		39	3
Tx > 1: Combination days on meds	135.8	GENEVA 008 & 009	118.2	153.4	95% CI normal	Gamma	8.98		229	1
Tx > 1: Brimonidine days on meds	127.5	GENEVA 008 & 009	106.7	148.3	95% CI normal	Gamma	10.61		144	1
Tx 1: Trabeculoplasty: % pts	0.24%	GENEVA 008 & 009	0.0%	1.3%	95% CI normal	Beta	0.00	213	1	213
Tx 1: Sclerectomy: % pts	0.24%	GENEVA 008 & 009	0.0%	1.3%	95% CI binomial	Beta	0.00	213	1	213
Tx 1: Aqueous Shunt: % pts	0.24%	GENEVA 008 & 009	0.0%	1.3%	95% CI binomial	Beta	0.00	213	1	213
Tx 1: Cryotherapy: % pts	0.24%	GENEVA 008 & 009	0.0%	1.3%	95% CI binomial	Beta	0.00	213	1	213

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Tx 1: Iridectomy: % pts	0.00%	GENEVA 008 & 009	0.0%	0.9%	95% CI binomial	None				
Tx 1: Sclerectomy: % pts	0.24%	GENEVA 008 & 009	0.0%	1.3%	95% CI binomial	Beta	0.00	213	1	213
Tx > 1: Trabeculoplasty: % pts	0.59%	GENEVA 008 & 009	0.1%	2.1%	95% CI binomial	Beta	0.01	218	1	216
Tx > 1: Sclerectomy: % pts	0.00%	GENEVA 008 & 009	0.0%	1.1%	95% CI binomial	None				
Tx > 1: Aqueous Shunt: % pts	0.00%	GENEVA 008 & 009	0.0%	1.1%	95% CI binomial	None				
Tx > 1: Cryotherapy: % pts	0.00%	GENEVA 008 & 009	0.0%	1.1%	95% CI binomial	None				
Tx > 1: Iridectomy: % pts	0.29%	GENEVA 008 & 009	0.0%	1.6%	95% CI binomial	Beta	0.00	170	0	170
Tx > 1: Sclerectomy: % pts	0.00%	GENEVA 008 & 009	0.0%	1.1%	95% CI binomial	None				
Retinal tears, Procedure 1: % of pts. (initial treatment)	0.48%	GENEVA 008 & 009	0.1%	1.7%	95% CI binomial	Beta	0.00	424	2	419
Retinal tears, Procedure 1: %	0.29%	GENEVA 008 & 009	0.0%	1.6%	95% CI	Beta	0.00	336	1	340

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
of pts. (retreatment)					binomial					
Retinal tears/detachments Procedure 1 cost	£689	National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures Category 1. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)	£418	£874	Lower/upper quartile unit cost (weighted by activity). SE is approximation based on IQR.	Log	0.02	846		
Retinal detachments, Buckling operations for attachment of retina: % of pts. (initial treatment)	0.24%	GENEVA 008 & 009	0.0%	1.3%	95% CI binomial	Beta	0.00	424	1	420
Retinal detachments, Buckling operations for attachment of retina: % of pts. (retreatment)	0.29%	GENEVA 008 & 009	0.0%	1.3%	95% CI binomial	Beta	0.00	513	1	340
Cataract cost	£892	National Schedule of Reference Costs 2008-09 for NHS Trusts: Non-Surgical Ophthalmology with length of stay 2 days	£521.64	£1,035.35	Lower/upper quartile unit cost (weighted by activity). SE	Log	0.01	2,578		

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
		or more & Non-Surgical Ophthalmology with length of stay 1 day or less. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)			is approximation based on IQR.					
Costs of vision loss: Community care unit cost	£6,708.00	Curtis L. Unit Costs of Health and Social Care 2009. Canterbury, UK: Personal Social Services Research Unit; 2009.	£2,548.00	£6,708.00	Lower bound is low cost community care package for the elderly (excluding accommodation costs)	Gamma	1061.24		40	168
Costs of vision loss: Residential care unit cost	£23,972.00	Curtis L. Unit Costs of Health and Social Care 2009. Canterbury, UK: Personal Social Services Research Unit; 2009.	£6,864.00	£47,996.00	Upper: Annual cost for local authority residential care. Lower: Annual cost	Gamma	10493.05		5	4593

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
					for local authority sheltered housing for older people (housing costs only)					
Costs of vision loss: Depression unit cost	£498.00	Colquitt JL, et al. Health Technol Assess. 2008 May;12(16):iii-iv, ix-201. Uplifted using pay and prices index 2008/09.	£498.00	£498.00	This value is not varied.	None				
Costs of vision loss: Hip replacement unit cost	£5,336.00	National Schedule of Reference Costs 2008-09 for NHS Trusts: Intermediate hip procedures for trauma without CC. Non-elective inpatient HRG code HA13C	£4,499.00	£6,033.00	Lower/upper quartile unit cost. SE is approximation based on IQR.	Log	0.01	244		
Costs of vision loss: Community care % uptake	6%	Colquitt JL, et al. Health Technol Assess. 2008 May;12(16):iii-iv, ix-201.	6.0%	40.0%	Low/High values in Colquitt et al.	Beta	0.09		0	7

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
Costs of vision loss: Residential care % uptake	30%	Colquitt JL, et al. Health Technol Assess. 2008 May;12(16):iii-iv, ix-201.	15.0%	56.0%	Low/High values in Colquitt et al.	Beta	0.10		5	12
Costs of vision loss: Depression % uptake	39%	Colquitt JL, et al. Health Technol Assess. 2008 May;12(16):iii-iv, ix-201.	6.0%	50.0%	Low/High values in Colquitt et al.	Beta	0.11		7	12
Costs of vision loss: Hip replacement % uptake	5%	Colquitt JL, et al. Health Technol Assess. 2008 May;12(16):iii-iv, ix-201.	0.5%	24.7%	Low/High values in Colquitt et al.	Beta	0.06		1	12
CRVO: trial probability of resolution (>=69)	50%	GENEVA 008 & 009	16%	84%	95% CI binomial	Beta	0.177	8	4	4
CRVO: trial probability of resolution (59-68)	67%	GENEVA 008 & 009	9%	99%	95% CI binomial	Beta	0.272	3	2	1
CRVO: trial probability of resolution (54-58)	42%	GENEVA 008 & 009	0%	100%	95% CI binomial	Beta	0.272	2	1	1
CRVO: trial probability of resolution (44-53)	100%	GENEVA 008 & 009	16%	100%	95% CI binomial	Beta		2	2	0
CRVO: trial probability of resolution (39-43)	0%	GENEVA 008 & 009	0%	98%	95% CI binomial	Beta		1	0	1
CRVO: trial probability of	0%	GENEVA 008 & 009	0%	52%	95% CI	Beta		5	0	5

Variable	Default value	Reference	Lower value	Upper value	Reference for Uncertainty	Distribution in PSA	S.E.	n	Alpha	Beta
resolution (<=38)					binomial					
BRVO: trial probability of resolution (>=69)	84%	GENEVA 008 & 009	66%	95%	95% CI binomial	Beta	0.066	31	26	5
BRVO: trial probability of resolution (59-68)	56%	GENEVA 008 & 009	30%	80%	95% CI binomial	Beta	0.124	16	9	7
BRVO: trial probability of resolution (54-58)	29%	GENEVA 008 & 009	4%	71%	95% CI binomial	Beta	0.171	7	2	5
BRVO: trial probability of resolution (44-53)	25%	GENEVA 008 & 009	1%	81%	95% CI binomial	Beta	0.217	4	1	3
BRVO: trial probability of resolution (39-43)	0%	GENEVA 008 & 009	0%	84%	95% CI binomial	Beta		2	0	2
BRVO: trial probability of resolution (<=38)	0%	GENEVA 008 & 009	0%	98%	95% CI binomial	Beta		1	0	1

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Table 154: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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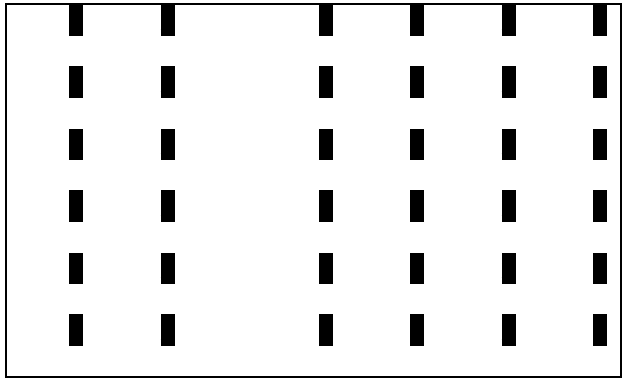
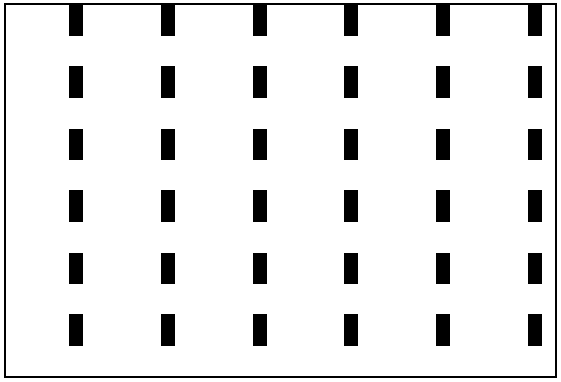
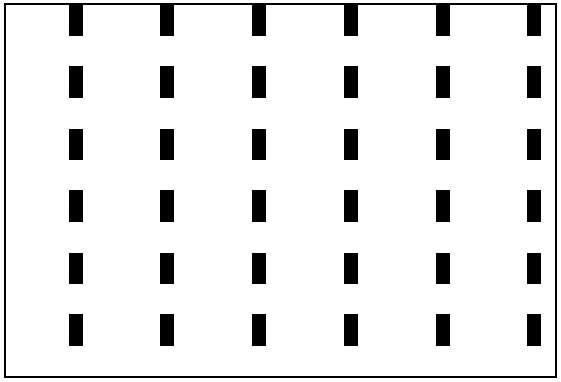
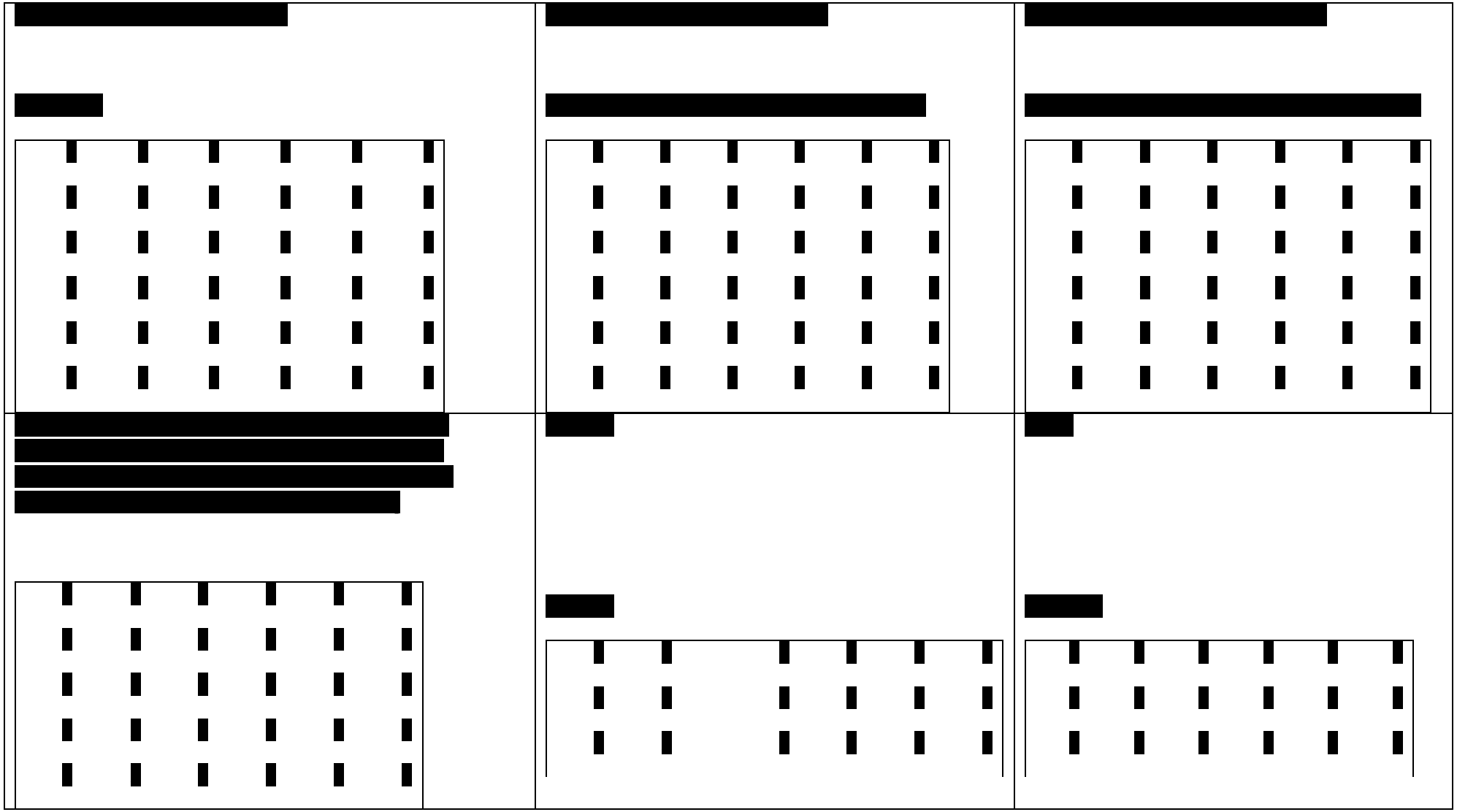
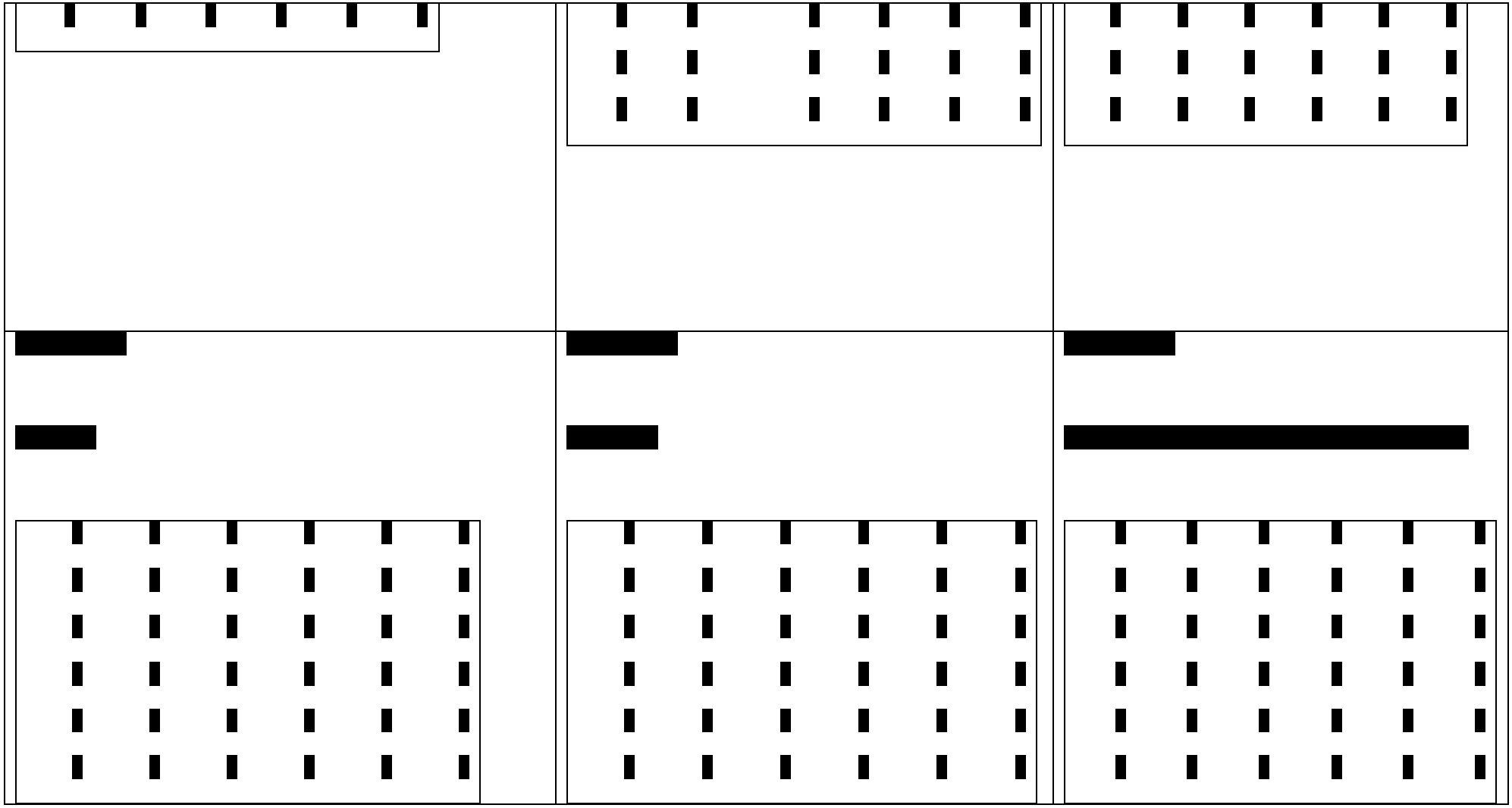
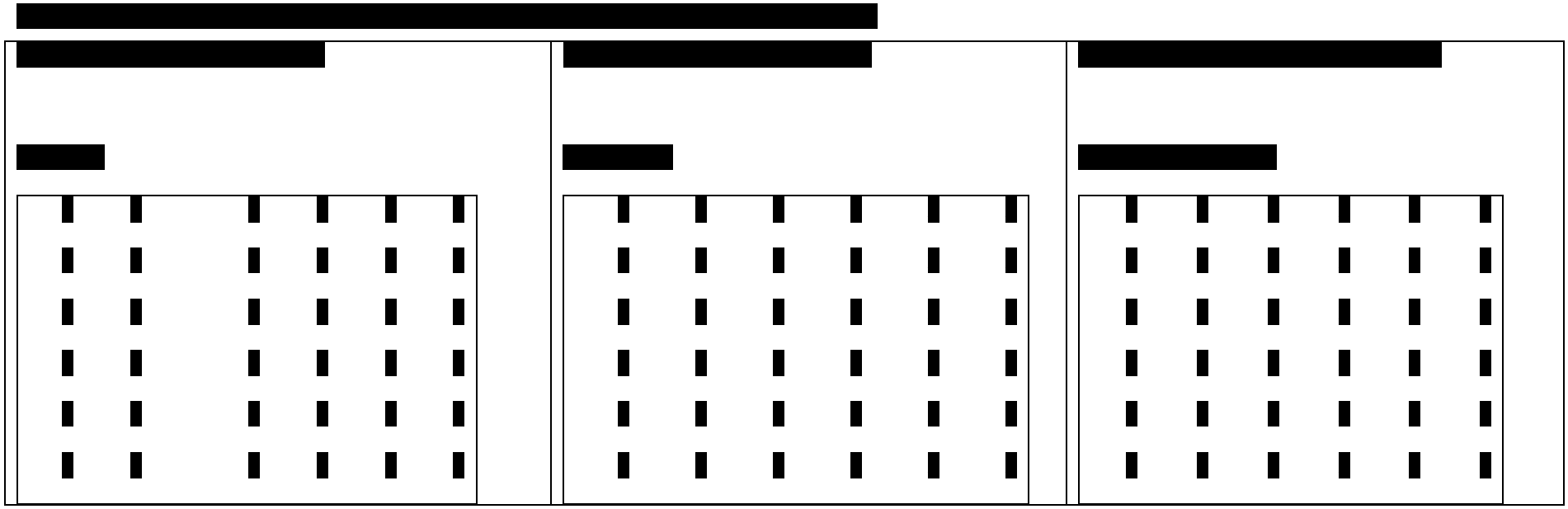
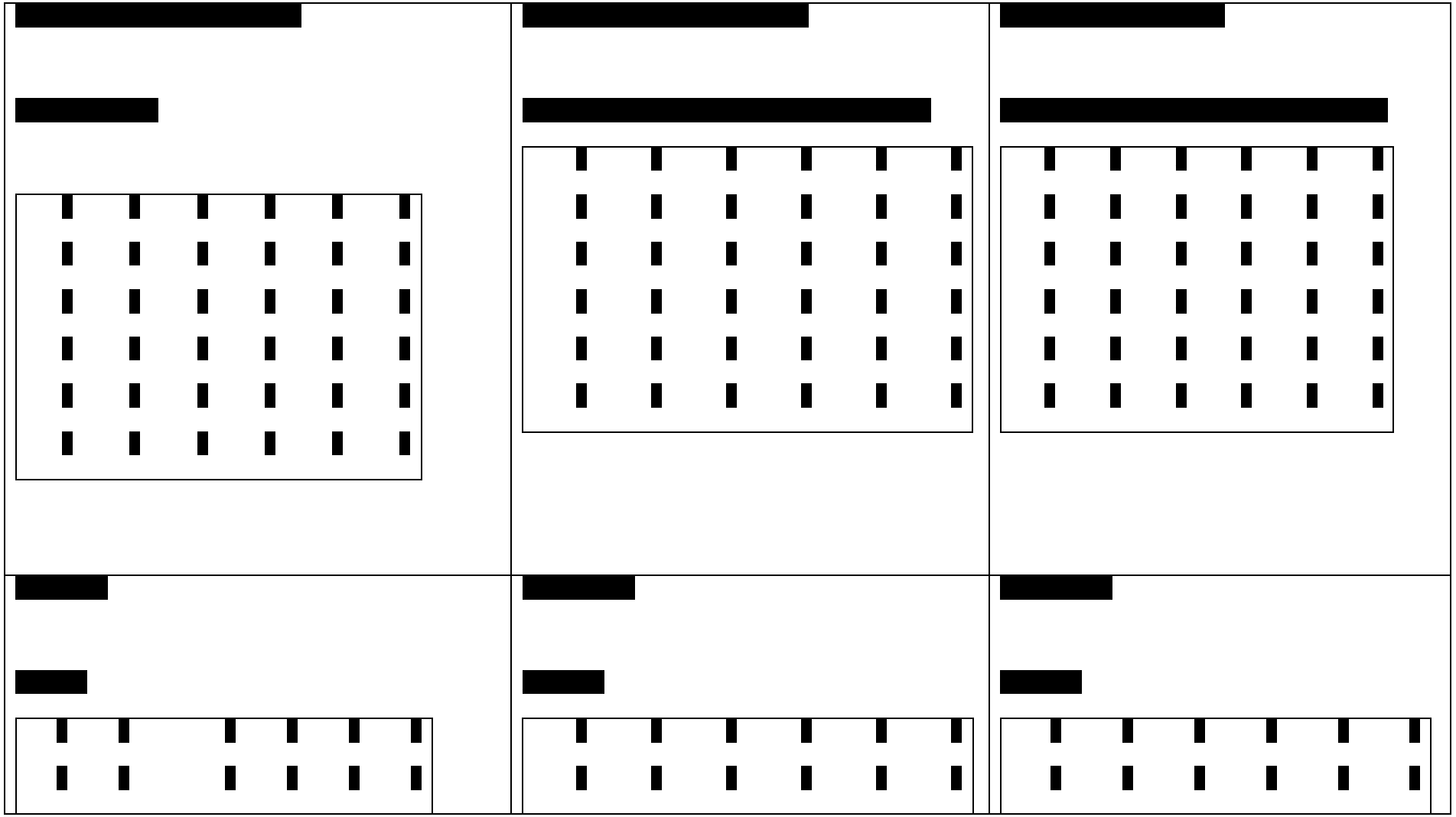
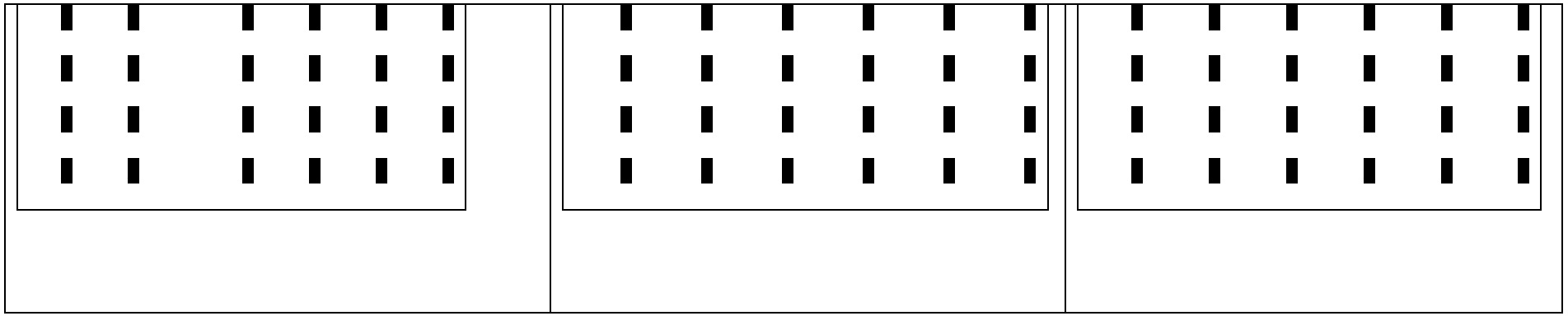
[redacted] 	[redacted] 	[redacted] 

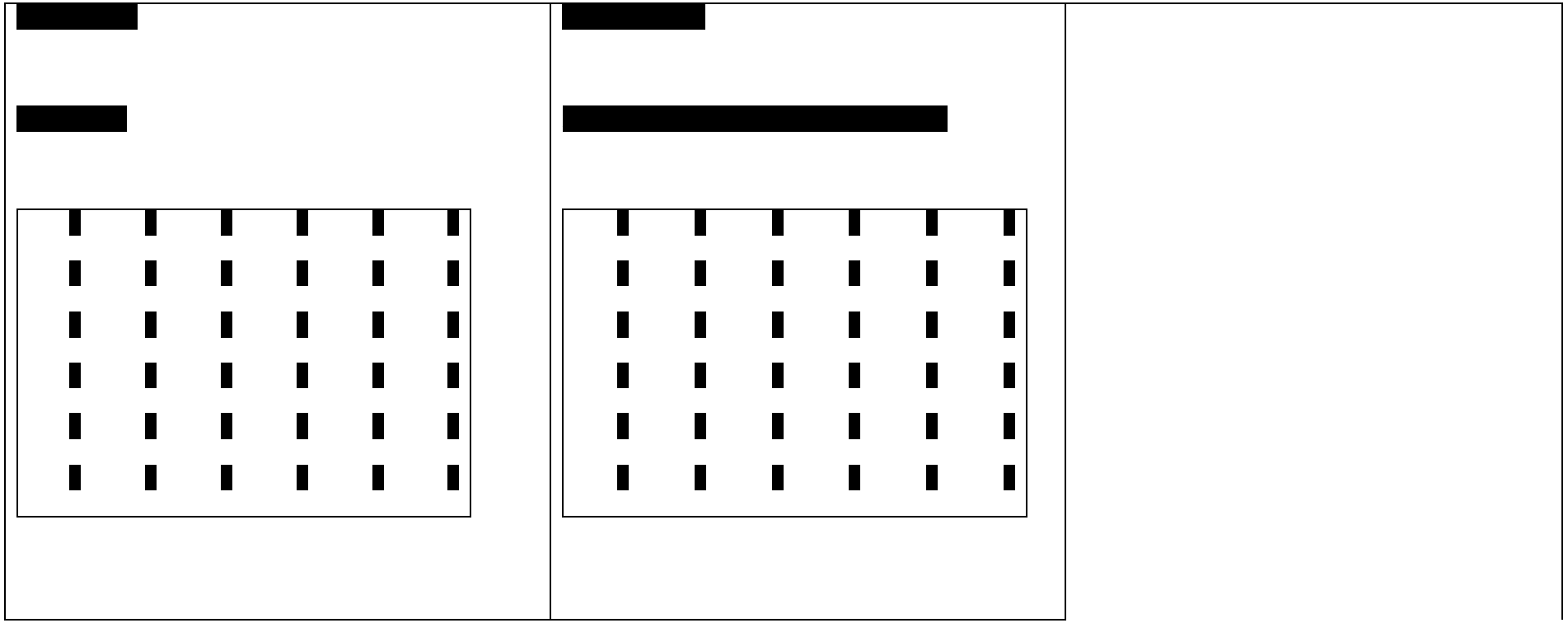


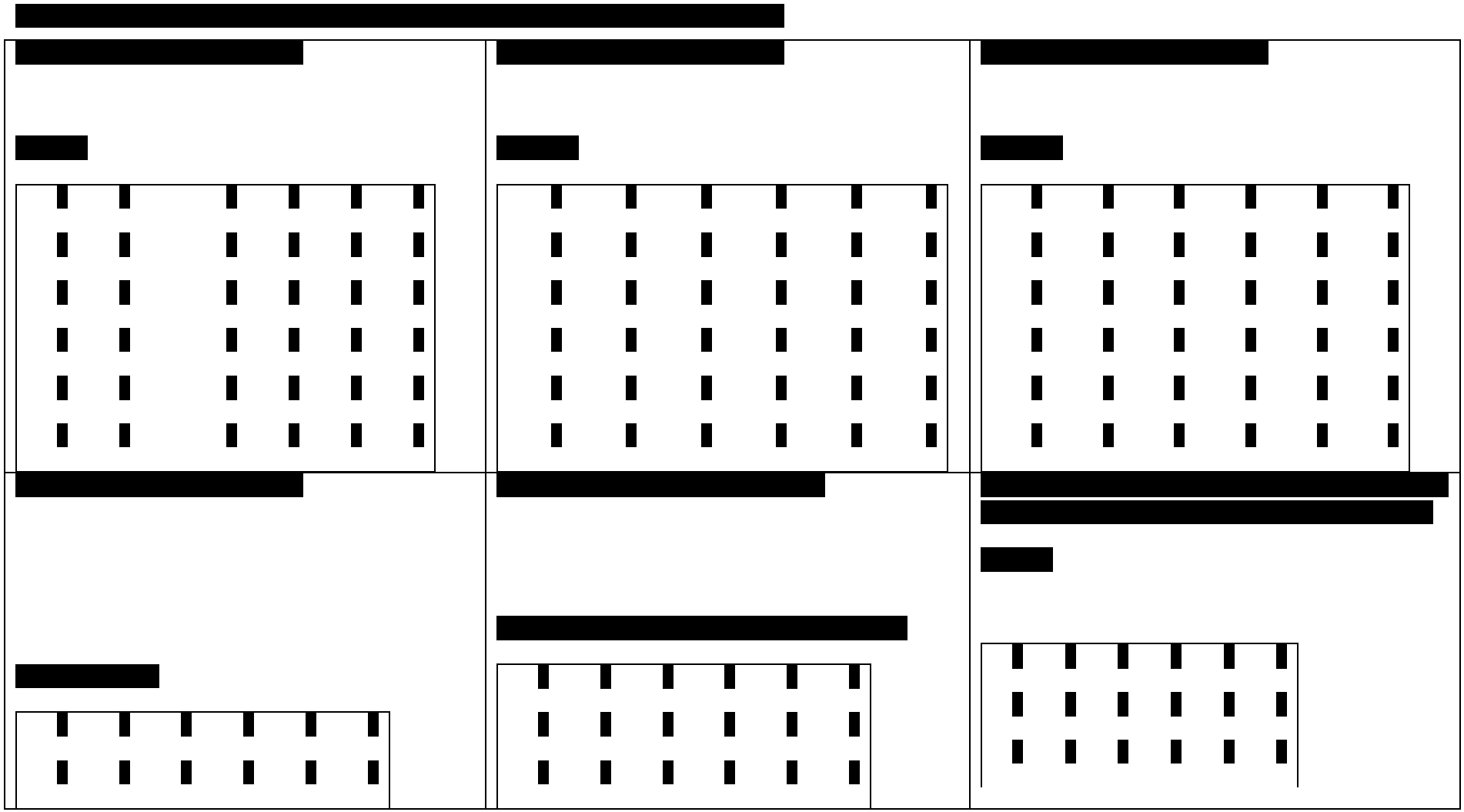


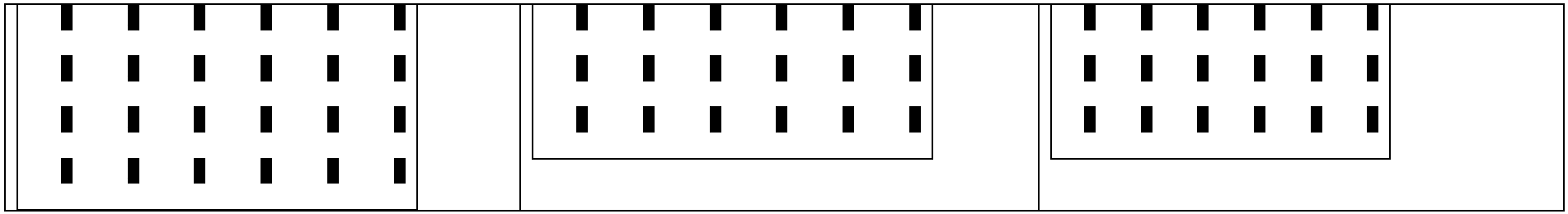


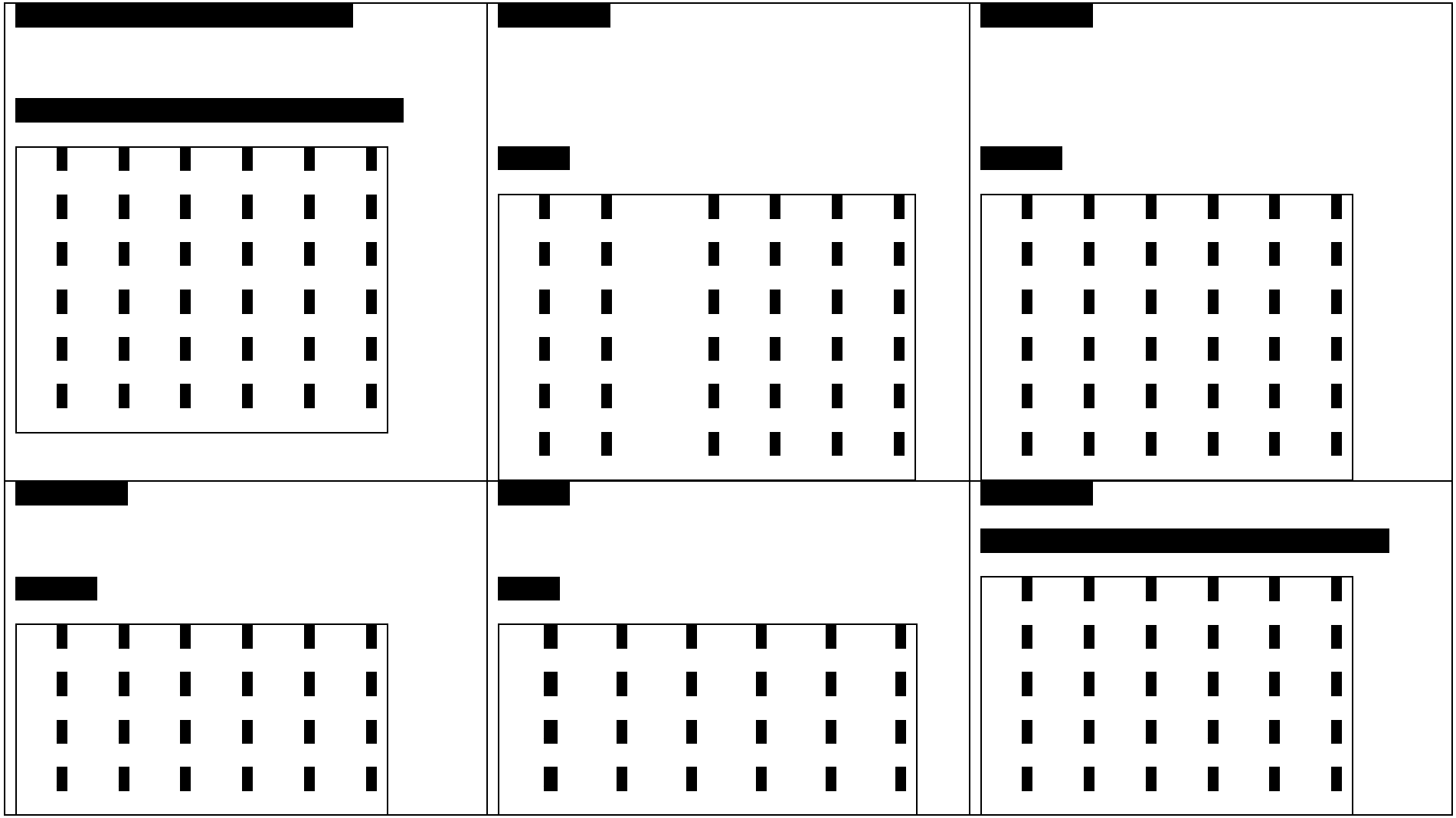


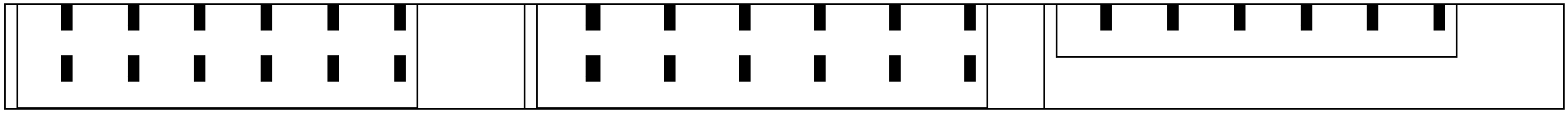












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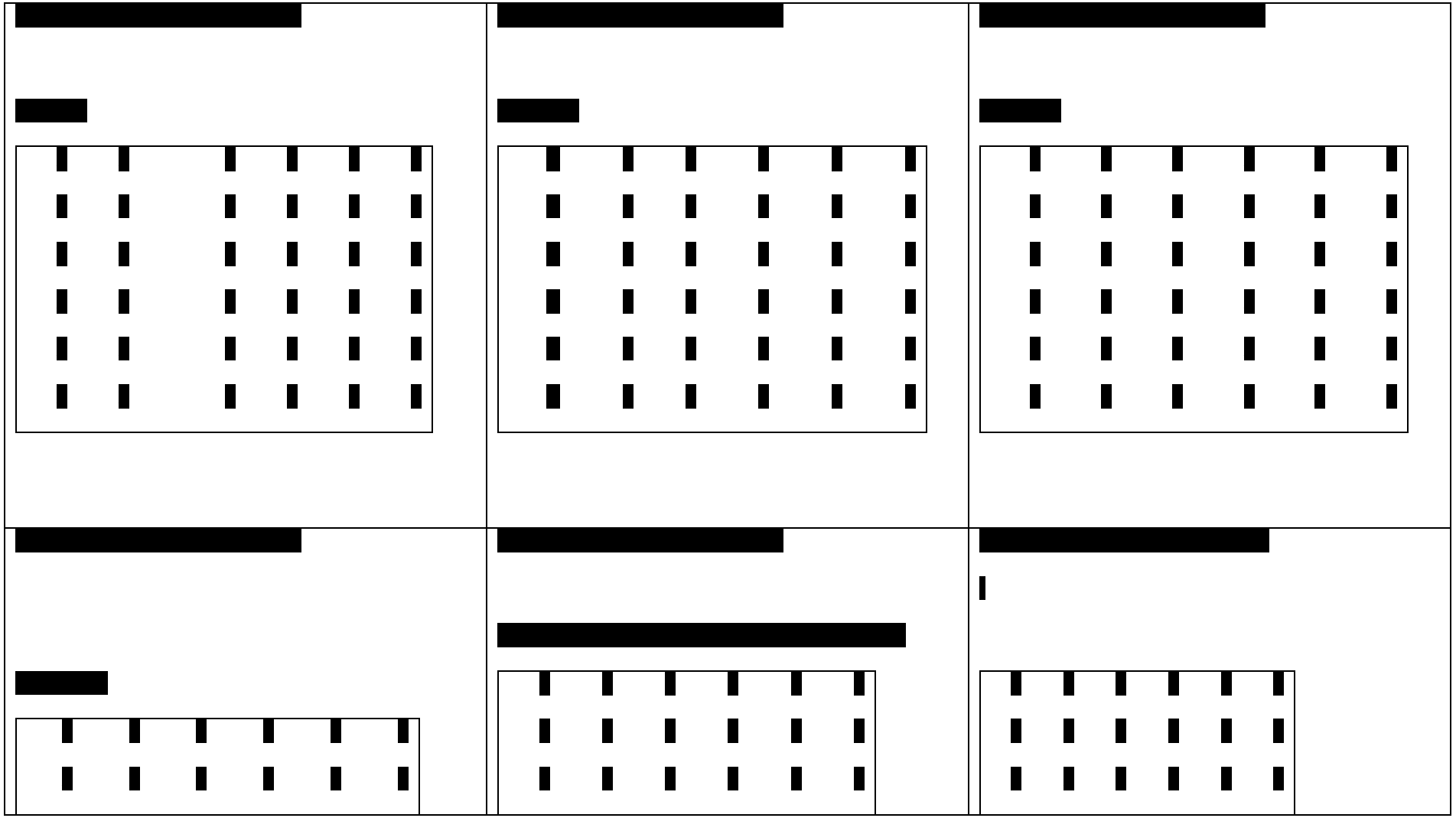
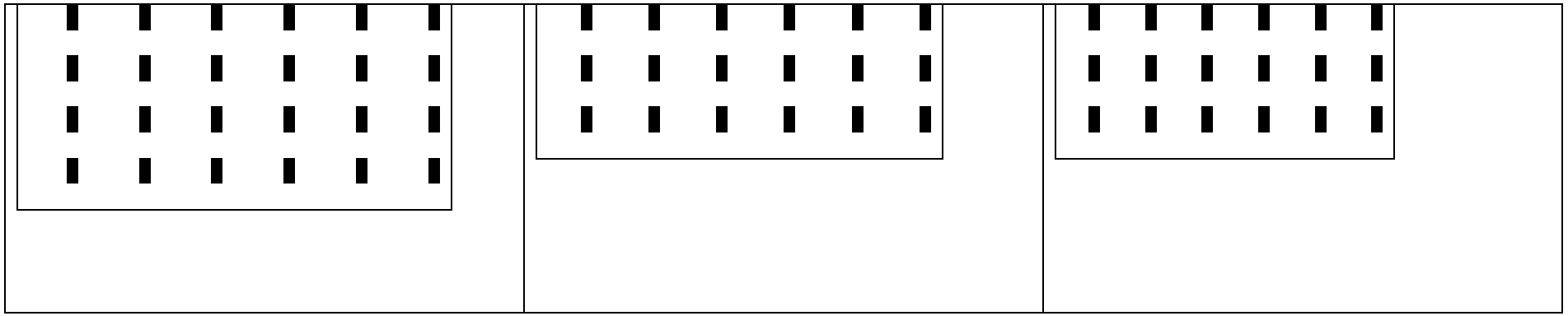
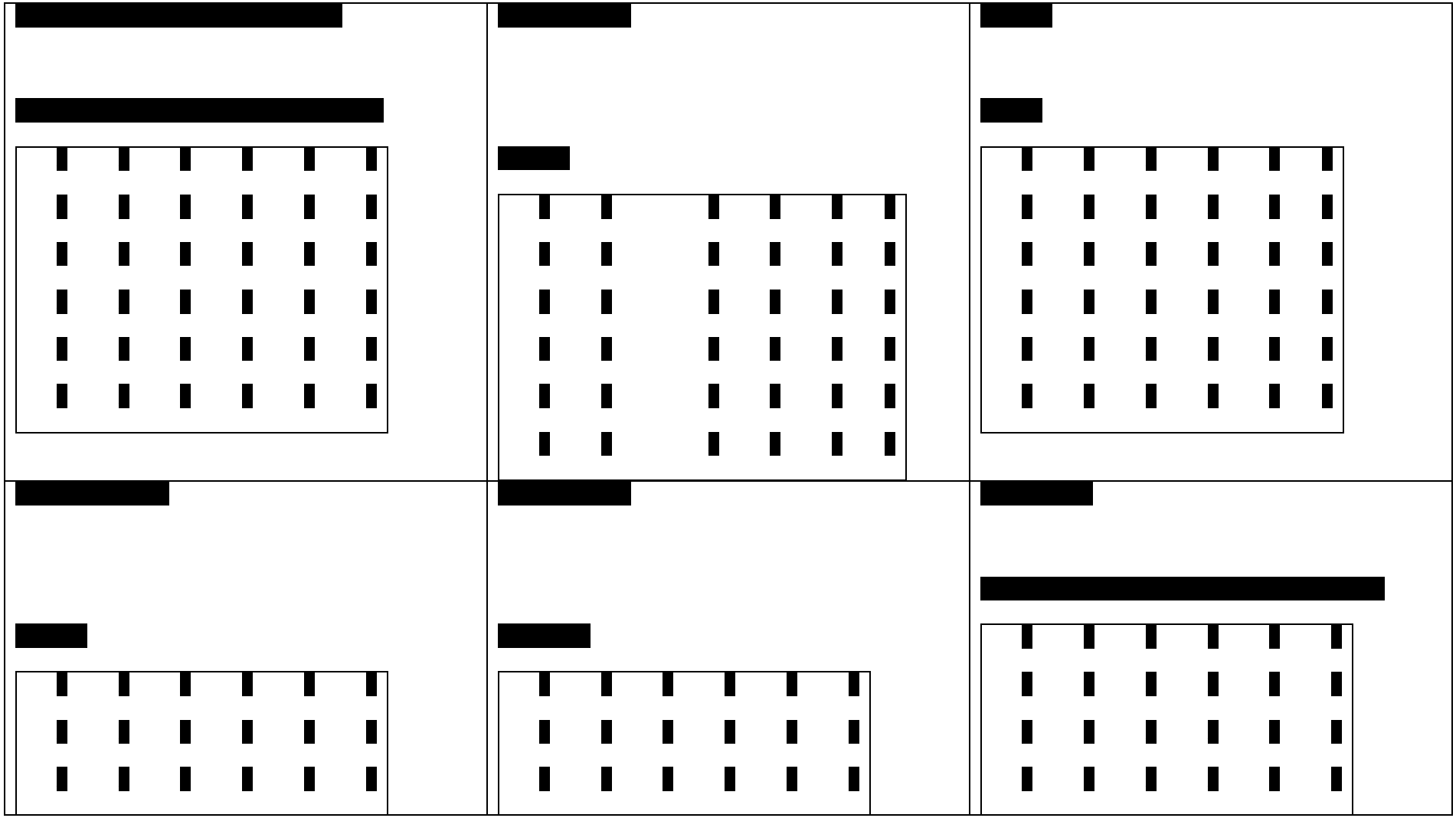
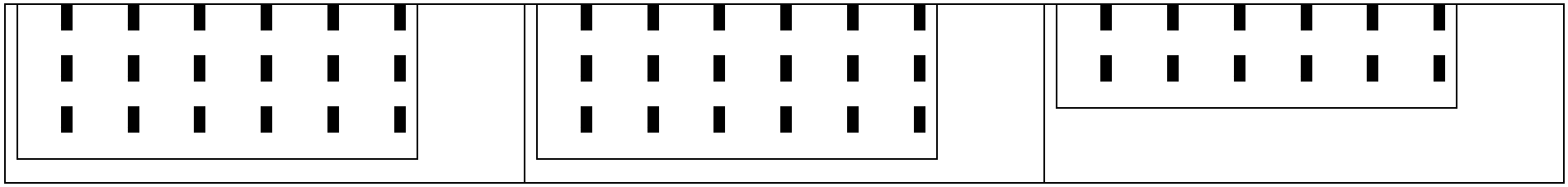








9.23 Appendix 23: Markov traces

Figure 44: Markov traces for CRVO and BRVO (used in estimation of all RVO)

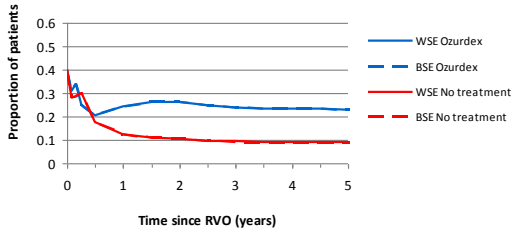
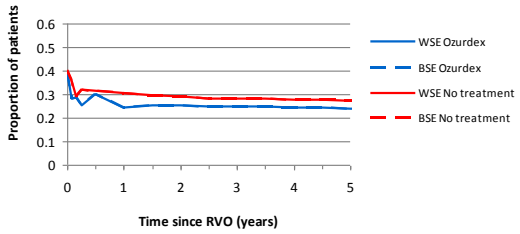
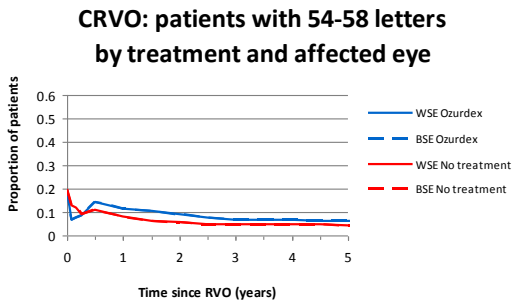
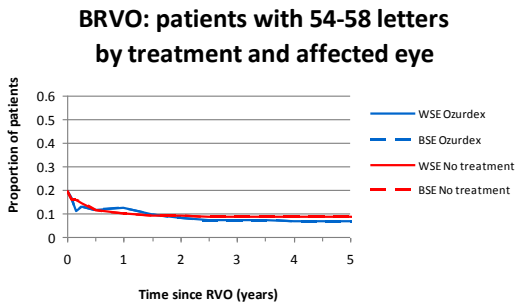
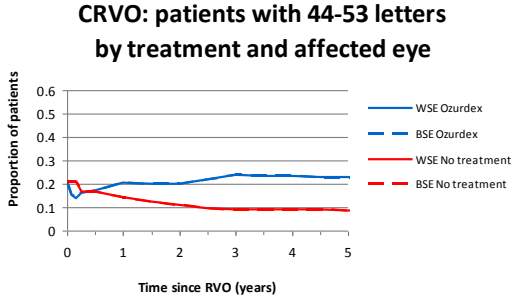
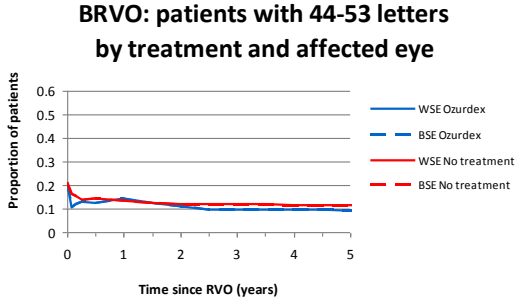
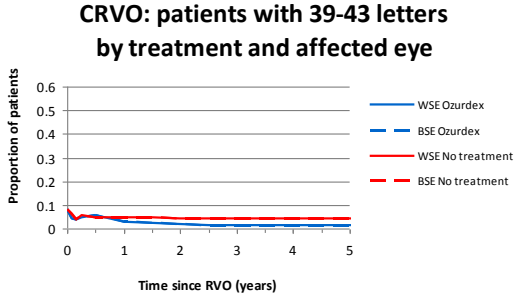
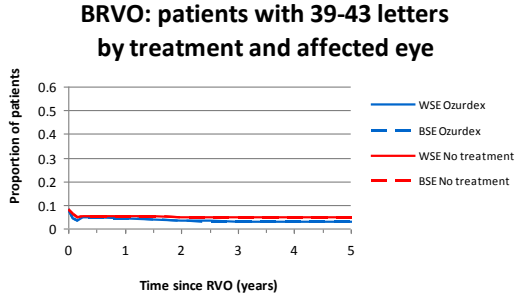
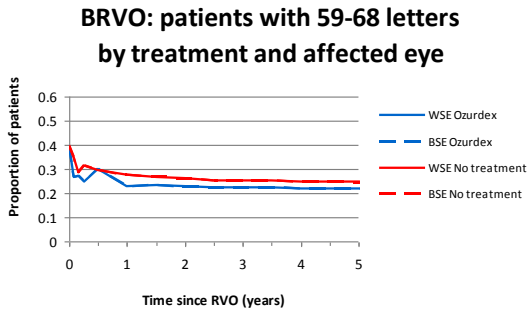
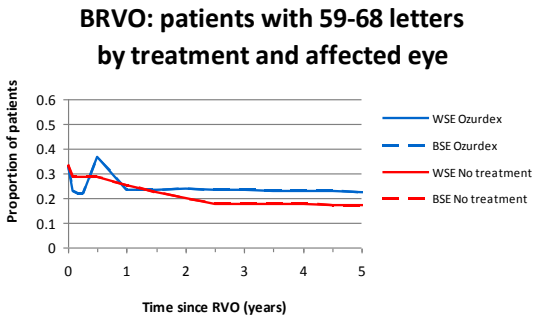
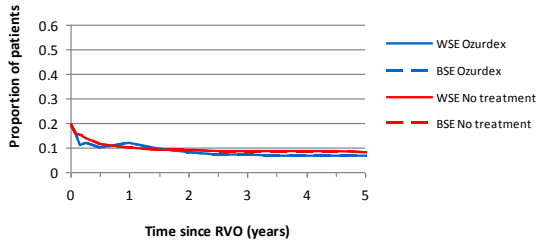
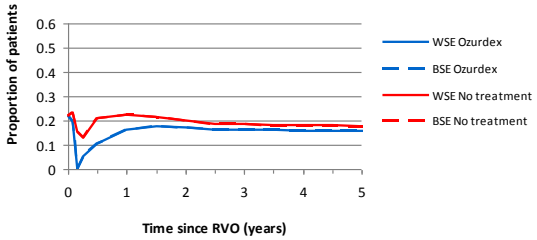
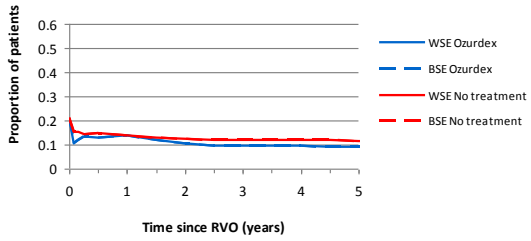
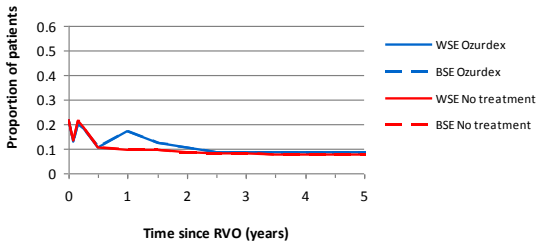
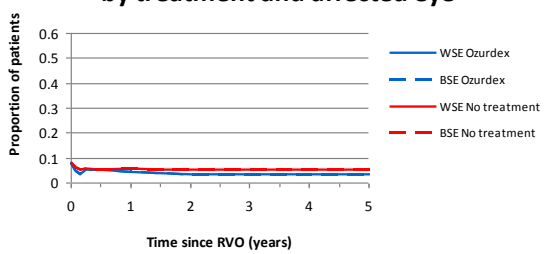
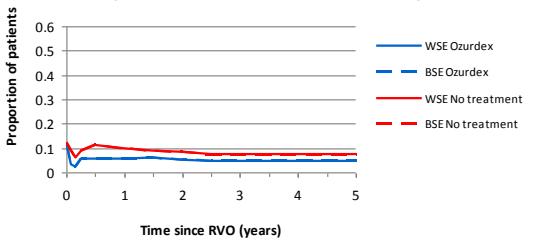
CRVO	BRVO
	
	
	
	

Figure 45: Markov traces for BRVO macular haemorrhage and BRVO with previous laser

BRVO with macular haemorrhage	BRVO with previous laser therapy
	
	
	
	

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- *an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined*
- *an executable electronic copy of the economic model has been submitted*
- *the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.*

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).