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)

Response to Evidence Review Group Questions

NOVEMBER 5, 2010

Section A: Clarification on effectiveness data

A1. Please can you provide the clinical trial reports for the GENEVA 008 and 009 studies and indicate on the checklist the confidentiality status of the information contained in the reports?

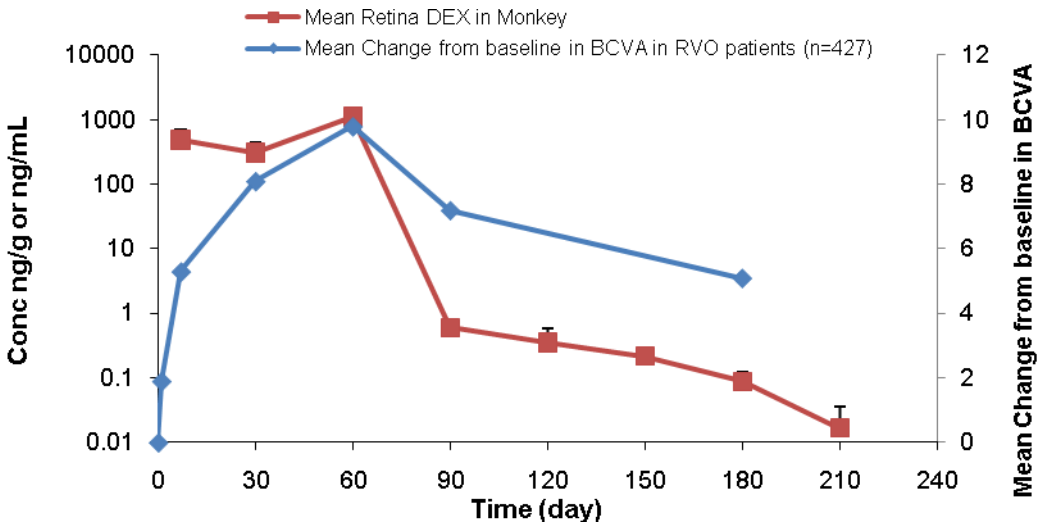
Please find the clinical study reports from 206207-008 and 206207-009 provided separately from this document.

A2. (Page 53, table 19.) Is there any variation in the volume of dexamethasone released from the implant over the course of 180 days (i.e. are there peaks rather than a steady release)? If so, please comment on how this variation may relate to the results in visual acuity at each time point (30, 60, 90, 180 days).

Ozurdex was designed to release dexamethasone in a broadly biphasic manner, with an initially high rate (loading phase) to rapidly reduce inflammation and oedema, and more gradually thereafter (maintenance phase) to enable the anti-inflammatory response to last for up to six months. Glucocorticosteroids such as dexamethasone exert their anti-inflammatory effects by influencing multiple signal transduction pathways including vascular endothelial growth factor (VEGF)(1-3). By binding to cytoplasmic glucocorticoid receptors, corticosteroids in high doses increase the activation of anti-inflammatory genes, while at low concentrations have a role in the suppression of activated inflammatory genes(2, 4), thus maintaining the anti-inflammatory response. The Ozurdex release profile is comparable to the 'pulse-dose' concept for systemic corticosteroid therapy, which is employed to reduce side effects .

For ethical reasons, the in vivo release and retina dexamethasone concentration-time profile of Ozurdex was determined in non-human primates as a close surrogate to the human eye (Figure 1).

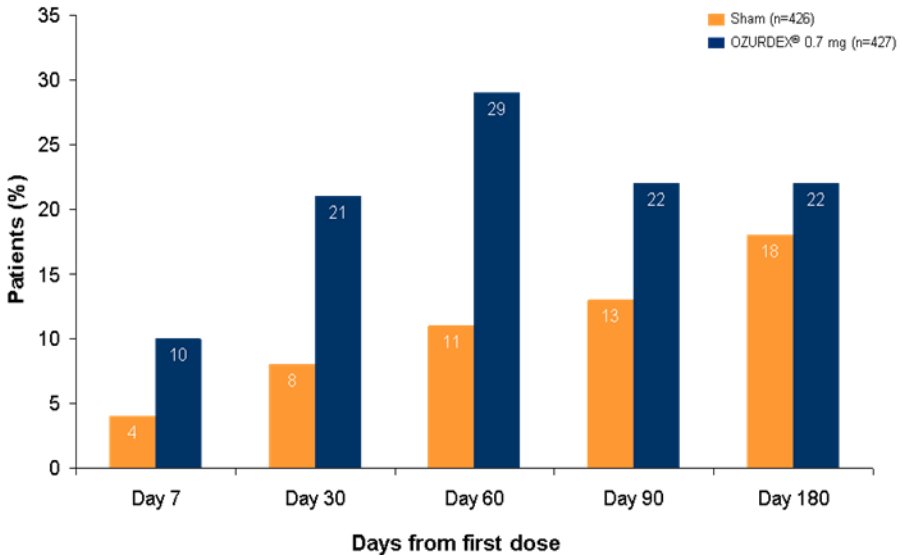
Figure 1: Mean (SD) Retina Concentrations in Monkey Following Intravitreal Administration of Ozurdex and Mean Change from Baseline in Best-Corrected Visual Acuity in RVO Patients Who Received OZURDEX (5)



Following administration of Ozurdex, there is a strong correlation between the retina dexamethasone concentration profile in monkeys (6) to the time-course of clinical efficacy observed in the GENEVA studies(5). Efficacy outcomes at each assessment point were provided demonstrating a peak effect in efficacy between days 60-90 and a clinical effect maintained up to 6 months (Figure 2).

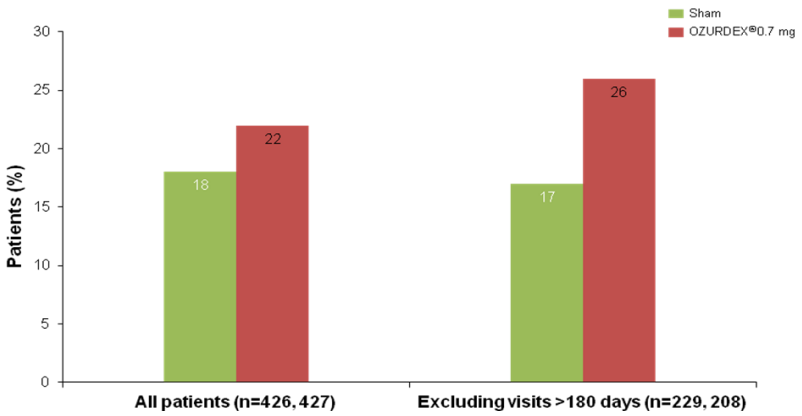
Individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with an improvement of ≥ 15 letters BCVA from baseline (in the study eye) was statistically significantly higher at days 30, 60 and 90 ($P \leq 0.039$) with Ozurdex versus Sham (Figure 2).

Figure 2: % of RVO pts achieving an improvement of ≥ 15 letters BCVA from baseline



A similar trend was observed at day 180; however the window for scheduled post-implant visits varied, and many patients were assessed for efficacy 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 (for 180 day visits up to and including day 180: 136-180), with Ozurdex (26%) versus Sham (17%) ($P \leq 0.017$) (Figure 3).

Figure 3: Effect of excluding visits beyond 180 days: BCVA improvement ≥15 letters



Therefore, the pharmacokinetic profile demonstrated by Ozurdex and the resulting clinical effect are consistent with a pulse dose therapeutic treatment concept and provide clinical benefit up to six months.

A3. The GENEVA trials involved treatment with a dexamethasone intravitreal implant at baseline, then no further retreatment until 180 days. In routine care, there would be more flexibility of dosing. Have you modelled a repeat dose in CRVO as soon as visual acuity starts to decline? If so, please describe the method, results and any assumptions made about efficacy of the second dose.

We have not modelled a repeat dose prior to day 180 in CRVO patients.

A4. (Page 21) Please provide a copy of the evaluation of the three most commonly used therapeutic interventions (laser photocoagulation, off-label use of VEGF inhibitors and corticosteroids) that was provided to the European Medicines Agency.

Allergan's responses to questions from the Europe Medicines Agency related to commonly used therapeutic interventions are provided as separate source documents.

A5. (Page 30, reference number 25.) The Haller paper mentions that some patients had "prohibited" interventions. Please clarify what these interventions were and the reason(s) why they were given.

The following seven patients had "prohibited" interventions in the study eye, and were excluded from the per protocol efficacy analyses (Table 1). The main reason for patients to receive an additional treatment was related to complications of the disease.

Table 1: Prohibited Interventions in the GENEVA Study

Patient	Treatment	Procedure/Treatment (description)	Study Days[a]	Reason for Procedure
2341-0424	Ozurdex	Retinal laser coagulation (grid)	169	Macular oedema
4395-3522	Ozurdex	Retinal laser coagulation (argon photo-coagulation)	180	Proliferative retinopathy
4311-2654	dexamethasone 350 µg	Retinal laser coagulation (panretinal photocoagulation)	33	Rubeosis
7873-3011	Sham	Laser sugeries	174	Retinal neovascularization in disc, of the iris, and of the angle
7871-1186	dexamethasone 350 µg	Retinal laser coagulation (panretinal photocoagulation laser)	108	Raised intraocular pressure
		Intravitreal steroid bevacizumab (Avastin)	169	Worsening macular oedema
4451-0373	Sham	Intravitreal injection bevacizumab (Avastin)	182	Branch retinal vein occlusion
4283-2205	Sham	Intravitreal injections triamcinolone acetonide	90	Macular cyst, macular exudates

a days from initial treatment

A6. (Pages 30-31 and 88-89.) Section 5.7 states that no indirect comparison could be conducted between bevacizumab or triamcinolone acetonide and dexamethasone intravitreal implant owing to absence of appropriate RCT evidence found in the systematic review. Please clarify whether studies of bevacizumab and triamcinolone were identified but excluded from the systematic review and, if so, provide details of these studies.

Studies of bevacizumab and triamcinolone were identified in the systematic review but subsequently excluded.

Firstly, some studies, which may have contained bevacizumab or triamcinolone would have been excluded on the basis that:

1. **The study did not report outcomes of interest, namely:**
    a. 15-letter gain from baseline in best corrected visual acuity (BCVA)
    b. 15-letter loss from baseline in BCVA
    c. Mean change from baseline in retinal thickness (micrometres)

2. **The study was not an RCT i.e. the exclusion of**
    a. Systematic reviews and/or meta analyses
    b. Non-systematic reviews
    c. Single-arm trials
    d. Letters or commentaries
    e. Case reports/series/surveys

3. **The study was not in the relevant patient group, i.e. the exclusion of**
    a. Studies conducted in paediatric and child (<17 years) populations
    b. Studies which did not investigate macular oedema associated with BRVO or CRVO

Secondly, studies were excluded if either intervention fell outside the scope of the defined literature search. Interventions included in the search were informed by the NICE scope. The inclusion criteria therefore specified pharmacological therapies including dexamethasone, bevacizumab and triamcinolone (Kenalog or equivalent), or observation/sham. Table 2 sets out details of the studies identified for bevacizumab and triamcinolone (Kenalog or equivalent) and excluded.

Table 2: Studies excluded on the basis of intervention

Reference	Drug therapies compared	Primary reason for exclusion
Avitabile, T., A. Longo, et al. (2005). "Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema." American Journal of Ophthalmology 140(4): 695-702.	**Intervention:** triamcinolone acetonide (TA) intraocular injections **Comparator:** macular laser grid photocoagulation (MLG) or both TA+MLG	Comparator not included in inclusions list. NB: Formulation of triamcinolone not reported.

Reference	Drug therapies compared	Primary reason for exclusion
Byeon, S. H., O. W. Kwon, et al. (2009). "Prolongation of activity of single intravitreal bevacizumab by adjuvant topical aqueous depressant (Timolol-Dorzolamide)." Graefes Archive for Clinical & Experimental Ophthalmology 247(1): 35-42.	**Intervention:** timolol-dorzolamide drops twice daily **Comparator:** no eye drops	Combination therapy - patients were pre - treated with bevacizumab and then randomly assigned to the arms.
Chung, E. J., H. Lee, et al. (2008). "Arteriovenous crossing sheathotomy versus intravitreal triamcinolone acetonide injection for treatment of macular edema associated with branch retinal vein occlusion." Graefes Archive for Clinical & Experimental Ophthalmology 246(7): 967-74.	**Intervention:** arteriovenous (AV) sheathotomy **Comparator:** intravitreal triamcinolone acetonide (IVTA) injection	Comparator not on included therapies list. NB: The formulation of triamcinolone was not “Kenalog or equivalent” (Tamceton)
Ip, M. S., I. U. Scott, et al. (2009). "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5." Archives of Ophthalmology 127(9): 1101-14.	**Intervention:** 1-mg doses of preservative-free intravitreal triamcinolone **Comparator:** 4-mg doses of preservative-free intravitreal triamcinolone	The formulation of triamcinolone was not “Kenalog or equivalent” (Trivaris)
Jonas, J. B., I. Kreissig, et al. (2005). "Cataract surgery combined with intravitreal injection of triamcinolone acetonide." European Journal of Ophthalmology 15(3): 329-35.	**Intervention:** cataract surgery and additionally receiving an intravitreal injection of 20 mg of triamcinolone acetonide **Comparator:** intravitreal injection of 20 mg triamcinolone acetonide without cataract surgery	Combination therapy NB: Formulation of triamcinolone not reported.
Oda J J, L. J. I. (2005) Sheathotomy vs. Nonsurgical Intervention in Branch Retinal Vein Occlusions. Iovs ARVO E-abstract 3290	**Intervention:** surgical intervention (pars plana vitrectomy and sheathotomy) **Comparator:** nonsurgical intervention (observation, focal laser, intravitreal kenalog).	Combination therapy compared with surgical intervention

Reference	Drug therapies compared	Primary reason for exclusion
Oh, J. Y., J. H. Seo, et al. (2007) Early versus late intravitreal triamcinolone acetonide for macular edema associated with branch retinal vein occlusion. Korean journal of ophthalmology : KJO 18-20	**Intervention:** a single intravitreal triamcinolone injection (4 mg/0.1 ml), patients with macular edema from BRVO; duration after onset of 3 months **Comparator:** a single intravitreal triamcinolone injection (4 mg/0.1 ml), patients with macular edema from BRVO; duration after onset <or= 3 months	The formulation of triamcinolone was not “Kenalog or equivalent”
Parodi, M. B., P. Iacono, et al. (2008). "Intravitreal triamcinolone acetonide combined with subthreshold grid laser treatment for macular oedema in branch retinal vein occlusion: a pilot study." British Journal of Ophthalmology 92(8): 1046-50.	**Intervention:** subthreshold grid laser treatment (SGLT) **Comparator:** infrared micropulse diode laser alone or in combination with intravitreal triamcinolone injection (SGLT-IVTJ)	Intervention was not on the included therapies list and triamcinolone was used as a combination therapy
Priglinger, S. G., A. H. Wolf, et al. (2007). "Intravitreal bevacizumab injections for treatment of central retinal vein occlusion: Six-month results of a prospective trial." Retina 27(8): 1004-1012.	**Intervention:** repeated intravitreal injections (1.25 mg) of bevacizumab.	Single arm study – there was no comparator
Rho D S, S. S. M. (2004) Combination Therapy for Pseudophakic Cystoid Macular Edema: Diclofenac Sodium 0.1% and Prednisolone Acetate 1% Versus Ketorolac Tromethamine 0.5% and Prednisolone Acetate 1%. Iovs ARVO E-abstract 2030	**Intervention:** combination therapy with diclofenac sodium 0.1% and prednisolone acetate 1% (D) **Comparator:** ketorolac tromethamine 0.5% and prednisolone acetate 1% (K)	Intervention or comparator was not on the included therapies list
Russo, V., A. Barone, et al. (2009). "Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion." Retina 29(4): 511-515.	**Intervention:** bevacizumab **Comparator:** macular grid laser photocoagulation (GLP)	Comparator (laser) was not on the included therapies list.

Reference	Drug therapies compared	Primary reason for exclusion
Scott, I. U., M. S. Ip, et al. (2009). "A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6." Archives of Ophthalmology 127(9): 1115-28.	**Intervention:** 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone **Comparator:** standard care (grid photocoagulation)	Comparator (laser) was not on the included therapies list. NB: The formulation of triamcinolone was not "Kenalog or equivalent"(Trivaris)
Wu, L., J. F. Arevalo, et al. (2009). "Comparison of two doses of intravitreal bevacizumab as primary treatment for macular edema secondary to branch retinal vein occlusions: results of the Pan American Collaborative Retina Study Group at 24 months." Retina (Philadelphia, Pa.) 29(10): 1396-1403.	**Intervention:**1.25 or 2.5 mg bevacizumab	Single arm study – there was no comparator
Wu, L., J. F. Arevalo, et al. (2008). "Comparison of two doses of intravitreal bevacizumab (avastin) for treatment of macular edema secondary to branch retinal vein occlusion: Results from the Pan-American collaborative retina study group at 6 months of follow-up." Retina 28(2): 212-219.	**Intervention:**1.25 or 2.5 mg bevacizumab	Single arm study – there was no comparator
Yamashita, T., A. Uemura, et al. (2006) Intraocular Pressure After Intravitreal Injection of Triamcinolone Acetonide Following Vitrectomy for Macular Edema. Iovs ARVO E-abstract 4256	**Intervention:** intravitreal injections of different doses of intravitreal triamcinolone acetonide (TA) at the end of pars plana vitrectomy (PPV)	Single arm study – there was no comparator

A7. (Page 25.) It is suggested that Trivaris will not be available in UK. Please clarify the source of this information.

Allergan is the global manufacturer of Trivaris® (triamcinolone acetonide ophthalmic solution). It was announced on November 1st during Allergan's 3rd quarter earnings release that Allergan would not commercialise Trivaris® and has no current plans to manufacture, commercialise, or out-license Trivaris®.

A8. (Page 47, table 14.) Please can you provide any further information to explain why there were only a few drop-outs due to lack of efficacy in the sham group?

When the studies began in 2004, there was a lack of evidence to support alternative treatment strategies, and there were no approved pharmacologic therapies for macular oedema. Additionally, a period of initial observation after disease onset was considered to be the standard of care, and sham was considered an appropriate control for the study for a six month period. This may account for the low drop-out rate. Furthermore, all patients would be evaluated for active treatment at the end of the initial six-month treatment period, which may have provided a benefit to the patient.

A9. (Page 54-55, tables 20, 22, 23.) It appears that the branch retinal vein occlusion (BRVO) macular haemorrhage (MH) and previous laser groups do better than the total BRVO group. Please can you comment on why this might be the case?

The proportion of patients with a ≥15 letters gain after Ozurdex treatment was very similar between All BRVO, BRVO-MH, and BRVO-previous laser groups (Table 3, taken from Tables 20, 22, 23 of the original submission). Although the response to sham injection was similar between BRVO-MH and All BRVO patients, a much lower proportion of patients with previous laser gained ≥15 letters after sham injection. Therefore, the treatment benefit appears to be larger in BRVO-previous laser group than in All BRVO group. It is likely that the BRVO-previous laser patients who were enrolled in GENEVA trials were less likely to improve without treatment than treatment-naive patients. Ozurdex provided visual acuity benefit in these patients previously treated with laser, as well as in those without previous laser with or without macular haemorrhage.

Table 3: Pooled data results for the proportion of patients achieving ≥15 letters

	All BRVO		BRVO-MH		BRVO Previous Laser	
Visit	**Ozurdex (n = 291)**	**Sham (n = 279)**	**Ozurdex (n = 255)**	**Sham (n = 260)**	**Ozurdex (n = 36)**	**Sham (n = 36)**
Day 30	21.3%†	7.9%	22.0%†	8.8%	22.2%§	2.8%
Day 60	29.6%†	12.5%	31.8%†	13.5%	27.8%†	0.0%
Day 90	23.7%††	14.7%	25.9%†	14.6%	27.8%¶	5.6%
Day 180	23.0%	20.4%	23.9%	21.5%	25.0%‡‡	5.6%

Note: BRVO-MH and BRVO-previous laser groups are not mutually exclusive.
† (P < 0.001); †† (P = 0.006); § (P = 0.028); ¶ (P = 0.011); ‡‡ (P = 0.022)

A10. (Page 61-62, table 28 and 29.) Please provide the percentage distribution of visual acuity at each time point for CRVO and BRVO separately (as in table 27) or clarify that these data are not available.

Table 4: Categorical change from baseline BCVA, ≥ 15 letters improvement, ≥ 15 letters worsening in patients with CRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009	
	Ozurdex (n =61)	Sham (n =72)	Ozurdex (n =75)	Sham (n =75)
Day 30	P=0.023†		P <0.001†	
≥ 15 letters improvement	16.4%	8.3%	25.3%	5.3%
≥ 5 and < 15 letters improvement	34.4%	27.8%	46.7%	21.3%
Between -5 to +5 letters	42.6%	44.4%	20.0%	52.0%
≥ 5 and < 15 letters worsening	3.3%	12.5%	4.0%	14.7%
≥ 15 letters worsening	3.3%	6.9%	4.0%	6.7%
Day 60	P < 0.001†		P <0.001†	
≥ 15 letters improvement	23.0%	12.5%	33.3%	5.3%
≥ 5 and < 15 letters improvement	44.3%	26.4%	41.3%	29.3%
Between -5 to +5 letters	26.2%	33.3%	14.7%	36.0%
≥ 5 and < 15 letters worsening	4.9%	19.4%	5.3%	16.0%
≥ 15 letters worsening	1.6%	8.3%	5.3%	13.3%
Day 90	P=0.050		P=0.023†	
≥ 15 letters improvement	16.4%	9.7%	18.7%	10.7%
≥ 5 and < 15 letters improvement	37.7%	31.9%	32.0%	22.7%
Between -5 to +5 letters	34.4%	31.9%	29.3%	34.7%
≥ 5 and < 15 letters worsening	4.9%	15.3%	10.7%	16.0%
≥ 15 letters worsening	6.6%	11.1%	9.3%	16.0%
Day 180	NS		NS	
≥ 15 letters improvement	11.5%	13.9%	24.0%	10.7%
≥ 5 and < 15 letters improvement	27.9%	25.0%	14.7%	21.3%
Between -5 to +5 letters	32.8%	26.4%	29.3%	30.7%
≥ 5 and < 15 letters worsening	18.0%	16.7%	14.7%	14.7%
≥ 15 letters worsening	9.8%	18.1%	17.3%	22.7%

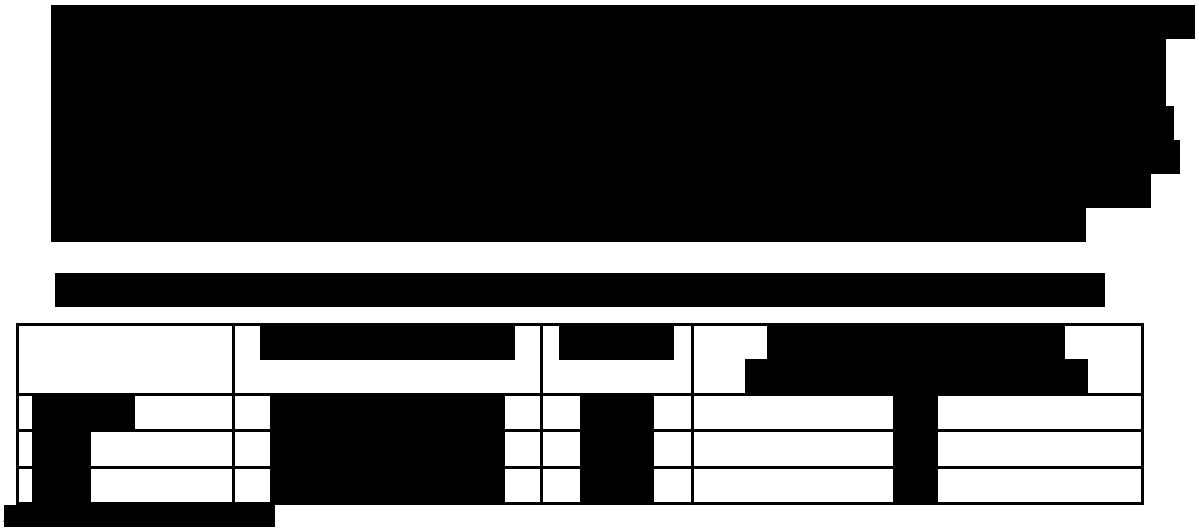
Abbreviations: NS, Not statistically significantly different;† Categorical change from baseline statistically significantly greater with Ozurdex compared with Sham

Table 5: Categorical change from baseline BCVA, ≥ 15 letters improvement, ≥ 15 letters worsening in patients with BRVO (- 180 days)

Visit	GENEVA 008		GENEVA 009	
	Ozurdex (n =140)	Sham (n =130)	Ozurdex (n =151)	Sham (n =149)
Day 30	P <0.001†		P <0.001†	
≥ 15 letters improvement	21.4%	6.9%	21.2%	8.7%
≥ 5 and < 15 letters improvement	45.0%	35.4%	49.7%	38.3%
Between -5 to +5 letters	27.9%	46.9%	23.8%	41.6%
≥ 5 and < 15 letters worsening	5.7%	8.5%	5.3%	10.7%
≥ 15 letters worsening	0.0%	2.3%	0.0%	0.7%
Day 60	P <0.001†		P <0.001†	
≥ 15 letters improvement	31.4%	9.2%	27.8%	15.4%
≥ 5 and < 15 letters improvement	40.0%	38.5%	50.3%	37.6%
Between -5 to +5 letters	24.3%	40.0%	21.2%	36.2%
≥ 5 and < 15 letters worsening	4.3%	10.8%	0.0%	8.7%
≥ 15 letters worsening	0.0%	1.5%	0.7%	2.0%
Day 90	P=0.004†		P=0.002†	
≥ 15 letters improvement	25.0%	13.8%	22.5%	15.4%
≥ 5 and < 15 letters improvement	40.7%	35.4%	51.7%	44.3%
Between -5 to +5 letters	24.3%	36.2%	23.8%	27.5%
≥ 5 and < 15 letters worsening	7.9%	12.3%	1.3%	8.7%
≥ 15 letters worsening	2.1%	2.3%	0.7%	4.0%
Day 180	NS		P=0.005†	
≥ 15 letters improvement	22.9%	20.8%	23.2%	20.1%
≥ 5 and < 15 letters improvement	37.9%	29.2%	45.0%	32.2%
Between -5 to +5 letters	27.9%	32.3%	25.8%	27.5%
≥ 5 and < 15 letters worsening	7.9%	13.8%	4.6%	13.4%
≥ 15 letters worsening	3.6%	3.8%	1.3%	6.7%

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

A11. (Page 69, paragraph 2.) Please provide the same data on the effect of delayed treatment on primary outcome for CRVO and BRVO separately.



A12. (Page 90-117.) The maximum number of doses is six doses. Do you have data on eye complications after 5-6 injections using a 22-gauge needle?

There are no data from completed clinical studies or from routine use in clinical practice that allows for an assessment of adverse effects from 5-6 injections using a 22 gauge needle.

A13. (Page 139-145.) In order to better understand the patient flow within the GENEVA studies, please tabulate the following absolute patient numbers where the total for day 180 and day 360 should remain as the overall modified intent-to-treat (mITT) population of the group under consideration at day 0, where the data is available for the dexamethasone intravitreal implant arm:

Table 7 and Table 8 below have been completed according to the table shells provided. The row labelled “Lost to follow-up” has been changed to “Discontinuation prior to scheduled visit” as lost to follow-up was only one of the reasons for patients to discontinue prior to day 180.

It should be noted that the patient numbers in the Table 7 and Table 8 are based on the information from case report form (CRF). On the CRF, although clinicians were informed to select “resolved” as the main reason for not retreated only when a patient had OCT≤250 μm and BCVA>84 letters, some clinicians still reported “resolved” when patients had OCT>250μm. Under the model definition of resolution (OCT≤250 μm), these patients (i.e., OCT>250μm) are categorized as unresolved in the cost-effectiveness model.

According to the CRF, some patients with OCT≤250 μm at Day 180 were not retreated due to safety or other concerns. These patients were categorized as “resolved” for the economic model based on the OCT criterion. In addition, since the economic model uses last-observation carry forward (LOCF) data, patients who discontinued prior to the Day 180 visit but had OCT≤250 μm on their last observation are also categorized as resolved in the model.

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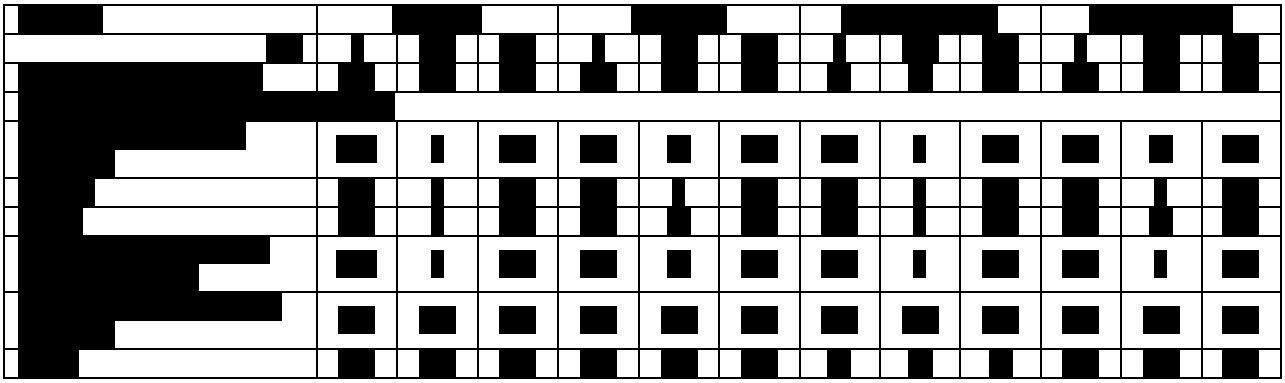

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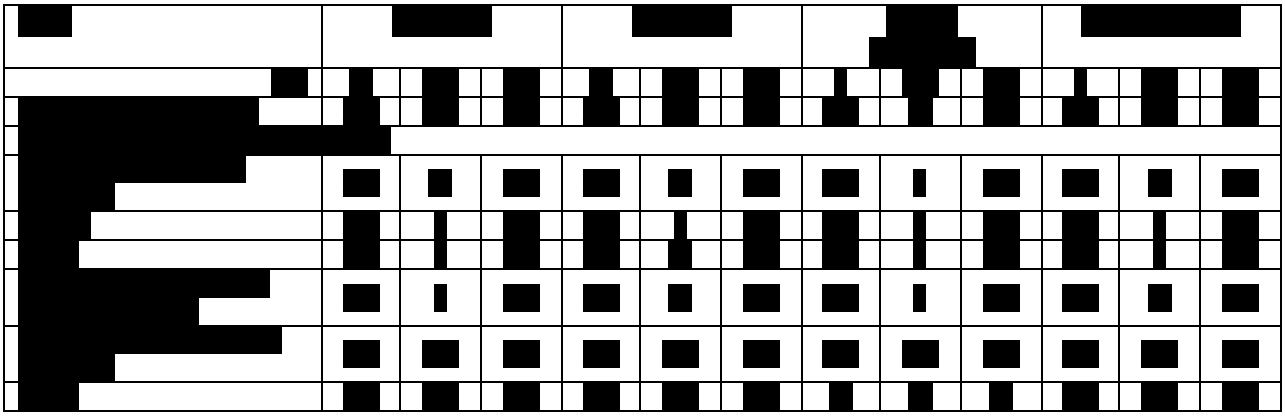

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Section B: Clarification on cost-effectiveness data

B1. (Page 139-145.) Please clarify which patient population within the dexamethasone intravitreal implant arm was used to calculate the day 0-30, day 30-60, day 60-90 and day 90-180 transition probability matrices (for example, the 421 patients receiving a dexamethasone injection at baseline; the 401 patients receiving an injection at baseline and entered the open label phase; the 341 patients receiving an injection at both baseline and day 180).

With reference to the question, the patient population used in the estimation of transition probabilities from day 0 to 180 represents the 421 patients who received a Ozurdex injection at baseline. Table 9 present the number of patients for each patient population who were considered in the estimation of transition probabilities at each time point.

Table 9: Patient composition for Ozurdex TPs

	Patient Population			
TP	**CRVO**	**BRVO**	**BRVO-MH**	**BRVO-PL**
Day 0-30	133	288	255	36
Day 30-60	133	288	255	36
Day 60-90	133	288	255	36
Day 90-180	133	288	255	36
Day 180-360	114	227	202	31

B2. Please also clarify which population within the dexamethasone intravitreal implant arm was used to calculate the day 180-360 transition probability matrices (for example, the 341 patients receiving a dexamethasone injection at both baseline and day 180; the 341 patients receiving a dexamethasone injection at both baseline and day 180 plus the 327 patients receiving a sham injection at baseline and a dexamethasone injection at day 180).

The patient population used for the estimation of transitional probabilities for days 180-360 in the Ozurdex arm are the 341 patients who received an injection at both baseline and day 180. Table 9 presents patient numbers used in the estimation of transition probabilities. BRVO-MH and BRVO-PL are subgroups of BRVO, and not mutually exclusive.

B3. Please clarify which patient population within the sham treatment arm was used to calculate the transition probability matrices (for example, the 423 patients receiving a sham injection at baseline; the 399 patients receiving an injection at baseline and entered the open label phase; the 327 patients receiving an injection at baseline and a dexamethasone injection at day 180).

The patient population used to estimate transitional probabilities from the sham arm of the GENEVA trials was the 423 patients whom received a sham injection at baseline. Table 10 presents patient numbers used in estimation.

Table 10: Patient composition for Observation TPs

	Patient Population			
TP	**CRVO**	**BRVO**	**BRVO-MH**	**BRVO-PL**
Day 0-30	147	276	260	36
Day 30-60	147	276	260	36
Day 60-90	147	276	260	36
Day 90-180	147	276	260	36

B4. (Page 139-145) There are a number of distinct transition probability matrices for CRVO, BRVO, BRVO with MH, BRVO with previous laser and BRVO of more than and 90 days or less within the electronic model. Please can you present the results from applying the distinct baseline distributions of each group rather than the pooled distribution across all subgroup analyses?

Appendix B4 presents the results of analysis whereby the distribution of patients at baseline for both BRVO and CRVO patient populations are based on the observed distribution at baseline for each population.

B5. (Page 86, 132, 141, 165 and elsewhere.) The clinical trial evidence suggests that the majority of patients needed re-treatment but there is currently no data on how many doses will be used in clinical practice. To address this uncertainty, please provide another scenario analysis (table 115) at two years with three injections.

NICE Clarification received November 3, 2010: To clarify, we would like a scenario analysis for 3 injections within two years with discharge at two years. So the last injection is at say 18 months. The underlying assumption here is that patients have reached a stable state by two years with no further injections given. Also, my apologies, there is a typo in the table number and this should be table 105.

Clarification was sought regarding the specific scenario requested by the review group. In order to attempt to understand the effects of treatment over 2 years the following assumptions were varied. All changes were made to a copy of the model version presented to the review group.

- Treatment. The question requests the modelling of 3 treatments over 2 years with a last injection at 18 months. Within the structure of the model, treatment is permitted only in 6-monthly cycles (as per the GENEVA trials). Therefore, we modelled two different sets of scenarios:
    - Scenario 1: Accounting for last treatment at 18 months. We assumed that the reviewers question referred to a maximum of 4 treatments (i.e. 3 re-injections) over 2 years (i.e. Ozurdex treatments at month 0, month 6, month 12 and month 18) (Table 11).

- Scenario 2: Accounting for 3 treatments over a two year period. Additional scenarios (5-8) are presented which more directly reflect the scenario requested, which details 3 treatments in 2 years and refers explicitly to stabilisation at 2 years. The model permits treatment in 6-monthly intervals and therefore does not allow 3 treatments with a final treatment at 18 months. In scenarios 5-8, treatment was assumed to occur at months 0, 6 and 12 only with all other assumptions as in scenarios 1-4 respectively (Table 12).

- Retreatment rates. Two distinct scenarios were considered:
  - Retreatment is 100% at month 6, month 12 and month 18 and 0% thereafter.
  - Retreatment is based on the GENEVA clinical trials and clinical expert opinion as detailed in the original submission document up to month 18, and 0% thereafter.

- Stabilisation assumptions. Two distinct scenarios were considered:
  - Stabilisation occurs at year 2 in all patient groups
  - Stabilisation occurs at year 2 in Ozurdex patients and year 2.5 (BRVO) and 3 (CRVO) in observation patients (as detailed in the original submission document)

- Non-retreated patients continue to receive a transition matrix weighted by the proportion of patients assumed to have resolved (until stabilisation), as detailed in the original submission document.

We therefore present the results of 4 scenarios for review.

Table 11: Additional scenario analyses performed 1

			ICER			
#	**Treatment rules**	**Time to stabilisation**	**All RVO**	**CRVO**	**BRVO-MH**	**BRVO prior laser**
1	100% pts treated at day 0, 180, 360, 540	2 years	£19,427	£8,282	£30,407	£1,447
2	100% pts treated at day 0, 180, 360, 540	Ozurdex pts.= 2 years Observation pts.= 2.5 years (BRVO) 3 years (CRVO)	£14,344	£4,428	£23,775	Ozurdex dominant

			ICER			
#	Treatment rules	Time to stabilisation	All RVO	CRVO	BRVO-MH	BRVO prior laser
3	As in original submission until month 18*, 0% thereafter	2 years	£7,817	£4,719	£9,748	Ozurdex dominant
4	As in original submission until month 18*, 0% thereafter	Ozurdex pts.= 2 years Observation pts.= 2.5 years (BRVO) 3 years (CRVO)	£3,782	£834	£5,911	Ozurdex dominant

*BRVO: 100% pts day 0, 78.8% pts at day 180, 18.5% pts at day 360, 18.5% pts at day 540
CRVO: 100% pts day 0, 85.7% pts at day 180, 63.0% at day 360, 63.0% pts at day 540

Table 12: Additional scenario analyses performed 2

			ICER			
#	Treatment rules	Time to stabilisation	All RVO	CRVO	BRVO-MH	BRVO prior laser
5	100% pts treated at day 0, 180, 360	2 years	£13,977	£4,860	£20,844	Ozurdex dominant
6	100% pts treated at day 0, 180, 360	Ozurdex pts.= 2 years Observation pts = 2.5 years (BRVO) 3 years (CRVO)	£9,037	£846	£15,804	Ozurdex dominant
7	As in original submission until month 12*, 0% thereafter	2 years	£6,139	£1,828	£8,710	Ozurdex dominant
8	As in original submission until month 12*, 0% thereafter	Ozurdex pts.= 2 years Observation pts.= 2.5 years (BRVO) 3 years (CRVO)	£2,023	Ozurdex dominant	£4,838	Ozurdex dominant

*BRVO: 100% pts day 0, 78.8% pts at day 180, 18.5% pts at day 360; CRVO: 100% pts day 0, 85.7% pts at day 180, 63.0% at day 360

B6. (Page 145-146 and 151-154.) From the text, it appears that values for the split of best seeing eye (BSE) and worst seeing eye (WSE), time to stabilisation of best corrected visual acuity (BCVA) [incl. natural history] and retreatment rates were taken from the panel held in New York on 30 September 2009. Please clarify to what extent the other panels on 12 November 2009, 12 May 2010 and other expert opinion contributed data on these aspects:

Table 13: Expert Panels

	30 Sep 2009	Nov 12 2009	May 12 2010
BSE:WSE split	Contributed	Confirmed as reasonable BSE (10%) WSE (90%)	.Confirmed BSE (10%) WSE (90%) as reasonable
Time to stabilisation of BCVA	Contributed	No contribution	Consensus through discussion c. 2 years BRVO and c. 2.5 years CRVO
Retreatment rates	Contributed	No contribution	No contribution

i. Where there were contributions from more than one panel, to what extent were the consensuses reached through discussion the same across the contributing panels?

Expert panels held in the UK were used to confirm the assumptions of the international expert panel held in New York. Confirmed assumptions were the BSE/WSE split. Additionally, they contributed to the discussion on the time to stabilisation based on current treatment practice. Please see Table 13.

ii. Please verify the BSE: WSE 90:10 ratio on page 151

The BSE:WSE ratio used in the base case analysis was 10:90, respectively. This percentage split was recommended by the New York Clinical Expert Panel as being representative of patients seen in clinical practice. Also, a pooled analysis of the BRAVO and CRUISE studies suggests that 92% of patients have poorer visual acuity in their study eye (see Section 6.9 of the original submission document for further explanation).

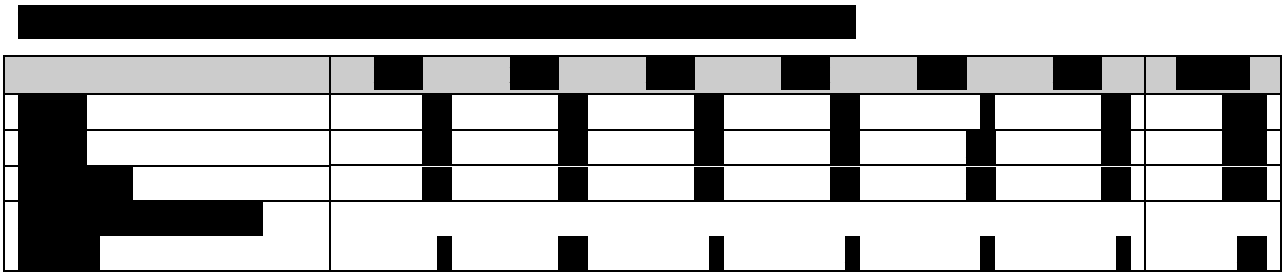
The BSE:WSE spilt in GENEVA 008 and 009 (3:97) was not considered representative of the patient population in clinical practice. Patients with a non-study eye ≤34 letters were excluded from these studies. This resulted in a smaller proportion of BSE patients than would be expected in clinical practice.

iii. Please clarify the extent to which information from the New York clinical expert panel was focused on the UK context.

The New York clinical expert panel had an international focus with representatives from several countries, including one clinician representing the UK.

B7. (Page 151-152.) For the base case the proportions retreated and not retreated with a 2nd injection at day 180 are described as taken from the pooled trial data. The proportions treated and not retreated with a 3rd injection and beyond are drawn from the New York expert panel. From the trial data please present a disaggregate analysis of the numbers of dexamethasone intravitreal implant patients retreated at day 180 disaggregated by health state: HS0, HS1, HS2, HS3, HS4 and HS5.

Table 14 details the number of patients retreated at day 180 in each health state by patient population.



B8. (Page 153.) Within the model, those patients who are not retreated are assumed to have either resolved or to have dropped out. Those having resolved have the identity matrix applied to them, while those who have dropped out have the sham matrix applied to them. The proportions of those not being treated who resolve are taken from trial data. Please clarify:

i. At what time point resolution was evaluated (e.g. day 180).

Resolution was evaluated at IT Day 180. For additional detail, please refer to A13 and B9.

ii. Whether any proportion of those assessed as resolved within the trial at day 180, and so contributing to the resolution estimates, received a second injection, split by CRVO and BRVO.

Resolution rates used in the model only apply to patients who were not retreated at IT Day 180.

B9. The patients estimated to have resolved within the model are given as percentages (shown below). Please clarify the absolute numbers of patients that the percentages of relate to, giving the numerator and the denominator.

	HS0	HS1	HS2	HS3	HS4	HS5
CRVO						
BRVO						

Table 15 details the patient counts used in the calculation of the probability of resolution by health state. For the derivation of these data from GENEVA trials, see Table 7a and Table 8a.

[redacted]

B10. (Page 160-161, section 6.4.9.) In terms of how the patient utility for a given health state is calculated, please clarify:

i. If only the WSE is affected and the patient is in HS2, is the utility value [redacted]?

[redacted]

ii. If only the BSE is affected and the patient is in HS2, is the utility value [redacted]?

[redacted]

iii. If the WSE is affected initially and is currently in HS2, with fellow eye involvement in the BSE with the BSE currently being in HS2 is the utility value [redacted]?

[redacted]

B11. (Page 160-161.) Please present the standard errors of the intercept and slope parameters within the two utility regression equations.

[redacted]

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

B12. (Page 160-161.) In terms of estimating the utility regressions was this undertaken for any particular time point within the trial, or was data pooled across different time points used?

The utility regressions were analysed cross-sectionally based on the data from IT Day 180.

B13. (Page 165, paragraph 3.) Please provide any evidence of whether monitoring of visual acuity with a view to earlier re-treatment would increase the number of visits required or whether it would condense the same number of visits into a shorter time period.

The medical resource use related to Ozurdex will depend on the model currently used for the administration of intravitreal injections and the funding arrangements hospitals have with primary care trusts. Currently, intravitreal injections are provide through 1-stop models, where diagnostic/monitoring tests and treatment occur on the same day, or 2-stop models, where diagnostic/monitoring tests occur during one visit and treatment is a separate visit.

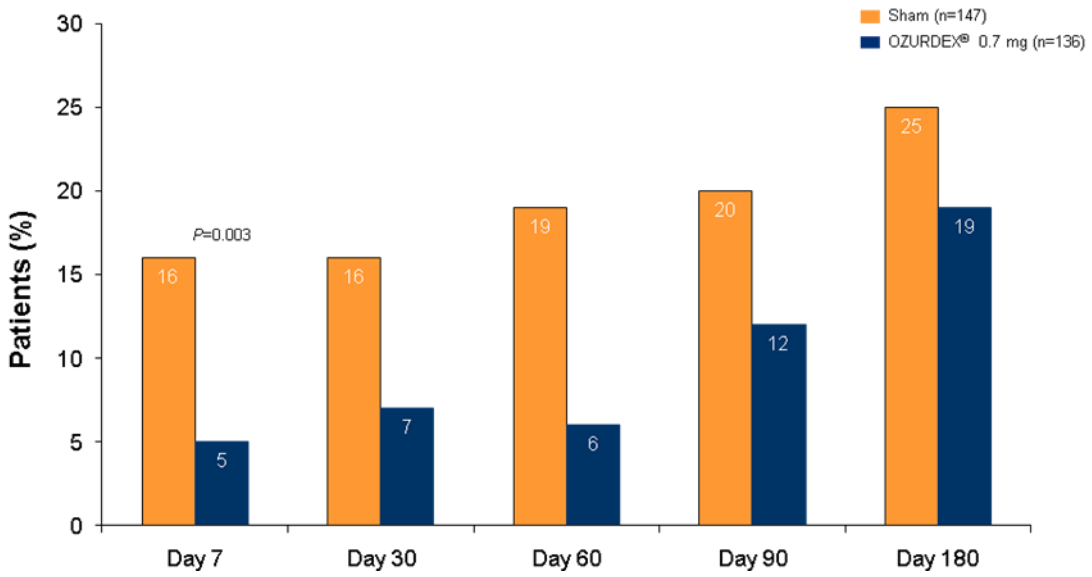
Currently the model assumes the following 12-month costs: 6 visits for monitoring, 2 visits for drug administration, 2 visits for the measurement of IOP. Therefore, for hospitals running a 1-stop model, the current model assumptions are likely to overestimate the number of visits and the resulting costs. Furthermore, 6 monitoring visits allows for follow-up every 2 months which would be sufficient for both 1-stop and 2-stop centres to monitor patients and allow for earlier retreatment. If Ozurdex was injected 3 times per year, it is unlikely that any additional monitoring visits would be required. In line with the current model assumptions, we would assume an additional visit for an IOP measure after injection which would increase the overall cost £73 per patient receiving a third injection.

B14. (Pages 177 and 180.) Please verify that the proportion of patients with the two best health states is similar between treated CRVO and observed CRVO.

The results presented on page 177 and 180 of the original submission document are correct. Table 118 shows that 39.8% of Ozurdex treated patients were in the top two health states at day 180. Table 121 shows that 40.82% of sham patients were in the top two health states at day 180 (GENEVA result). Note that the distribution of patients in the tables discussed above will differ slightly to the distribution of patients used in the estimation of ICERs because of differences in baseline distribution which are discussed on p. 176 paragraph 1. Estimates of the latter distributions can be taken from the 'External Validation' page with the correct patient populations and baseline distributions specified.

In the GENEVA study, Ozurdex patients were less likely to decline to a BCVA of 35 letters or less in the study eye (Figure 14). This is consistent with health state distribution seen in the model at day 180. The poorest two health states contained 28.6% of Ozurdex patients and 33.3% of Sham patients at day 180 (GENEVA result) in CRVO patients.

Figure 4: CRVO BCVA of 6/60 (35 letters) or worse: 6-month data



B15. (Page 181, tables 124-127.) Please clarify how the data for life years have been calculated.

We assume the calculation of life years (LYs) in the prepared questions relates to the values presented in Table 124 onwards in the original submission document. The model allows the estimation of total LYs by setting 'Summary!K19' equal to 1. This has the effect of replacing utility values with '1', thereby estimating LYs for all living patients. Where the model reports outputs in QALYs, the values produced now report LYs (note that this labelling is not dynamic and so this may be the source of any confusion experienced). LYs continue to be discounted.

In order to extract LYs (and QALYs) by health state, a VBA macro was used. This can be accessed through the 'results' module. The cells L22:Q22 on the 'Summary' page present the utility values by health state and WSE/BSE. Setting K19=1 populates this array with '1' as described. To estimate life years for each health state, the health state of interest (by WSE/BSE) was retained as '1' whilst all others were changed to zero. Total and incremental LYs by health state and WSE/BSE were then recorded using cells D49:F59 on the 'Summary' page.

Electronic model

B16. In checking the results for BRVO with MH, setting D32 equal to 4 the results for BRVO do change to those of the submission: £7953 per QALY. But this also changes the CRVO cost effectiveness to £5,803 per QALY. There is no obvious reason why the cost effectiveness for CRVO should change and this suggests there may be some error in the coding of the model. Please clarify if this is the case, and any changes necessary to correct the model structure.

The ERG observation, as noted, is correct. However, there is not a coding error in the electronic model. Rather, the observation results because the model functionality and reference case assumption is that when there is fellow eye occurrence (FEO), 34.5% of occurrences are CRVO (specified together by D35 and F8) and 65.5% BRVO (F35). That is, the cost effectiveness for CRVO includes the possibility of FEO of BRVO, and vice versa. This is discussed on page 150 of the original submission document.

In terms of how this is applied in the model reference case, changing the patient sub-population (by setting D32 to 4, for example) specifically affects:

- The baseline distribution (shown in L13:Q13; K13 is 0 in the reference case, so the baseline distribution is derived from the individual patient data from the GENEVA trial for the selected BRVO and CRVO subgroup)

- The costs and benefits for the WSE for both CRVO and BRVO because of fellow eye involvement (the reference case has F8=1 to specify that fellow eye involvement will have RVO of both types with the distribution given by D35, the proportion of patients with a CRVO).

The model allows the baseline distribution to be set using one of four options (0= GENEVA (reference case) , 1=user specified distribution, 2=single VA health state, 3=Normal distribution with specified mean and standard deviation). The model also allows fellow eye involvement to be of only the same type as the index RVO (set F8=0).

If fellow eye involvement is restricted to same type of RVO, (e.g., set F8=0), and the trial baseline distribution is not used (K13≠0, eg K13=1), changing D32 (BRVO subgroup) does not affect the CRVO model outputs in J47:M60. When the baseline distribution is derived from the trial data, changing the patient sub-population changes the baseline distribution to reflect the new specification of which patients to include when calculating the distribution. (This distribution is weighted according to the proportion of CRVOs specified in D35.)

The effects of changing these model parameters are consistent with the intended model structure and functionality.

B17. As a face validity check, please consider the following:

	100% RVO to ME conversion			50% RVO to ME conversion		
	All RVO	CRVO	BRVO	All RVO	CRVO	BRVO
Discounted		All	All		All	All
Ozurdex						
Cost	£12,245	£14,962	£10,815	£10,567	£13,363	£9,095
QALY	11.6916	11.6246	11.7269	11.6350	11.5638	11.6725
No treatment						
Cost	£10,578	£13,126	£9,236	£7,873	£10,432	£6,526
QALY	11.465	11.319	11.5424	11.449	11.295	11.5307
Ozurdex-no treatment						
Cost	£1,667	£1,836	£1,578	£2,694	£2,931	£2,569
QALY	0.23	0.31	0.18	0.19	0.27	0.14
ICER	**£7,368**	**£6,008**	**£8,554**	**£14,502**	**£10,884**	**£18,119**

The average total QALYs fall if the proportion of RVO resulting in ME is reduced from 100% to 50%, and falls further if the proportion is reduced to 0%. Similar effects appear to be the case if the method of modelling fellow eye involvement is changed to a simple rate calculation: a lower rate of fellow eye involvement worsens the aggregate patient QALYs. This seems counterintuitive and may suggest a logical flaw in the model structure, which if the case, could have a major impact given the importance of fellow eye involvement to the cost effectiveness argument. Please clarify if this is the case, and any changes necessary to correct the model structure.

The ERG's observation is correct. That is, the increase in QALYs as the proportion of patients with fellow eye involvement increases is counterintuitive and reflects a logic error (that fortuitously does not greatly affect the calculated ICERs). Description of the programming error, corrections for the model, and implications for the model output follow.

In describing the model error, it is important to first review the 3 steps of the model method of accumulating costs and benefits for patients who had an index WSE RVO followed by BSE fellow eye occurrence (FEO) at time T:

1. The costs and QALYs for an index WSE patient from Day 0 are accumulated up to (and including) time T.

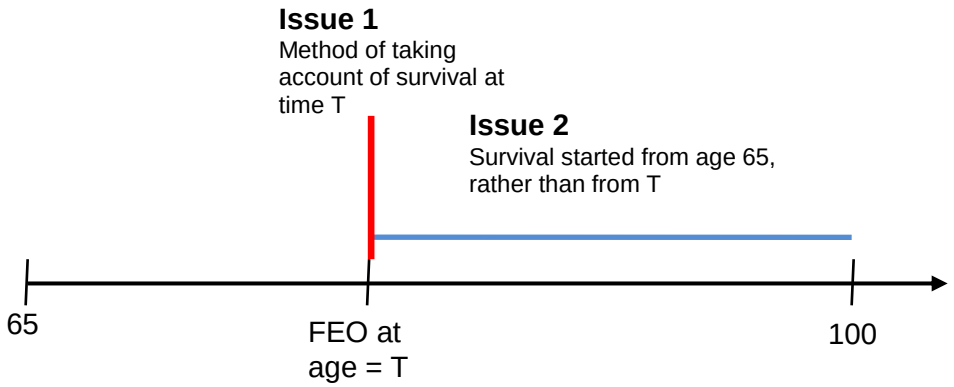
2. Thereafter, the costs and QALYs for this formerly index WSE patient are accumulated as a BSE FEO patient displaced in time by T years. For example, in the first cycle after time T, the costs and QALYs that are calculated as a BSE FEO patient in the first half year are accumulated; and in the second cycle after

time T, the costs and QALYs as a BSE patient in the second half year are accumulated.

3. These costs and QALYs apply for the proportion of alive BSE FEO patients and are discounted and applied only within the time horizon of the model.

Review of the method used in the submitted model identified two issues. Issue 1 relates to the method of taking account of survival at time T for BSE FEO patients. Issue 2 relates to the implicit assumption of the survival of patients after their BSE FEO at time T. Both issues are described in detail below in Figure 5:

Figure 5: Identified Model Issues



Issue 1

Issue 1 relates to the method of taking account of survival at the time of fellow eye occurrence. In the submitted model, survival at the time of fellow eye occurrence was taken into account when calculating the proportion of patients who had fellow eye occurrence at each time instead of being used when calculating the costs and benefits for patients after the fellow eye occurrence.

The correction is to take account of survival at the time of fellow eye occurrence when calculating the costs and benefits after the time of fellow eye occurrence and to remove this factor when calculating the proportion of patients who had FEO at each time.

Issue 1 was identified by noting that in the submitted model the QALY increment that is added in the first half-year after a FEO is that for the first half-year of an index RVO in the BSE. In the first half-year of an index RVO in the BSE, all patients are alive (i.e., no deaths have occurred) whereas when there is a FEO at time T years, some patients would have died. For example, if patients enter the model at age 65, approximately 82% are still alive ten years later.

Issue 1 can be addressed by making the following changes to the model:

1. Change CG17:DJ17 to not take account of survival at the time of the FEO

An example of the change in the formula for cell CG17 is:

Submitted model: Summary!$D$10*CG16*
IF($CI$8=0, IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))

Correction: Summary!$D$10*
IF($CI$8=0,IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))

The difference between these formulae is that the multiplicative term CG16 is present in the submitted model and absent in correction. The updated cell for CG17 can be replicated by dragging the bottom right corner across to cell DJ17. Cell DK17 should be left unchanged. Cell CH13 should be changed from 1-DK13 to SUMPRODUCT(CG17:DJ17,CG16:DJ16), so that this proportion is displayed as in the submitted model (i.e., the overall proportion taking account of mortality).

2. Change CG18:DJ18 and FA18:GD18 to take account of survival at the time of the FEO

An example of the change in the formula for cell CG18 is:

Submitted model*: 1/(1+$D$18)^CG15

Correction: CG16/(1+$D$18)^CG15

*The formula in the submitted model is mathematically equivalent to that shown here (CG18 = 1/(1+$D$18); CG19 = CG18*$CG$18, with CG19 replicated by dragging to DJ18.)

The difference between these formulae is that the multiplicative term CG16 is absent in the submitted model and present in the correction. The updated cell for CG18 can be replicated by dragging the bottom right corner across to cell DJ18. The formula for FA18:GD18 refers to the discount rate for benefits ($E$18) instead of that for costs ($D$18).

These changes need to be made in both the CRVO and BRVO sheets. The corrections change the method of taking account of survival of patients at the time of the FEO.

The corrections to address Issue 1 are expected to result in a minimal change in the ICERs and in the difference in cost and QALYs between the treatment groups. The corrections do, however contribute to correcting the counterintuitive observation, so that QALYs will increase as the proportion of FEO decreases.

A draft version of an updated model implementing these corrections for Issue 1 is completed. It thus applies mortality at the time of the BSE FEO rather than via the proportion of patients with FEO at each time, T. In this draft model, the correction appears to have a minimal impact on the ICERs; for example, the all RVO ICER changes from £7,368 in the submitted model to £7,403 in the draft updated model. This is because the two calculations are, fortuitously, almost a rearrangement of the same terms.

The corrections for Issue 1 address the QALY observation for most cases, and in those cases where not, the counterintuitive observation results from Issue 2, which is described and addressed in the next section.

Issue 2

Issue 2 reflects that the submitted model assumes that survival of patients after FEO is implicitly assumed to be that of patients at the time of their index RVO. For example, if patients enter the model at age 65 and have FEO at age 75, only 47% would be expected to survive to age 85 (47% is the 10-year survival of 75 year olds) whereas the submitted model assumes 78% (10-year survival of 65 year olds) would do so. This leads to an overstatement of costs and benefits after the time of FEO in the submitted model.

In the reference case, these patients enter the model at age 64.5 years. The table below presents 1, 2, 5 and 10 year survival of patients who have their RVO at different ages. Issue 2 arises because the survival is assumed as in the first column (age 65) but patients who have a FEO in later years will have survival according to the later columns.

Table 17: Survival of patients with an RVO in their BSE, by age at RVO.

Year after Index	Age at BSE FEO (years)				
RVO	**65**	**66**	**70**	**75**	**80**
0	1.00	1.00	1.00	1.00	1.00
1	.99	.99	.99	.98	.96
2	.97	.97	.96	.93	.88
5	.91	.91	.86	.77	.63
10	.78	.76	.65	.47	.28

Source: Calculated using submitted model for sham treated CRVO patients, undiscounted. (England and Wales life table for 2006-08, with hazard rates multiplied by 1.54 for patients in HS5)

Table 17 shows that there would be negligible difference in the survival for patients who are 1 year older (compare columns for ages 65 and 66) or in the first year after their BSE FEO (compare proportions along the second row). In contrast, there are substantial differences for patients whose BSE FEO is several years after their index RVO, especially several years after the BSE FEO.

However, three factors are expected to reduce the impact of this on the QALY (and cost) estimates from the model:

1. BSE FEO, if it occurs, usually occurs early. The data in the Hayreh paper to which the Weibull model used in the reference model was fitted clearly shows this (see below).

2. Mortality in the cohort further reduces the proportion of patients with BSE FEO in later years.

3. Discounting reduces the impact of QALYs accumulated in later years.

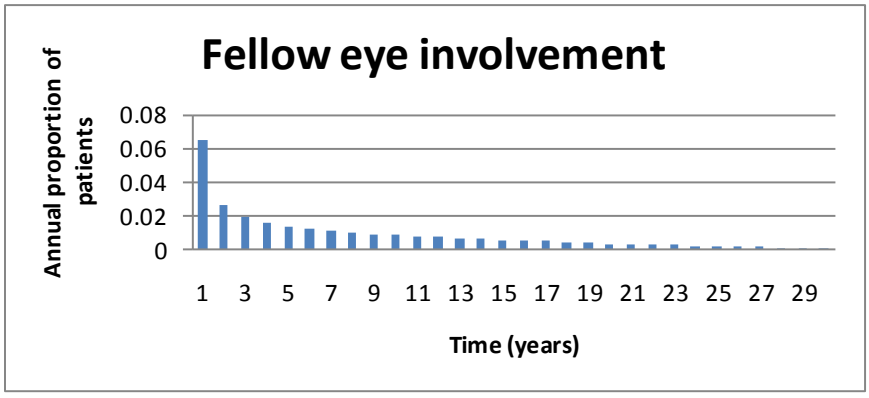
Issue 2 also applies to estimated costs and any overstatement of benefit is accompanied by a corresponding overstatement of cost. In any cycle, both benefits and costs are overstated by the same multiplicative factor that depends on the relative survival of the patients with BSE FEO compared with that for patients with an index RVO in their BSE. This means that ICERs (difference in cost divided by difference in benefit) will be much less affected than the cost and benefit components. However, because the multiplicative factor varies with the time of and the time after the FEO, it is not possible to predict the likely direction and magnitude of the ICER if Issue 2 were resolved.

The programming required to resolve Issue 2 requires the costs and benefits after FEO to be calculated taking account of the age of the patients at each cycle after the time of FEO. Because of the differential mortality between health states when the RVO is in the BSE and the possibility of further transitions between health states, this calculation may need to be done using detailed distributions by health states, rather than with the sum of the alive health states (which is the basis for the [relatively] compact algorithm used in the submitted model). Because FEO can occur at any of the 30 years (or not at all), the fellow eye calculations require, in essence, replicating the model for BSE 30 times.

A practical way to assess the unintended effect of not taking account of the older age of patients at the time of FEO (Issue 2) is to use the model option of a constant rate of FEO over a shorter period.

The shape parameter for the Weibull distribution for FEO is much less than 1 reflecting that most RVOs occur early (e.g., 6.5% in the first year, 2.6% in the second year). Figure 6 (which is in cells BR1:BX9 in the CRVO sheet in the submitted reference case) shows the proportion of patients who have FEO in each year. The proportion is calculated using the Weibull estimates of annual FEO, weighted: by survival.

Figure 6: Annual Proportions of Patients with Fellow Eye Occurrence



The model allows the user to specify a constant rate of FEO over a specified time. For example, in the Summary sheet, setting D8=0 [use constant rate], D9=5% [constant rate] and F9=4 years [time period] reaches a cumulative proportion of 20% of patients (compared with the Weibull curve estimate after 30 years of 34%) and produces an all RVO ICER of £8,828. Trying various combinations of constant rates and time periods shows that the ICER depends most on the cumulative proportion of patients with less variation with the time period over which this occurs.

Table 18: Overall modelled ICER for constant rate of FEO, by constant rate and time period of FEO.

Annual rate of FEO (%) [Summary!D9]	Period of FEO (years) [Summary!F9]	Total FEO (%) [D9*F9]	All RVO ICER [Summary!D60]
7.5	2	15	£11,034
3	5	15	£12,205
1.5	10	15	£13,503
10	2	20	£7,812
5	4	20	£8,828
4	5	20	£9,181
2.5	8	20	£10,097
2	10	20	£10,672
15	2	30	£2,762
6	5	30	£4,397
3	10	30	£6,116
2	15	30	£7,802
Weibull		34	£7,368

Source: Submitted model, reference case, with constant rate of FEO option used

Because the ICERs appear to depend more on the total cumulative proportion of FEO than the time over which these occur, it appears that Issue 2 does not greatly affect the ICERs that include the effect of FEO.

B18. Within the 'Transitions' worksheet it appears that the transition probability matrices for those in the dexamethasone arm not treated, rows 63:75, rely upon the two matrices in columns CN:CZ when the assumption is that they are a weighted average of the identity matrix and the SHAM2 matrix D90-D180. Relying upon the two matrices in columns CN:CZ appears to suggest that these transition probability matrices are invariant through time. There might be some concerns around this if the assumptions for dexamethasone and sham transition probability matrices subsequent to D180 are not as per the base case assumptions; e.g. decay is assumed for these. Please clarify if this is the case.

In the reference case, transition probability matrices are assumed time invariant for patients who are not retreated between D180 and D1080 for CRVO (and to D900 for BRVO). However, the electronic model provides flexibility to address uncertainty around patients' visual acuity after treatment stops.

1. On the transition worksheet, users can specify various transition matrices for those who are not retreated. The selection of matrix can vary by model cycle between D180 and D1080.

2. For the not treated group, one of the options (i.e., Matrix 6) allows for separate and different transition probability matrices for resolved (OCT≤250 µm) and unresolved (OCT>250µm) patients.

3. The transition probabilities in Matrix 6 are calculated based on the weighted sum of the separate resolved and unresolved matrices. The selection of resolved and unresolved matrices and the proportion of patients with resolved RVO by health state and treatment cycle are specified on the Retreatment worksheet.

Thus, the electronic model allows specification of time variant transition probability matrices across a range of assumptions using trial data and user specification. Additional detail and clarification of the functionality are provided below:

A. Specification of transition probability matrices beyond day 180

Overall, transition matrices for D180 onwards are specified on the Transitions sheet using one of six codes (1 to 6) within the section defined by columns AM through CO and rows1 through 11. These codes are:

1. Sham D90-D180
   [(ae31:aj36)^2 or (ae54:aj59)^2]

2. Ozurdex D180-D360
   [aw65:bb69 or aw80:bb85]

3. Identity (no change)
   [co17:ct22]

4. Decay (before Year 3)
   [cw17:db22], [uses Summary!j34 as decay parameter]

5. Decay (after Year 3)
   [de17:dj22], [uses Summary!j35 as decay parameter]

6. Matrix calculated using proportion resolved
   [see Retreatment sheet and rows 63:75]

The matrices for codes 1 and 2 are calculated from individual patient data from the GENEVA trial for patients randomised to the sham and Ozurdex treatment groups. Code 3 is the identity matrix, which corresponds to no change between the VA health states. Codes 4 and 5 are decay matrices, where patients in a given health state have a set probability of moving to the next worse health state in each model cycle. The two decay parameters are set in Summary!J34 and Summary!J35.

For the reference case, Matrix 6 is repeatedly assumed for patients who are not retreated between D180 and D1080 for CRVO (and to D900 for BRVO). Matrix 6 (which allows selection of an integrated matrix of both not treated resolved and not treated unresolved patients) is specified as the weighted sum of two user selected matrices (based on the same codes 1 through 5 defined in the preceding paragraph). Specification of which matrix is applied for not treated resolved and not treated unresolved is defined on the Retreatment worksheet.

B. Specification of matrix 6 components within the Retreatment worksheet

Specification of transition matrix to apply to resolved and unresolved matrices

On the Retreatment worksheet (cells N37 and N38 for CRVO and N57 and N58 for BRVO), the user selects the transition matrices to be applied to non treated resolved and non treated unresolved Ozurdex patients. Matrices 1 to 5 are the same as the options available for all patients in the Transitions sheet, discussed above. Thus, the options are:

1 Sham D90-D180

2 Ozurdex D180-D360

3 Identity (no change)

4 Decay (before Year 3)

5 Decay (after Year 3)

For the reference case, resolved RVOs are assumed to follow Code 3, an identity (no change) transition matrix while unresolved RVO patients follow Code 1, the sham matrix (untreated natural history) previously described for the model.

Specification of proportion of patients resolved by cycle and health state

The proportion of patients whose RVO has resolved after each potential Ozurdex treatment is specified in rows 43-47 (for CRVO patients) and 63-67 (for BRVO patients) in the 'Retreatment' worksheet. Three options are available for the proportion resolved, and may vary by half-yearly cycle:

- Option 0: the proportion of patients whose RVO was resolved by D180 after the first treatment in GENEVA trials (code 0 in column n; trial proportions are given in p50:u50 (CRVO) and p70:u70 (BRVO)), which varies according to the health state.

- Option 1: a fixed proportion of patients (code 1 in column n; the constant proportion specified in column m). A different constant may be specified for each treatment cycle.

- Option 2: user-specified (code 2 in column n; the user specified proportions are in columns p:u), which may vary according to the health state and treatment cycle.

Option 0 "trial data on probability of resolved" is selected in the model reference case for each treatment cycle.

Options 1 and 2 allow the specification of time variant resolved rate. For example if the user selects Option 1, in any of the cells N43:N47, the proportion must be specified in

the corresponding cell in column M. If 0.3 is selected it is assumed that 30% of patients in each health state resolve for the given treatment cycle.

If the user selects Option 2, the proportion of resolved patients in each health state is specified in the corresponding cells of columns P:U for the given treatment cycle.

Options 0-2 can be separately specified for each cycle, allowing for time variant matrices.

Please note that although the labels on B43:B48 and B63:B68 refer to "Last treatment at T", the corresponding resolution rates apply to patients who were last treated at or before T.

C. Computation of matrix 6 on Transition sheet

When the transition matrix specified in the 'Transitions' sheet is code 6 (i.e., using columns AM to CO and rows 1 to 11), each row of the transition matrix specific to that cycle is calculated as the weighted sum of the corresponding row of the transition matrix for:

- patients whose RVO has resolved (code specified in Retreatment sheet cell n37 (CRVO) and n57 (BRVO)); and
- patients whose RVO has not resolved (code specified in Retreatment sheet cell n38 (CRVO) and n58 (BRVO)).

The weights are the proportion of RVOs that have been resolved (p_{th}) and have not been resolved (1-p_{th}), where these proportions can vary with re-treatment number (t) and health state (h).

The calculation of the matrices for the five cycles beginning at D180, D360, D540, D720 and D900 is in rows 62 to 76 in the Transitions sheet.

The matrix for patients whose RVO has resolved is calculated in cells CN63:CS68 (CRVO) and CN70:CS75 (BRVO), based on the matrix codes specified in the Retreatment sheet in cells N37 (CRVO) and N57 (BRVO). The matrix for patients whose RVO has not resolved is calculated in cells CU63:CZ68 (CRVO) and CU70:CZ75 (BRVO), based on the matrix codes specified in the Retreatment sheet in cells N38 (CRVO) and N58 (BRVO).

The matrices to be used for each treatment cycle for CRVO and BRVO are calculated in cells AN63:CC75. For example, the 'code 6' matrix for the D180→D360 cycle for CRVO is calculated in AN63:AS68 using the array formula:

```
{=TRANSPOSE(Retreatment!$D$43:$I$43)*$CN$63:$CS$68
 +(1-TRANSPOSE(Retreatment!$D$43:$I$43))*$CU$63:$CZ$68}
```

The vector of the proportions of resolved RVOs in each health state (ie {p_{th}, h=0 ... 5}) is taken from cells D43:I43 on the Retreatment sheet and multiplied by the matrix for resolved RVOs (which was calculated in CN63:CS68). The vector of the proportions of not resolved RVOs in each health state (ie {1-p_{th}, h=0 ... 5}) is calculated from cells

D43:I43 on the Retreatment sheet and multiplied by the matrix for not resolved RVOs (which was calculated in CS63:CZ68). These two components are added together to produce the matrix displayed in AN63:AS68.

When the vector of the proportion of resolved RVOs varies with time (as can be specified in the Retreatment sheet), the 'code 6' matrices will also vary with time. However, in the reference case, this vector has been specified as being constant with time (ie, $p_{th} = p_h$, h=0 ... 5), resulting in the 'code 6' matrices being constant with time.

The transition matrices that are specified in rows 5 and 10 in the Transitions sheet apply for all patients who were not treated that cycle (for example, AV5 specifies the transition matrix for Ozurdex-treated CRVO patients who were not treated at D360, which includes patients who were not retreated at D180 as well as those retreated at D180 but not D360). This is the row for which code 6 (as described above) makes most sense. When code 6 is specified, the transition matrix is calculated as above. For example, if AV5 is set to 6, the transition matrix is calculated using the re-treatment probabilities in cells D44:I44 on the Retreatment sheet. (Although the label in B44 on the Retreatment sheet is 'Last treatment at D180', the patient group to which the matrix applies is patients last treated at or before D180.)

B19. The ERG has attempted to reconstruct the cohort flow of the model as a cross check to that submitted. Given time constraints, this has not been cross checked and the ERG does not suggest that this accurately models the decision problem. The ERG modelled BRVO cohort flow is a simple copy of the ERG modelled CRVO cohort flow with Search and Replace of some text, as outlined in the Comments worksheet.

Within the ERG Cross Check mortality is not modelled within the cohort flow, but is rather applied at the final summation as a conditioner on the accrued QALY within the relevant cycle, much like the application of the discount rate. As such, as a simplification the ERG Cross check does not currently implement a mortality multiplier for blindness. The cohort flow should broadly correspond to that of the submitted model if within the submitted model; the mortality multiplier for blindness is set equal to 1; the retreatment proportions as set equal to 1; and, the cycle hazards of death are set equal to 0.

Steady state from cycle 10		HS0	HS1	HS2	HS3	HS4	HS5
ERG Cross Check Adj. Submission	CRVO DEXA CRVO DEXA	[redacted]					
ERG Cross Check Adj. Submission	CRVO SHAM CRVO SHAM	[redacted]					
ERG Cross Check Adj. Submission	BRVO DEXA BRVO DEXA	[redacted]					
ERG Cross Check Adj. Submission	BRVO SHAM BRVO SHAM	[redacted]					

Given this there seems to be reasonable correspondence between the ERG Cross Check and the submitted model in terms of the main cohort flow. Matters become more complicated in terms of the modelling of fellow eye involvement. Given the concerns around the impact of changing the rate of fellow eye involvement on total QALYs as outlined above this is a particularly important aspect of the model to understand.

This aspect of the submitted model is particularly difficult to follow and some account of the logical structure of the modelling of this aspect would be much appreciated. It is appreciated that this is not a trivial description, and as a consequence the simplest description would explain the logic and associations between and resulting calculations underlying:

The response to this question describes the formulae in the submitted model.

- ***the mortality adjusted incidence of cells CG17:DJ17 and the no fellow eye involvement due to no incidence [or death] of cell DK17***

  Cells CG17:DJ17 calculate the proportion of patients who have FEO each year as the proportion expected if there is no mortality (p_t) times the proportion of patients who are still alive (CG16:DJ16). The latter proportion is copied from column P, taking account of there being two cycles per year (ie column P gives proportion alive each half-year while row 16 (CG16:DJ16) is a transposed version that is collapsed to years). The proportion p_t is the proportion of RVOs that would be eligible for treatment with Ozurdex (Summary!D10, described in the spreadsheet as 'Proportion of FEO converting to ME') times either a constant rate or the Weibull estimate of the proportion having FEO. Model parameters relating to the constant rate or the Weibull are shown in CG7:CL12, with a graph of the proportion of patients in each year shown in BR1:BX9. CH13 shows the expected cumulative proportion of patients who would have had FEO over 30 years, and is 1-DK17 (which is 1-the sum of the 30 probabilities in CG17:DJ17).

An example of the formula used, for CG17, is:

```
Summary!$D$10 * CG16 *
IF($CI$8=0,
        IF($CK$10>=CG15,$CI$10,0),
        1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11) ) )
```

- ***the FA40:GD158 and the distinction between elements above the principle diagonal and those below it***

  This array shows the cumulative discounted QALYs that accrue to patients who have a treated fellow eye in the year implied by the column (e.g., FA for at end of Year 1). The shaded cells above the principal diagonal are for patients before they have FEO, and each row within these shaded cells is the cumulative discounted QALY up to and including the half-year [as implied by the row] in WSE RVO patients (which is stored in column GE). For example, the formula in FA40 is $GE40.

  The elements below the principal diagonal successively add in the QALY increment for a half-year cycle for the BSE. The QALY increment is for the half-year relative to the position of the element below the principal diagonal. For example, FA42 is:

  ```
  FA41 + $B42*FA$18*$GI40
  ```

  where FA41 is the cumulative discounted QALY at the end of the previous half-year cycle and $GI40 is the discounted QALY increment for a BSE in the second half-year of the model (since FA42 is two elements below the principal diagonal). The QALY increment in $GI40 is discounted for the time of FEO by multiplying by $FA18, the discount factor at that time. This term is added only while within the model time horizon ($B42 is either 1 (included) or 0 (excluded)).

  Note: The unequal model cycles in the first half-year necessitate some special processing for the first element under the principal diagonal so that the location of the corresponding QALY increment is correctly specified. The QALY increment is in GI24 and not GI39, which would have been contiguous with the other discounted QALY increments in column GI.

- ***GE40:GE158 which appears to be the cumulative (discounted?) QALY among WSE patients never having had fellow eye involvement***

  GE40:GE158 is the cumulative discounted QALY for patients with an index WSE who never have FEO. After the first 3 years (eg GE45), the discounted QALY increment is the utility ($J$17:$O$17) weighted proportion of patients who are in each health state, discounted ($E45) and added only if within the time horizon of the model ($B45). The proportion of patients in each health state is the average of the proportion before and after taking account of mortality in that cycle (= (J45:O45 + AC45:AH45)/2). The unequal model cycles in the first half-year and the different re-treatment possibilities mean that the formulae for GE40 and GE41:GE44 are slightly more complex than those for after Year 3.

- ***GF40:GF158 which appears to be the cumulative (discounted?) QALY among all WSE patents***

  Each cell in GF is the weighted sum of the cumulative discounted QALYs for WSE patients who had FEO at the end of Year 1, Year 2, ..., Year 30 (columns FA:GD), or never (column GE), where the weights are the expected proportions of patients in each of these categories ($CG$17:$DK$17). For example, GF40 has the formula:

  SUMPRODUCT(FA40:GE40,$CG$17:$DK$17)

  (The calculation of CG17:DJ17 has been explained above, and is the vector of the proportion of alive patients who have FEO by the end of each year; that is survival of patients at the time of FEO (Issue 1 identified in B17) is taken into account in these cells in the submitted model).

- ***GG40:GI158 relating to the BSE calculation***

  Column GG has the cumulative discounted QALY for patients with a BSE RVO of the same type (e.g., CRVO in the CRVO worksheet).

  Column GH is the discounted QALY increment for each half-year for a BSE with an RVO of the same type as the sheet (the label for this column, 'BSE /cycle xRVO', means that it is the QALY increment for a CRVO in the BSE in the CRVO sheet and for a BRVO in the BSE in the BRVO sheet).

  Column GI is the discounted QALY increment for a FEO of an RVO of either type (calculated from columns GH in the CRVO and BRVO worksheets; this takes account of the distribution of RVOs if RVOs of either type are specified).

  For example, GI40 has the formula

  CRVO!GH40*$HW$11+BRVO!GH40*$HW$12

  where HW11 and HW12 (= 1-HW11) are the proportions of CRVO and BRVO RVOs, respectively. In the submitted reference model, the RVOs are specified to be of either type (since cell F8 in the Summary sheet is 1), so HW11 is 0.345 (= cell D35 in the Summary sheet) and HW12 is 0.655 (= 1-0.345).

- ***GH40:GH158 averaging between WSE and BSE***

  Column GH as described above contains the discounted QALY increment for each half-year for a BSE with an RVO of the same type as the sheet.

  Column GJ is a weighted average of the cumulative discounted QALYs for WSE (column GF) and BSE (column GG), weighted by the proportion with WSE (which is specified in cell Summary!D7 and copied to cell CD10 of the CRVO and BRVO sheets). For example, GJ40 has the formula:

  GF40*$CD$10+GG40*(1-$CD$10)

Again, as a brief face value check subtracting GF40:GF158 from GE40:GE158 initially results in a positive number with this increasing as time progresses moving down the column but this then starts to fall and turn negative, this possibly giving rise to what appear to be the counterintuitive results around varying the proportion of fellow eye involvement as outlined under clarification point E12 above.

Please refer to Question B.17 for a description of the identified issues, the corrections required and their impact on the model output.

Given the above, please clarify whether you are aware of any other logical errors within:

i. The logical structure as applied within the modelling for the derivation of parameter values as derived from expert opinion

No issues identified.

ii. The logical structure as applied within the modelling for the derivation of parameter values as derived from publications within the literature

No issues identified.

iii. The logical structure of the electronic model itself

Review of the model structure and programming did not identify any issues other than 1 and 2, as described above with the exception that the calculation of LYs in rows 161 and 164 in the CRVO and BRVO sheets did not include half the contribution of the cell for patients who had a sixth treatment. These calculated quantities are used to calculate the quantities in rows 162 and 165, which are not used elsewhere in the model and, in particular, do not affect any of the summary statistics. An example of the change in the formula is that for cell J161:

Submitted model:
J178+$C$3*(SUMPRODUCT($B$25:$B$28,J25:J28+J26:J29)
+SUMPRODUCT($B40:$B157,J40:J157+J41:J158))/2

Correction:
J178+$C$3*(SUMPRODUCT($B$25:$B$28,J25:J28+J26:J29)
+$B$29*J$29
+SUMPRODUCT($B40:$B157,J40:J157+J41:J158))/2

If so, please indicate any changes necessary to correct the model structure and describe the expected impact on the results presented in the submission.

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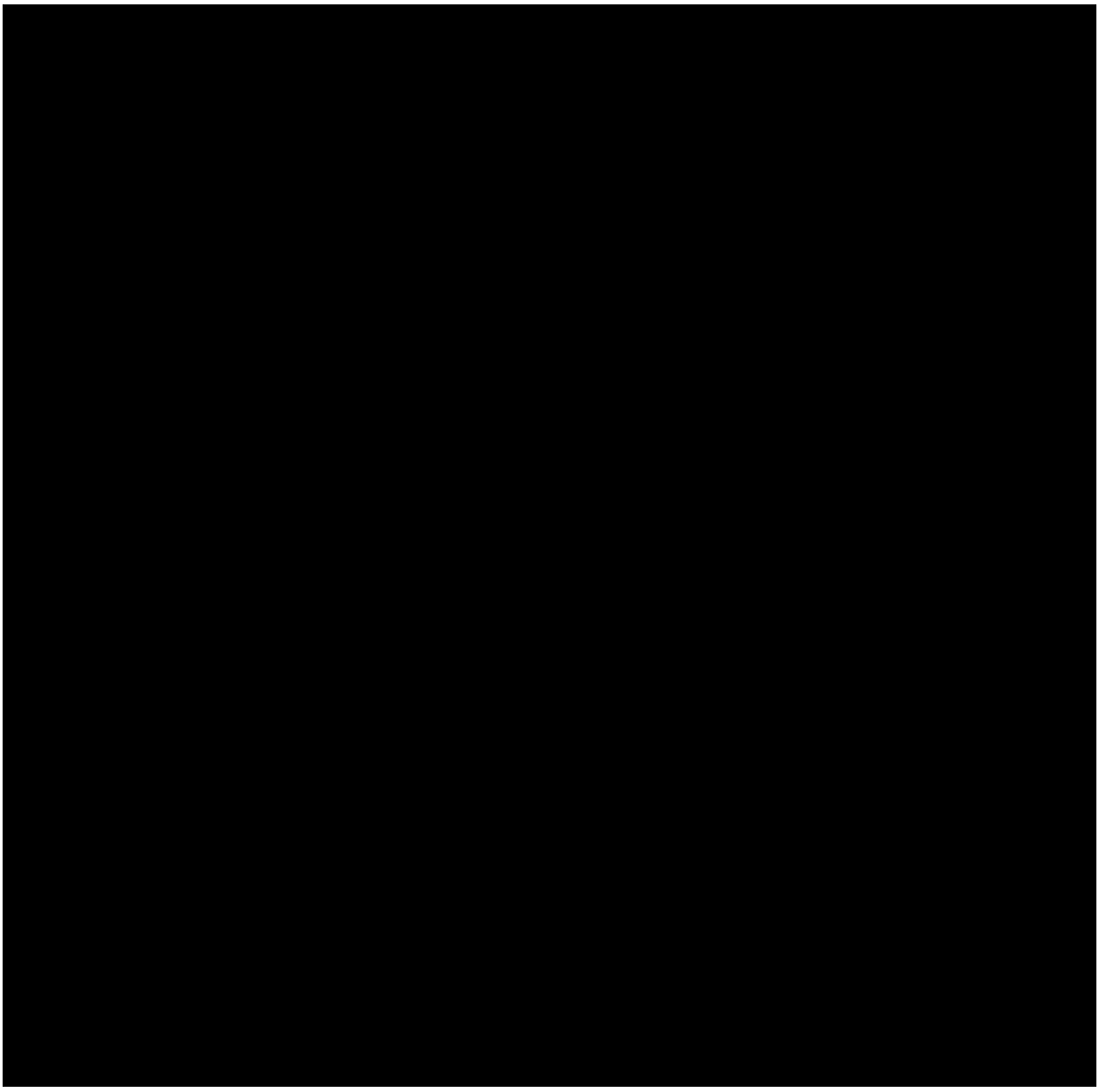
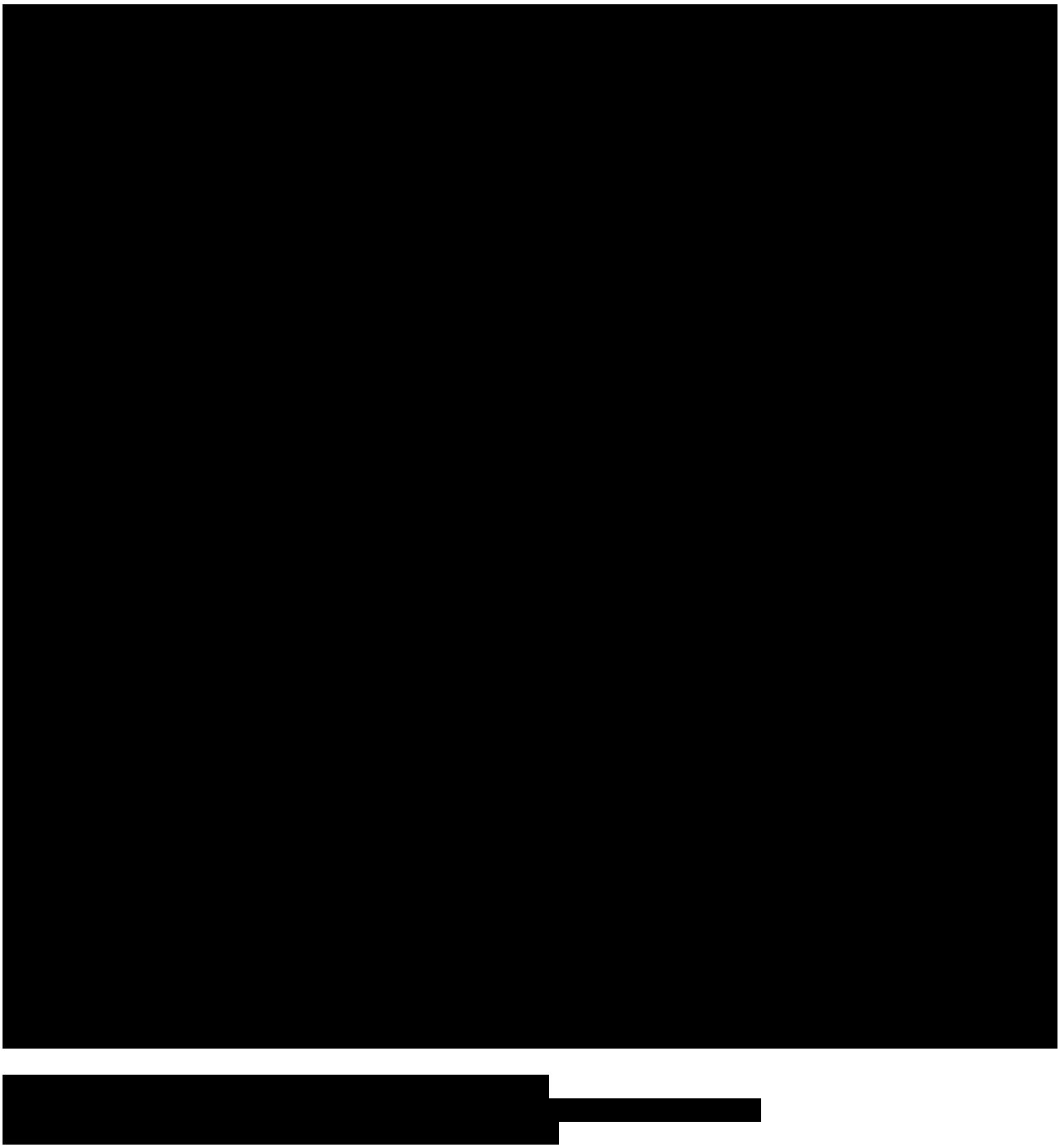
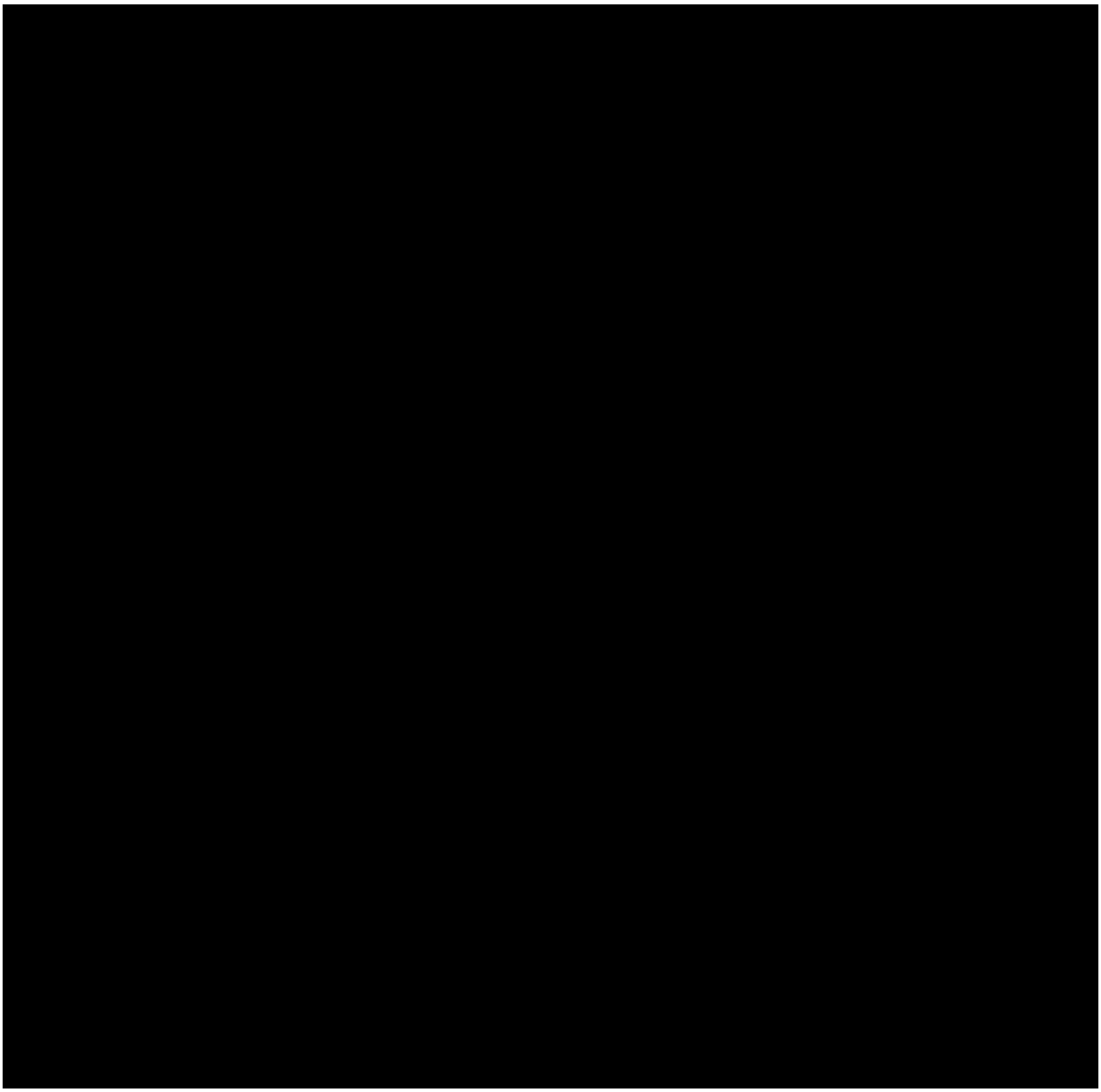
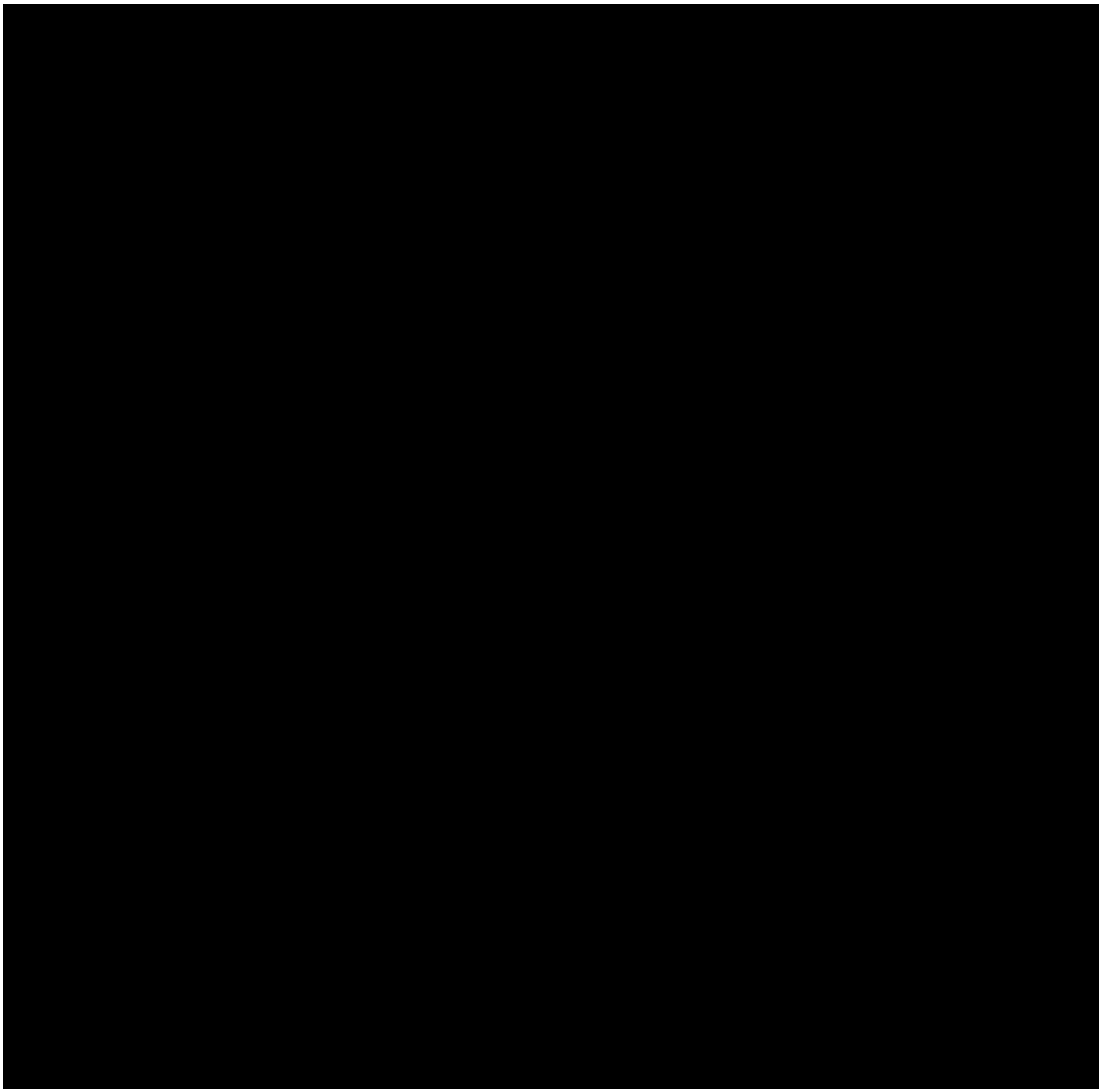
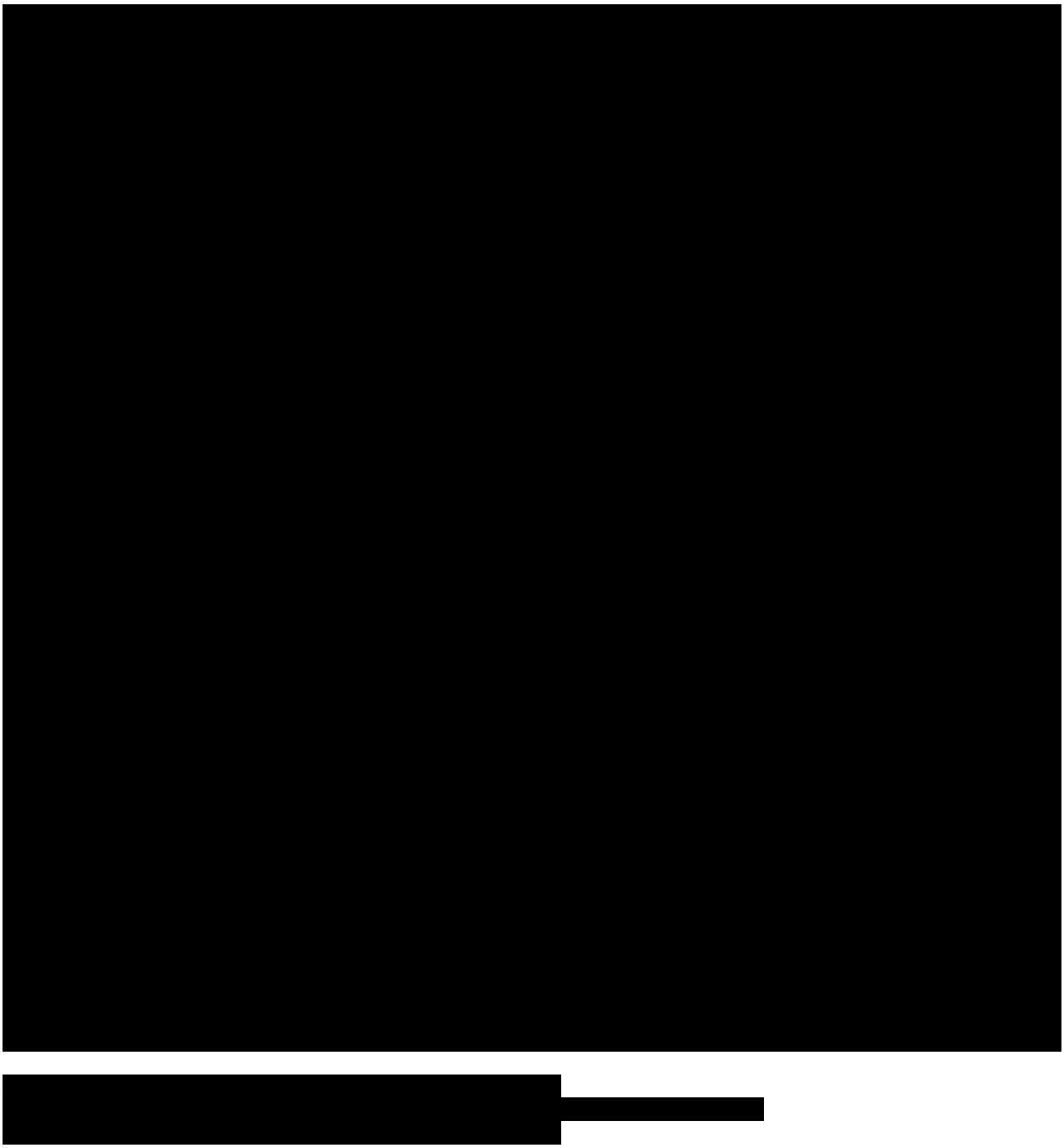
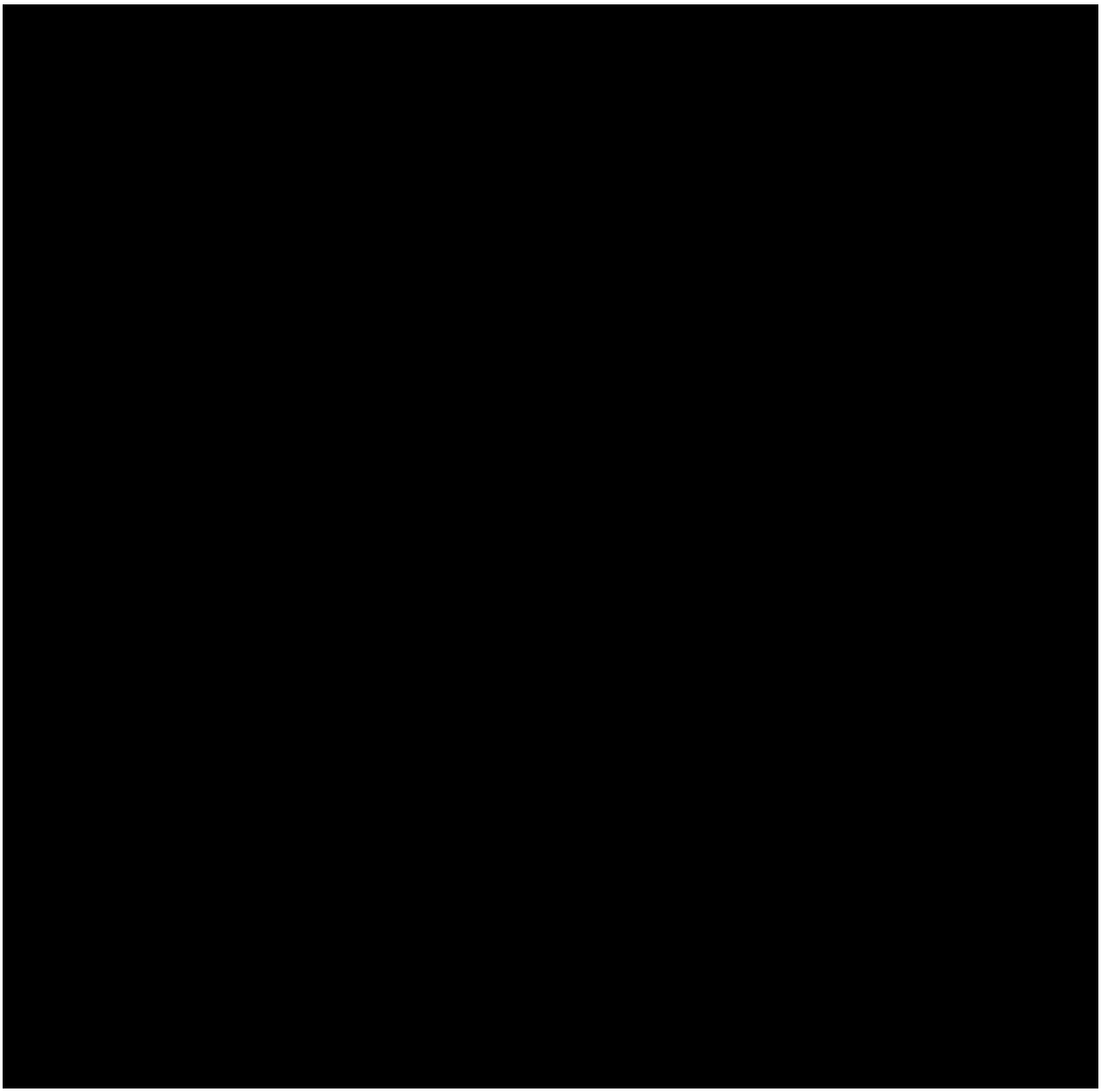


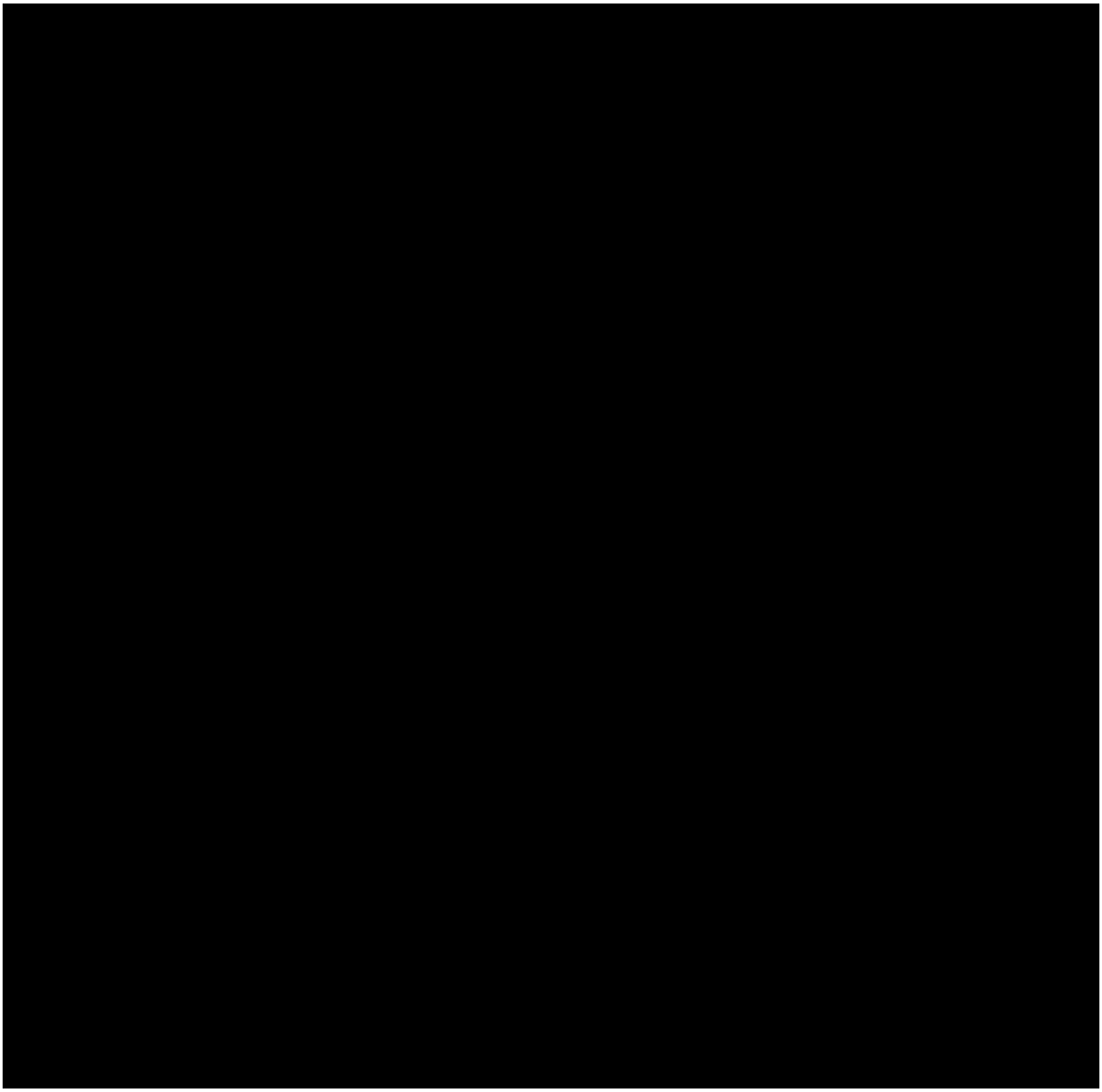


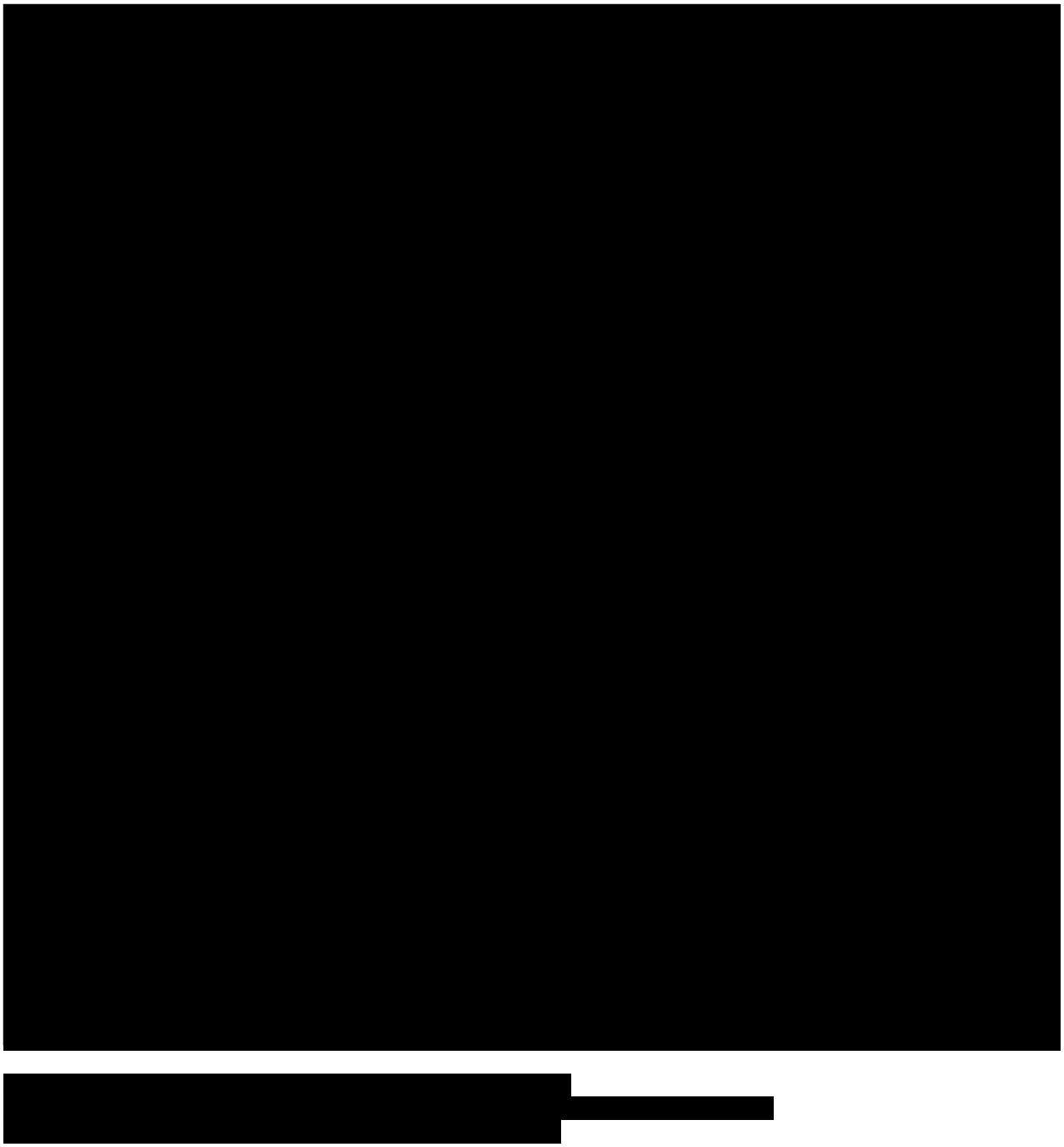












Appendix B4: Additional analyses using population specific baseline distributions

Clinical outcomes from the model

Table 19: Comparison of trial and model outcomes in Ozurdex treated patients with CRVO

Health state	Baseline		Day 180		Day 360	
	GENEVA 008&009 result	Model result	GENEVA 008&009 result	Model result	GENEVA 008&009 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 20: Comparison of trial and model outcomes in Ozurdex treated patients with BRVO-macular haemorrhage.

Health state	Baseline		Day 180		Day 360	
	GENEVA 008&009 result	Model result	GENEVA 008&009 result	Model result	GENEVA 008&009 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 21: Comparison of trial and model outcomes in Ozurdex treated patients with BRVO with previous laser.

Health state	Baseline		Day 180		Day 360	
	GENEVA 008&009 result	Model result	GENEVA 008&009 result	Model result	GENEVA 008&009 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%

Table 22: Comparison of trial and model outcomes in observation (sham) patients with CRVO

Health state	Baseline		Day 180	
	GENEVA 008&009 result	Model result	GENEVA 008&009 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 23: Comparison of trial and model outcomes in observation (sham) patients with BRVO-macular haemorrhage

Health state	Baseline		Day 180	
	GENEVA 008&009 result	Model result	GENEVA 008&009 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 24: Comparison of trial and model outcomes in observation (sham) patients with BRVO with previous laser

Health state	Baseline		Day 180	
	GENEVA 008&009 result	Model result	GENEVA 008&009 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%

Accumulation of QALYs and LYs

Table 25: 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

Table 26: 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

Table 27: BRVO with 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

Table 28: BRVO with prior 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

Disaggregated incremental QALYs and costs

Table 29: 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%

Table 30: BRVO with 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%

Table 31: BRVO with prior 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%

Table 32: 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%**

Table 33: 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%**

Table 34: Costs by category- BRVO with 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%**

Table 35: Costs by category - BRVO with prior 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%**

Table 36: Base-case results – all RVO

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

Table 37: Base-case results – CRVO

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

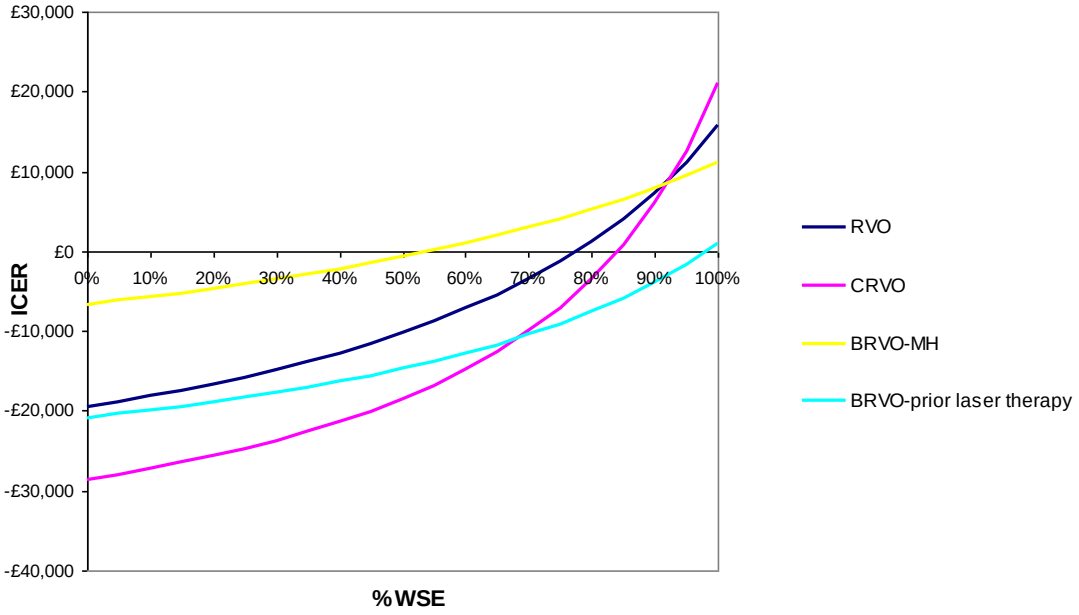
Table 38: Base-case results – BRVO-macular haemorrhage

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

Table 39: Base-case results – BRVO with prior laser

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus observation (QALYs)
Observation	£14,184	14.28	11.24	-	-	-	-
Ozurdex	£12,966	14.39	11.56	-£1,218	0.11	0.31	Dominant

Figure 7: Varying %WSE



Results of subgroup analysis

Table 40: 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

Table 41: 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