Dexamethasone intravitreal implant for diabetic macular oedema

ERRATUM

As a result of the redaction process, please note that there may be minor discrepancies between the page numbers in this erratum and those in the redacted ERG report

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BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
11	Text relating to dosing regimen of dexamethasone in PLACID and BEVORDEX trials amended to reflect pro re nata [PRN] nature of the dosing regimens.
13	Text relating to the results of the subgroup analyses in 'people with prior laser or prior anti-VEGF therapy without prior steroid therapy' amended to reflect these were from the MEAD studies.
51	Text reference to Section X amended to Section 4.2.
58	Text relating to use of ranibizumab amended.
72	Text relating to dosing regimen of dexamethasone in PLACID and BEVORDEX trials amended to reflect pro re nata [PRN] nature of the dosing regimens.
86	Numerical data for discontinuations in the MEAD studies added.
102	Text reference to Table X amended to Table 24.
103	Text reference to Table X amended to Table 25.
104	Text reference to Table X amended to Table 25.
108	Text relating to TRSAE in NCT00035906 amended.
109	Text relating to pseudophakic subgroup data amended to reflect availability of post hoc safety and efficacy data from PLACID.
114	Text reference to Table X amended to Table 31.
115	Text reference to Table X amended to Table 32.
121	Incorrect text relating to the European Marketing authorisation application has been deleted.
122	Label has been added to Box 11a and cited in the text.
123	Text relating to reason for exclusion of studies from the base case NMA amended to reflect <12 month exclusion criterion.
148	Text relating to the European marketing authorisation for dexamethasone has been amended.
157	Reference to 'Section 0' has been amended to 'Section 6.1.2.2' in Table 45 (5th line, 2nd column, referring to S4: Structural assumptions)
161	In 2nd line, reference to 'Section 0' has been amended to 'Section 5.4.4.2'.
203	The ERG has added the following sentence in the second paragraph: "The ERG used the relevant data directly from the electronic version of the economic model (rather than from the tables in the CS), to avoid errors due to the use of rounded figures in the tables."
204-205	Tables 64 and 65 (and related text) have been amended following re-calculations using data from the electronic version of the economic model rather than from the rounded figures provided by the company in the CS.
206	Last rows (transitions from health state 6) in Tables 66 and 67 have been amended.
219	The following sentence has been added at the end of the first paragraph: "this is because the latter figure refers only to the proportion of phakic patients who had had cataract surgery in the study eye". The following sentence has been deleted from the end of first paragraph: "The ERG is unclear as to why there is this discrepancy between the two figures, but the figure in the EMA report confirms that the incidence of cataract is probably higher that what would be expected if cataract was developed only as a result of underlying DM". In addition, the word 'assessment' has now been correctly spelled (second line of first paragraph).
278	In Table 106 caption the reference to CS has been amended from 'pgs 317-425' to 'pgs 417-425'.

278 & 281	In Table 106, the footnote to Scenario 2 has been amended and the footnote to scenario 3 has been removed.
283	The ERG has added the following sentence: “The ERG noted that the company used an average of 1.5 appointments for bilateral treatment with fluocinolone acetonide, instead of 1.75, which was the correct figure. The ERG was unable to provide the correct figures in Table 109 due to time constraints, but notes that the impact on the results is only minor”.
288	In 11th line, reference to ‘Section 0’ has been amended to ‘Section 5.4.4.2’.
296	Correct cross-references to sections are provided in place of ‘Error! Reference source not found’.
315-316	The figures in Table 128 and in preceding relevant text have been amended.
319	Table 133: The ICER of bevacizumab versus laser (6th column) and all figures for watch and wait (5th row) have been amended.
441, 444, 446	The instructions for calculations in analysis C7 have been amended to reflect that the changes should be made in cells C32:G32 and not C32:C36
448	The sentence above calculation sheet for analysis C14 has been omitted as it was redundant.
453-455	Results for watch and wait have been amended in scenarios “all model corrections”, C5, C6, C11, C12

- 024: dexamethasone (5 monthly) versus ranibizumab;
- PLACID: dexamethasone (6 monthly PRN) + laser photocoagulation versus laser photocoagulation;
- BEVORDEX: dexamethasone (4 monthly PRN) versus bevacizumab.

The two MEAD studies were identical in study design and provide the key data for dexamethasone in the CS although this is versus sham which was not a comparator of interest in the final scope issued by NICE. NCT00035906 limited treatment with dexamethasone to one dose and compared it with observation alone, which again was not a comparator listed in the final scope issued by NICE. However, based on the EU marketing authorisation for dexamethasone, the ERG considers observation and sham to be appropriate comparators for some of the populations for whom dexamethasone would be a treatment option. This is because observation and sham can be considered surrogates for watch and wait.

The ERG has concerns that 024 and BEVORDEX do not utilise the dexamethasone dosing regimen authorised in the UK; both utilise more frequent dexamethasone regimens than the EU marketing authorisation 6 monthly recommended minimum re-treatment period.

In view of the differences between each of the trials, with the exception of the MEAD studies, the ERG considers the company's decision to report each trial separately to be appropriate. The ERG notes that the company reported the MEAD studies separately, combined in a pooled analysis and also combined in a meta-analysis.

The ERG does not consider 024 or BEVORDEX to address the decision problem as they do not use the licensed treatment regimens for dexamethasone in the UK and so these studies are not discussed in detail in this report.

The MEAD studies and NCT00035906 were 3-armed RCTs, with one of the treatment groups being a lower dose of dexamethasone than that licensed for use in the UK (dexamethasone 350µg). The ERG thus does not consider data from this trial arm of relevance to this review and does not present or discuss the data in this report.

MEAD-010 contained 494 randomised patients (328 patients randomised to the two treatment arms of interest to this review) and MEAD-011 contained 554 randomised patients (373 patients in the two treatment arms of interest to this review). Both MEAD studies lasted for 36-39 months. PLACID enrolled and randomised 253 patients for 12-15 months planned follow-up, and in NCT00035906 there were 171 DMO patients randomised (although only 114 were randomised to treatment arms of interest to this review, i.e. dexamethasone 700µg or observation) and follow up was planned for 180 days. Efficacy analyses were based on the ITT (randomised) populations and safety analyses

difference with more AEs in the dexamethasone + laser group compared with the laser alone group in PLACID.

In terms of subgroup analyses of relevance to the decision problem, the mean BCVA change from baseline with dexamethasone for the pseudophakic patients in the MEAD studies was statistically significant at all time points compared with sham. In addition, the pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population (6.5 letters in the pseudophakic subgroup compared with 3.5 in the whole trial ITT population). This could be a result of the impact of cataract adverse effects in the phakic patients in the whole trial population.

There were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline in the MEAD study who were randomised to dexamethasone compared with the whole study (ITT) population due to the absence of primary cataract AEs. The company reported that the most common ocular AE reported in the pseudophakic subgroup was IOP increase although fewer patients in the dexamethasone group (24.7%) experienced raised IOP compared with those in the dexamethasone group for the total MEAD (safety) population (36.0%).

Dexamethasone generally resulted in greater reduction in CRT and improvement in BCVA compared with sham in the MEAD subgroup analyses in people with prior laser or prior anti-VEGF therapy without prior steroid therapy.

Safety data suggest a similar safety profile for dexamethasone in the subgroup of patients with any prior treatment (including prior corticosteroid therapy) to that seen in the whole trial (safety) population of the pooled MEAD studies, with higher incidences of ocular adverse events in the dexamethasone group compared with the sham group.

The company also presented data in the CS from an NMA comprising of 11 RCTs (five dexamethasone RCTs and six RCTs for comparators with one additional trial included in the sensitivity analyses) in the CS. The comparisons considered in the NMA were:

- whole trial DMO population for trials reporting data on the proportion of patients achieving at least a 10 letter gain from baseline at 12 months or proportion of patients achieving at least a 10 letter loss from baseline at 12 months;
- subgroup analysis for those pseudophakic at baseline (in the absence of subgroup data the whole trial data were used);

sensitivity analysis 1 (SA1): including the FAME trial for fluocinolone acetonide in the network that was excluded as it reported data for patients achieving a 15 letter improvement from baseline at month 12 rather than a 10 letter improvement (10 letter data were estimated for this analysis);

The secondary efficacy and safety endpoints of the six key trials presented in the CS varied across the trials but included change in BCVA at specified post-baseline time points, proportion of patients with improved or worsened vision, change in CRT at specified post-baseline time points, change in total leakage area at specified post-baseline time points along with safety and HRQL measures. Further details on the outcomes of each individual trial are provided in Section 4.2.

The ERG note that BCVA assessments for the study eye were the most commonly reported vision outcomes in the RCTs in the CS and where assessed, BCVA in both eyes was generally assessed as a safety outcome in the clinical trials, but was not specifically reported for any of the clinical trials presented within the CS.

The ERG also notes that contrast sensitivity was reported only for the MEAD studies with no numerical data presented in the CS. The ERG considers that the need for cataract surgery is a subjective outcome and the company's reporting of cataract adverse effect is appropriate to address this outcome in the final scope issued by NICE. The HRQL data collected and reported from the RCTs was generally based on the NEI-VQ-25 vision specific QoL tool.

To summarise, given the available clinical data for dexamethasone, the ERG considers that the outcome data presented in the CS by the company are appropriate to address the outcomes listed in the final scope issued by NICE.

3.5 Timeframe

There was no specific recommendation on the treatment time frame specified in the final scope issued by NICE, and the duration of treatment varied across the six dexamethasone clinical trials from 1 dose of dexamethasone to a maximum of 39 months of treatment (administered ≥ 6 monthly as required). The ERG notes from discussion with clinical experts that treatment with dexamethasone could be expected to be continued for longer than 3 years in clinical practice. The ERG thus acknowledges that long-term safety and efficacy data for dexamethasone are limited by the trial durations.

The ERG notes that the company's NMA was based on 12-month outcome data. The ERG requested clarification on this decision when there were 3-year clinical trial outcome data available for dexamethasone. The company's response is presented in Box 10.

Box 10. Company's rationale for use of 12 month outcome data in the NMA (Company's response to clarification, A7, pg 6)

Within the clinical evidence base identified for use in the MTC, BCVA letter gain or loss analysis was more commonly reported at 12-months, more than at any other time point. This was the primary efficacy analysis time point in five of the seven comparator trials used in the MTC models.

the decision problem. The ERG notes that the company did limit study inclusion to studies over 6 months in duration. The company's justification for this decision was, "studies of less than 6 months duration were excluded on the basis that the DEX700 implant provides dexamethasone treatment coverage for up to this period and therefore comparisons at earlier timepoints are inappropriate and do not help assess the benefit of DEX700 to the long-term management of DMO" (CS, pg86). The ERG does not consider this to be an acceptable exclusion criteria as studies of shorter duration could still be of importance in assessing the short term safety of dexamethasone. In addition, this 6 month restriction could have resulted in the exclusion of potentially relevant studies of the comparators from the network meta-analysis as some of the comparators potentially have shorter review and re-treatment periods, e.g. ranibizumab. However, due to time constraints, the ERG is unable to comment further on the likelihood of missing studies and any potential impact this may have on the overall results.

4.1.3 Details of RCTs included in the review of clinical effectiveness

The company reported that combining the results of the original search and updated database search with the findings from the conference proceeding searches and other searches resulted in the identification of 4,441 potentially relevant citations.

These 4,441 citations comprised of 2,541 from the database searches, 1,891 from the conference proceeding searches and 9 from other sources.

Of the additional 9 citations, 7 were identified through confidential Allergan in house sources: 4 clinical study reports (MEAD-010, MEAD-011, PLACID, 024), the manuscript for the pooled MEAD data analysis[51], the protocol for BEVORDEX (Gillies *et al.* 2010[61]) and subgroup analysis of the ETDRS study to align patient with current practice[67]. The company reported that another citation (abstract presented at conference, 2011) was identified through reference review of an existing systematic review[68] and the 9th citation was identified through review of clinicaltrials.gov.[69]

After deduplication, there were a total of 3,400 articles which were assessed at level 1 (abstract screening) and 2,728 of them were excluded from further review. The remaining 675 citations were reviewed at level 2 as full text articles where available. Level 2 screening resulted in the identification of 65 RCTs in 90 publications for inclusion in the SR. Reasons for exclusion included non-RCT study design (n = 163), article not available (n = 5), post-hoc/pooled analysis (n = 46), study duration <24 weeks (n = 34), abstract only with not enough detail to assess study in full (n = 10), article unavailable (n = 5). Of the 65 RCTs meeting the eligibility criteria, 6 investigated the clinical efficacy and safety of dexamethasone 700µg (Table 9). The remaining 59 RCTS provided data on the comparators specified in the decision problem and thus contribute only indirect evidence. They will be discussed in Section 4.6.

4.2.1 Detailed description of included RCTs

The six RCTs included in the CS providing clinical safety and/or efficacy data for dexamethasone 700µg compared the following:

- MEAD-010 and MEAD-011: dexamethasone (6 monthly *pro re nata* [PRN]) versus sham;
- NCT00035906: dexamethasone (1 treatment only) versus observation;
- 024: dexamethasone (5 monthly) versus ranibizumab;
- PLACID: dexamethasone (6 monthly PRN) + laser photocoagulation versus laser photocoagulation;
- BEVORDEX: dexamethasone (4 monthly PRN) versus bevacizumab.

The two MEAD studies were identical in study design and provide the key data for dexamethasone in the CS although this is versus sham which was not a comparator of interest in the final scope issued by NICE. NCT00035906 limited treatment with dexamethasone to one dose and compared it with observation alone, which again was not a comparator listed in the final scope issued by NICE. However, based on the EU marketing authorisation for dexamethasone, the ERG considers observation and sham to be appropriate comparators for some of the populations for whom dexamethasone would be a treatment option. This is because observation and sham can be considered surrogates for watch and wait.

The ERG has concerns that 024 and BEVORDEX do not utilise the dexamethasone dosing regimen authorised in the UK; both utilise more frequent dexamethasone regimens than the EU marketing authorisation 6 monthly recommended minimum re-treatment period. The final RCT, PLACID includes dexamethasone plus laser which was listed as an intervention of interest in the final scope issued by NICE.

In view of the differences between each of the trials, with the exception of the MEAD studies, the ERG considers the company's decision to report each trial separately to be appropriate. However, the ERG does not consider 024 or BEVORDEX to address the decision problem as they do not use the licensed treatment regimens for dexamethasone in the UK and so these studies are not discussed further in this report. However, the data from both trials are provided in Appendix 9.6 for information because they enable direct head-to-head comparisons of dexamethasone with ranibizumab and bevacizumab, two comparators of interest listed in the final scope issued by NICE. In addition, the MEAD studies and NCT00035906 were 3-armed RCTs, with one of the treatment groups being a lower dose of dexamethasone than that licensed for use in the UK (dexamethasone 350µg). The ERG

study treatment. Statistical analysis for all secondary outcomes was performed with a 2-sided alpha level of 0.05.

In general, the ERG considers the company's approach to the statistical analysis of the data in the dexamethasone RCTs to be appropriate. However, the ERG would like to highlight that the use of LOCF is only likely to be robust when patients have stable disease prior to discontinuing. This is unlikely to be the case in the MEAD studies. The high discontinuation rate within the MEAD studies (35.9% dexamethasone vs 56.6% sham)[51] suggests that this is likely to have a substantial impact on the results. The ERG is unable to ascertain in which direction this bias might affect the results.

4.4 Summary statement

For this STA, six RCTs (MEAD-010, MEAD-011, PLACID, BEVORDEX, 024 and NCT00035906) were included in the clinical effectiveness section of the CS to provide clinical data on dexamethasone for the treatment of DMO. However, the ERG considers only four of the RCTs to be of direct relevance to the decision problem (MEAD-010, MEAD-011, PLACID and NCT00035906) because the remaining two studies used doses of dexamethasone that are not authorised for use in the UK. The ERG thus reports and critiques only the four RCTs deemed applicable to the decision problem in this report.

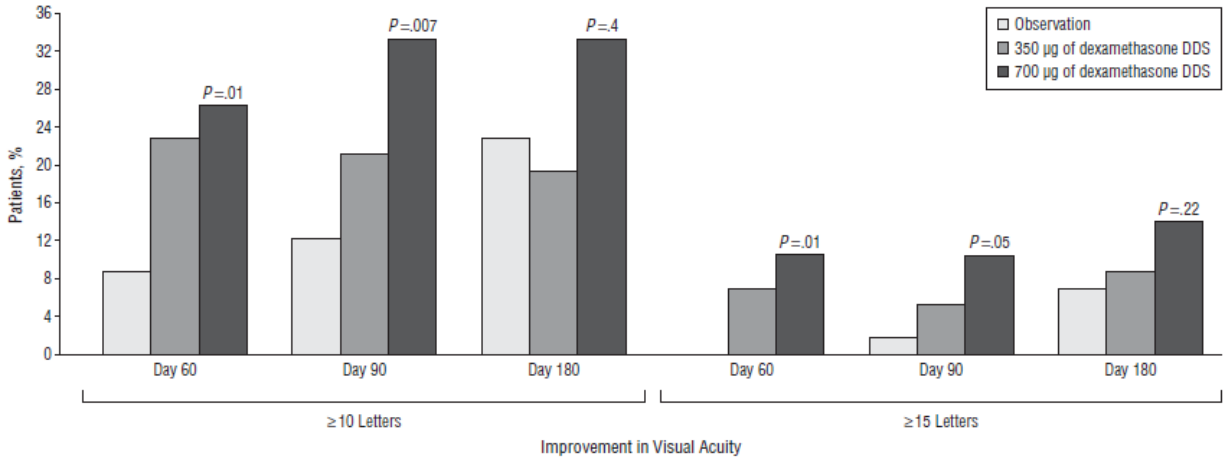
The ERG considers that the inclusion and exclusion criteria of the four RCTs were acceptable to address the each trial's objectives. In addition, the ERG notes that the baseline characteristics of the randomised populations of the trials appeared to be generally balanced between trial arms. Although no formal assessment was provided in the CS. However, the ERG and clinical experts have concerns regarding the applicability of the trials to the populations for which dexamethasone has EU marketing authorisation.

The interventions in the RCTs were dexamethasone 700µg intravitreal implant (MEAD studies and NCT00035906) or dexamethasone 700µg intravitreal implant plus laser photocoagulation (PLACID). The comparators varied across the trials. In the MEAD studies the comparator was sham, in PLACID it was laser alone and in NCT00035906 it was observation.

The ERG considers that the outcome data reported from RCTs appeared to be broadly consistent with the data collected in the trials. However, the ERG notes that BCVA both eyes requested in the NICE final scope was not reported in the CS for any of the trials.

associated with a statistically significant improvement at days 60 and 90 compared with observation. This pattern of effect was also seen in the number of patients achieving at least a 15-letter improvement in visual acuity (Figure 11).

Figure 11: DMO patients achieving a BCVA improvement of at least 10 letters from baseline at all time points in NCT0035906, n (%) (reproduced from CS, Figure 27, pg 180)



Key: BCVA, best corrected visual acuity
Source: Haller et al. 2010[60]

It was reported in the CS that at Day 90, there was a mean decrease from baseline CRT of 132.3µm with dexamethasone (n=11) and an increase of 30.2µm in the observation group (n=19). This difference was based on observed data and was statistically significant, favouring treatment with dexamethasone (p<0.001). Day 180 data for this outcome was not reported in the publication cited by the company or in the CS.

There were two deaths in the dexamethasone 700µg group of the DMO subgroup of patients enrolled in trial NCT00035906 and no deaths in the sham arm. There were no details reported in the CS on the cause of these deaths and so it is unclear if they could be related to treatment exposure.

4.5.3 Safety and adverse events

MEAD studies

The company reported that dexamethasone was well tolerated in the MEAD studies with low discontinuation rates due to adverse events (AEs), low treatment-related serious AE (TRSAE) rates and no deaths deemed attributable to treatment (Table 24). The company also reported that both discontinuations and adverse event rates were positively correlated with increased treatment exposure

and that the overall incidence of AEs adjusted for treatment exposure time was similar among treatment groups although numerical data to support this were not presented in the CS.

There were more treatment-related adverse events (TRAEs) in patients treated with dexamethasone compared with sham in each of the MEAD studies and these TRAEs were mainly ocular in both treatment groups (Table 24). The ocular TRAEs that occurred in >2% of patients in either treatment group in the MEAD studies are presented in Table 25.

Table 24: Safety profile across the MEAD trial programme, n (%) (adapted from CS Table 42, pg 242)

	MEAD-010		**MEAD-011**		**MEAD Pooled**	
	DEX700 (n=160)	**Sham (n=164)**	**DEX700 (n=187)**	**Sham (n=186)**	**DEX700 (n=347)**	**Sham (n=350)**
All adverse events	153 (95.6)	124 (75.6)	180 (96.3)	157 (84.4)	333 (96.0)	281 (80.3)
Ocular	142 (88.8)	97 (59.1)	172 (92.0)	131 (70.4)	314 (90.5)	228 (65.1)
Study eye	139 (86.9)	85 (51.8)	157 (84.0)	118 (63.4)	296 (85.3)	203 (58.0)
Non-study eye	82 (51.3)	66 (40.2)	116 (62.0)	91 (48.9)	198 (57.1)	157 (44.9)
Non-ocular	106 (66.3)	90 (54.9)	135 (72.2)	117 (62.9)	241 (69.5)	207 (59.1)
Treatment related AE	115 (71.9)	31 (18.9)	129 (69.0)	59 (31.7)	244 (70.3)	90 (25.7)
Ocular	115 (71.9)	30 (18.3)	129 (69.0)	59 (31.7)	244 (70.3)	89 (25.4)
Study eye	115 (71.9)	30 (18.3)	129 (69.0)	59 (31.7)	244 (70.3)	89 (25.4)
Applicator	46 (28.8)	18 (11.0)	60 (32.1)	34 (18.3)	106 (30.5)	52 (14.9)
Treatment	102 (63.8)	13 (7.9)	110 (58.8)	30 (16.1)	212 (61.1)	43 (12.3)
Non-study eye	0	0	0	0	0	0
Non-ocular	2 (1.3)	1 (0.6)	1 (0.5)	0	3 (0.9)	1 (0.3)
Serious AE	52 (32.5)	34 (20.7)	63 (33.7)	49 (26.3)	115 (33.1)	83 (23.7)
Ocular	11 (6.9)	5 (3.0)	22 (11.8)	11 (5.9)	33 (9.5)	16 (4.6)
Study eye	9 (5.6)	2 (1.2)	15 (8.0)	2 (1.1)	24 (6.9)	4 (1.1)
Non-study eye	3 (1.9)	3 (1.8)	12 (6.4)	9 (4.8)	15 (4.3)	12 (3.4)
Non-ocular	45 (28.1)	30 (18.3)	49 (26.2)	40 (21.5)	94 (27.1)	70 (20.0)
Treatment related SAE	4 (2.5)	1 (0.6)	12 (6.4)	0	16 (4.6)	1 (0.3)
Discontinuations due to AE	20 (12.5)	16 (9.8)	25 (13.4)	24 (12.9)	45 (13.0)	40 (11.4)
Deaths related to treatment	0	0	0	0	0	0

Abbreviations used in the table: AE, adverse event; DEX700, dexamethasone 700µg; SAE, serious adverse event.
Source: Boyer *et al.* 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Data on file – Summary of Safety[86]

The most common ocular TRAEs with dexamethasone were cataract formation and raised IOP, and the most common ocular TRAE with sham was conjunctival haemorrhage (Table 25).

Table 25: Treatment-related ocular adverse events in the study eye that occurred in >2% of patients in any treatment group across the MEAD trial programme (adapted from CS Table 43, pg246)

	MEAD-010		**MEAD-011**		**MEAD Pooled**	
	DEX700 (n=160)	**Sham (n=164)**	**DEX700 (n=187)**	**Sham (n=186)**	**DEX700 (n=347)**	**Sham (n=350)**
IOP elevation	56 (35.0)	3 (1.8)	40 (21.4)	5 (2.7)	106 (30.5)	8 (2.3)
Cataract	44 (27.5)	7 (4.3)	57 (30.5)	14 (7.5)	101 (29.1)	21 (6.0)
Conjunctival haemorrhage	29 (18.1)	15 (9.1)	28 (15.0)	19 (10.2)	57 (16.4)	34 (9.7)
Cataract sub capsular	18 (11.3)	6 (3.7)	16 (8.6)	5 (2.7)	34 (9.8)	11 (3.1)
Cataract nuclear	10 (6.3)	3 (1.8)	5 (2.7)	4 (2.2)	15 (4.3)	7 (2.0)
Conjunctival hyperaemia	9 (5.6)	4 (2.4)	4 (2.1)	6 (3.2)	13 (3.7)	10 (2.9)
Eye pain	7 (4.4)	3 (1.8)	6 (3.2)	6 (3.2)	13 (3.7)	9 (2.6)
Conjunctival oedema	7 (4.4)	2 (1.2)	6 (3.2)	2 (1.1)	13 (3.7)	4 (1.1)
Vitreous haemorrhage	6 (3.8)	0	6 (3.2)	0	12 (3.5)	0
Vitreous floaters	6 (3.8)	0	4 (2.1)	1 (0.5)	10 (2.9)	1 (0.3)
Ocular hypertension	4 (2.5)	0	16 (8.6)	5 (2.7)	20 (5.8)	5 (1.4)
Lenticular opacities	3 (1.9)	0	5 (2.7)	0	8 (2.3)	0
Cataract cortical	1 (0.6)	2 (1.2)	5 (2.7)	5 (2.7)	6 (1.7)	7 (2.0)
Abbreviations used in the table: DEX700, dexamethasone 700µg; IOP, intraocular pressure. Source: Boyer *et al*. 2014[51]; CSR 206207-010[54]; CSR 206207-011[55]; Summary of Safety[86]						

Raised IOP was reported in 36.0% of patients treated with dexamethasone in the MEAD studies pooled analysis although only 30.5% of these were deemed related to treatment (Table 25). In terms of the magnitude of the rise in IOP, 27.7% of dexamethasone patients experienced an IOP rise ≥10mmHg at any visit during the MEAD study period; 32.0% experienced an IOP ≥ 25mmHg and 6.6% had an IOP ≥ 35 mmHg at any visit during the MEAD study period. The company reported that neither the incidence nor magnitude of IOP elevation increased over time with repeated dexamethasone treatments and that the IOP generally resolved after each injection (Figure 12).

Figure 12: Mean IOP by visit within the treatment cycle over the MEAD study period – pooled analysis (reproduced from CS, Figure 50, pg 244)

patients in the dexamethasone + laser group received IOP-lowering medications compared with 1.6% in the laser alone group.

In total, 22 patients (17.6%) treated with dexamethasone + laser therapy experienced a cataract adverse event compared with 9 patients (7.1%) treated with laser therapy alone. Treatment-related cataract in the study eye was reported in 8/91 phakic patients treated with dexamethasone + laser (8.8%) compared with none of the 95 phakic patients treated with laser alone. The company reported in the CS that cataract surgery was performed in similar numbers of patients in both treatment arms: 6 patients in the dexamethasone + laser arm and 5 patients in the laser alone arm.

NCT0035906

The most common ocular adverse events reported in DMO patients enrolled in NCT0035906 were anterior chamber cell, anterior chamber flare and vitreous haemorrhage (Table 28). The company reported in the CS that there were no statistically significant between-group differences in the occurrence of any non-ocular adverse events. In addition, the ERG notes that it is reported that there were no treatment related cases of retinal detachment or endophthalmitis in either group.[60]

Table 28: Ocular adverse events reported in at least 10% of patients in any group at any time during NCT0035906, n (%) (reproduced from CS, Table 56, pg 264)

	DEX700 (n=53)	**Observation (n=57)**
Anterior chamber cell	14 (26.4)	1 (1.8)
Anterior chamber flare	11 (20.8)	5 (8.8)
Vitreous haemorrhage	12 (22.6)	3 (5.3)
Eye pain	5 (9.4)	2 (3.5)
VA reduced	9 (17.0)	6 (10.5)
Vitreous disorder	8 (15.1)	2 (3.5)
Increased IOP	5 (9.4)	0
Conjunctival haemorrhage	4 (7.5)	0
Maculopathy	4 (7.5)	1 (1.8)
Eye irritation	8 (15.1)	2 (3.5)
Vitreous floaters	9 (17.0)	0
Abnormal sensation in eye	8 (15.1)	2 (3.5)
Macular oedema	3 (5.7)	5 (8.8)
Eye pruritus	4 (7.5)	1 (1.8)
Retinal haemorrhage	6 (11.3)	12 (21.1)
Diabetic retinopathy	6 (11.3)	8 (14.0)

Abbreviations used in the table: AE, adverse event; DEX700, dexamethasone 700µg; IOP, intraocular pressure; VA, visual acuity.
Source: Haller *et al*. 2010[(60)]

IOP elevation to ≥25mmHg during the 180 day study follow-up period was reported in 13.2% of the dexamethasone safety population (n=53) compared with 0% of patients in the observation group. Eight patients (15%) in the dexamethasone safety population experienced an IOP increase of ≥10mmHg compared with one patient in the observation group. The company reported that all IOP rises were successfully managed with either observation or topical IOP lowering medication.

There was no significant difference in the number of cataract adverse events among the study groups in NCT00035906. There was also no between-group difference in the progression (at least 1-grade increase on slit lamp examination) in any type of cataract However, no further details or numerical data were presented in the CS for these outcomes.

4.5.4 Subgroup analyses: pseudophakic patients

Efficacy results were presented for the pseudophakic subgroup of patients from the MEAD studies and also from PLACID. However, the results from PLACID were from a *post-hoc* subgroup analysis based on analysis windows used in the company's NMA and economic modelling. The efficacy results from the pseudophakic subgroup in PLACID were not reported in detail in the CS and, as they were *post-hoc*, the ERG reports only the results from the NMA in this report (Section 4.7.2). In addition, safety results for this subgroup were presented from both PLACID and the MEAD studies. The ERG notes that the safety data for PLACID were again from *post-hoc* subgroup analyses although they were not for outcomes reported in the NMA; the ERG reports the data provided in the CS below. The ERG considers any data presented from NCT00035906 on pseudophakic patients would have been potentially misleading as they would have been based on very small numbers of patients.

[redacted]

The mean BCVA change from baseline with dexamethasone for the pseudophakic patients in the MEAD studies was statistically significant at all time points compared with sham (Figure 14 and Table 29).

Figure 14: Mean BCVA change from baseline for pseudophakic patients in the MEAD trial programme, ETDRS letters – pooled analysis (reproduced from CS, Figure 17, pg 159)

Deaths related to treatment	0	0
Abbreviations used in the table: AE, adverse event; DEX700, dexamethasone 700µg; SAE, serious adverse event Source: Allergan EMEA Questions and Allergan Responses[88]		

The incidence of SAEs in the pseudophakic subgroup was similar in the dexamethasone group (36.5%) compared to the sham group (36.0%). The causes of the ocular SAEs seen in the two dexamethasone patients were vitreous adhesion and macular oedema. There was no difference in the number of discontinuations due to adverse events based on study treatment group: 13% of pseudophakic patients in each group discontinued due to an AE.

The ocular AEs occurring in >2% of pseudophakic patients are presented in Table 31. The ERG note that the most common ocular AE reported was IOP increase although compared with the total study (safety) population fewer patients in the pseudophakic subgroup treated with dexamethasone (24.7%) experienced raised IOP compared with the total MEAD (safety) population (36.0%). The company reported that similar trends to the whole study (safety) population were observed in terms of the timing of IOP AEs suggesting there is no cumulative effect on IOP with dexamethasone re-treatments (no numerical data presented in the CS for the pseudophakic subgroup). It was reported in the CS that IOP-lowering medication was prescribed to 32.9% of pseudophakic patients randomised to dexamethasone during the MEAD study period; this is lower than the number of patients in the dexamethasone group of the whole trial (safety) population who required IOP medication during the study (41.5%).

Table 31: Ocular adverse events in the study eye that occurred in >2% of patients in either the DEX700 or sham treatment group across the MEAD trial programme, pseudophakic subgroup, n (%) (reproduced from CS Table 46, pg 250)

	DEX700 (n=85)	**Sham (n=100)**
IOP increased	21 (24.7)	7 (7.0)
Conjunctival haemorrhage	16 (18.8)	17 (17.0)
Conjunctival hyperaemia	6 (7.1)	8 (8.0)
Cataract*	5 (5.9)	2 (2.0)
Macular fibrosis	4 (4.7)	3 (3.0)
Posterior capsule opacification	4 (4.7)	6 (6.0)
Visual acuity reduced	4 (4.7)	1 (1.0)
Ocular hypertension	4 (4.7)	2 (2.0)
Retinal neovascularisation	4 (4.7)	2 (2.0)
Vitreous floaters	4 (4.7)	2 (2.0)
Conjunctival oedema	4 (4.7)	0

Diabetic retinal oedema	4 (4.7)	2 (2.0)
Eye pain	3 (3.5)	5 (5.0)
Vitreous detachment	3 (3.5)	4 (4.0)
Macular oedema	3 (3.5)	3 (3.0)
Retinal haemorrhage	3 (3.5)	4 (4.0)
Eyelid ptosis	3 (3.5)	2 (2.0)
Dry eye	2 (2.4)	5 (5.0)
Retinal aneurysm	2 (2.4)	3 (3.0)
Conjunctivitis	2 (2.4)	2 (2.0)
Vitreous opacities	2 (2.4)	2 (2.0)
Corneal abrasion	2 (2.4)	4 (4.0)
Corneal erosion	2 (2.4)	2 (2.0)
Keratitis	2 (2.4)	1 (1.0)
Macular cyst	2 (2.4)	0
Pruritus	2 (2.4)	0
Uveitis	2 (2.4)	0
Retinal exudates	1 (1.2)	4 (4.0)
Blepharitis	1 (1.2)	8 (8.0)
Conjunctivitis allergic	0 (0.0)	4 (4.0)
Abbreviations used in the table: DEX700, dexamethasone 700µg; IOP, intraocular pressure. Note: * adverse events identified as 'cataract' were secondary cataract. Source: Allergan EMEA Questions and Allergan Responses[172]		

The results of the safety and adverse events analyses in pseudophakic patients in PLACID are presented in Table 32. In comparison to the whole trial (safety) population of PLACID (Section 4.5.3), there were fewer events (%) for each of the safety outcomes reported in Table 32 in the pseudophakic subgroup. However, as or the whole trial (safety) population, dexamethasone + laser was associated with more adverse events compared to laser alone in the pseudophakic subgroup (85.7% vs. 75.0%).

Table 32: Safety profile in pseudophakic patients in PLACID, n (%) (reproduced from CS Table 54, pg 260)

	DEX700 + laser (n=35)	**Laser (n=32)**
All adverse events	30 (85.7)	24 (75.0)
Ocular adverse events in study eye	24 (68.6)	14 (43.8)
Ocular treatment-related adverse events in study eye	12 (34.3)	5 (15.6)
Abbreviations used in the table: DEX700, dexamethasone 700µg. Source: Clinical Story PLACID Final[(82)]		

- proportion of patients achieving at least a 10 letter gain from baseline at 12 months; or
- proportion of patients achieving at least a 10 letter loss from baseline at 12 months.

The company's rationale for selecting these outcomes for the NMA is presented in Box 11.

Box 11. Company rationale for the choice of outcomes in the NMA (CS pg 185)

The proportion of patients achieving at least a 10-letter improvement or worsening in BCVA from baseline at month 12 was chosen as this is a clinically meaningful endpoint that can also be applied within the economic model to move patients between health states.
Abbreviations used in the box: BCVA, best corrected visual acuity; NMA, network meta-analysis.

The ERG notes that the company included a sensitivity analysis for the outcome of proportion of patients achieving at least a 15 letter gain from baseline at 12 months in the CS. The ERG also notes that a 15-letter improvement in BCVA was the primary efficacy outcome in the MEAD studies although the 10-letter improvement was reported as a secondary outcome. The clinical experts to the ERG agree with the company that a 10-letter improvement or worsening in BCVA is a clinically meaningful change in visual acuity. However, the ERG is not sure as to what the most appropriate time point to assess this outcome within the NMA is. The ERG does not consider the 12 month timeframe to be appropriate for use in the economic model; the rationale for this is discussed in Section 5. However, the ERG notes that the majority of the clinical trials used in the company's NMA report this outcome data at 12 months. The ERG notes that based on the efficacy findings for dexamethasone in the whole trial population, 12 month data may bias the results against dexamethasone because of the impact of cataract adverse effects on the visual acuity. Data at 12 months in the pseudophakic subgroup would be unaffected by this potential confounder.

The same methods used for study appraisal, study inclusion, data extraction and quality assessment the systematic review of RCTs described in Section 4.1 were used in the NMA trial selection process. Treatment arms from multi-arm trials that did not include a comparator of interest were not included in the analyses as per the eligibility criteria. Sham treatment and no treatment arms were assumed to be the same in the NMA and were thus pooled in the NMAs. The ERG has concerns as to the impact the pooling of sham and no treatment arms may have had on the efficacy estimates from the NMA as the absence of blinding in the no treatment arms could have impacted the results. However, the ERG notes that had the company not assumed equal efficacy for sham and no treatment then it would not have been possible for the company to conduct the NMA as this assumption creates the only link in the network between the dexamethasone MEAD studies and the rest of the network.

The BCVA data from each of the trials was split into the following three categories:

- worsening, defined as loss of 10 or more letters at 12 months;
- stable, defined as loss or gain of <10 letters at 12 months; and
- improvement, defined as gain of 10 or more letters at 12 months.

The stable vision group for each trial was calculated by subtracting the total number of patients from the number of patients losing 10 or more letters and the number of patients gaining 10 or more letters.

The company conducted the NMAs in WinBUGS (version 14) (MRC Biostatistics Unit, Cambridge, UK), using R (version 3.1.1) as an interface. All NMA results reported in the CS were from random effects models. The company's justification for the choice of the random effects model is presented in Box 11a.

Box 11a. Company's justification for the choice of the random effects model for the NMA's (Company's response to clarification, A11, pg 8)

Only a random-effects model was fitted to the data as there was no reason to believe à priori that the heterogeneity between studies would be zero. The trials are not homogenous in terms of trial design e.g. rescue therapy rules. Therefore a random-effects model was deemed a more appropriate choice as it incorporates a between-study heterogeneity parameter.

The relative risk (RR) and probability of being in each of the three groups of vision were estimated using Markov Chain Monte Carlo (MCMC) methods. The WinBUGs model used a multinomial likelihood with a probit link function to estimate the relative treatment effects. The multinomial model that was used was able to account for trial data where only one of the categories of vision was reported. A binomial likelihood using a probit link function was fitted to the trials with a sham/no treatment arm and it considered only data for the outcome of loss of at least 10 letters. The ERG notes that for one of the sensitivity analyses conducted in the CS (sensitivity analysis 2 [SA 2]) a binomial likelihood with a logit link function model was used. The company reported, and the ERG can confirm, that the models used were in-line with the recommendations in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[89]

A subgroup analysis was conducted to assess the impact of being pseudophakic at baseline on the efficacy outcomes. However, not all trials reported suitable subgroup data or even lens status at baseline. The ERG notes that the treatments where lens status is mostly likely to be expected to influence efficacy results is the corticosteroid therapies, i.e. dexamethasone and fluocinolone acetonide. The dexamethasone studies in the network all reported pseudophakic subgroup data apart from BEVORDEX. Total population data was used in the absence of pseudophakic subgroup data from the studies not reporting pseudophakic subgroup data as the company deemed it to be, "a

reasonable representation of the estimated treatment effect in such patients" (CS, pg 193). Whilst subgroup data from each trial would have been preferable, the ERG agrees with the company's approach in the absence of such data from the non-corticosteroid therapy trials.

The company also conducted two sensitivity analyses for the NMA. These were as follows:

- Sensitivity analysis 1 (SA1): including the FAME trial for fluocinolone acetonide in the network. In order to do this the company estimated data for 10 letter improvement from the data reported for patients achieving a 15 letter improvement from baseline at month 12. The method used to calculate this data were clarified by the company during the clarification question stage and the company's response is reported in Box 12.
- Sensitivity analysis 2 (SA2): using the outcome of 'gaining 15 or more letters at 12 months'. The company conducted this analysis to assess the impact of using the 15 letter observed data for FAME instead of the estimated data in SA1 for the proportion of patients achieving a 10 letter improvement from baseline at month 12 data affected the results.

Box 12. The company's explanation for how the 10 letter improvement data were calculated for FAME (Company's response to clarification, A14, pg 10).

All trials within the clinical RCT evidence base that reported data for both ≥15 letter gain and ≥10 letter gain at 12 months were included in the calculation of the mean multiplication factor.

A relationship was established between ≥10 letter gain and ≥15 letter gain i.e. for each trial, a multiplying factor was calculated to get from ≥15 letter gain to ≥10 letter gain. The average (mean) of these individual multiplication factors was calculated to be 1.989. This overall mean multiplication factor was subsequently applied to the 15 letter gain data presented for the FAME study2 to estimate the 10 letter gain data.

Of note, at the time of this analysis, BEVORDEX was only available in abstract form3 in which only ≥10 letter gain data was presented. Therefore data from this trial was not included in the mean multiplication factor calculation.

In addition, in response to clarification question A8, the company conducted an additional analysis that used the end point data from each of the studies excluded on the basis that they reported only <12-month data. The company reported in the response to clarification question A7 that only one study was excluded from the base case NMA for this reason (NCT00035906). The company conducted an updated analysis including the end-point data from NCT00035906, a study with 6-month outcome data for dexamethasone versus observation and provided the results (Section 4.7.5).

4.6.2 Outcomes reported in the NMAs

The clinical outcomes reported from the NMAs in the CS were:

- loss of 10 or more letters at 12 months; and

- pseudophakic patients in the dexamethasone group of the MEAD studies achieved a much greater improvement in BCVA compared to the whole trial ITT population. This could be a result of the impact of cataract adverse effects in the phakic patients in the whole trial population.
- There were fewer ocular AEs in the study eye in patients with a pseudophakic lens at baseline in the MEAD study patients who were randomised to dexamethasone compared with the whole study (ITT) population due to the absence of primary cataract AEs.
- The most common ocular AE reported in the pseudophakic subgroup was IOP increase although fewer patients in the dexamethasone group (24.7%) experienced raised IOP compared with those in the dexamethasone group for the total MEAD (safety) population (36.0%).
- Safety data suggest a similar safety profile for dexamethasone in the subgroup of patients with any prior treatment (including prior corticosteroid therapy) to that seen in the whole trial (safety) population of the pooled MEAD studies, with higher incidences of ocular adverse events in the dexamethasone group compared with the sham group.

4.9.2 Clinical issues

- UK marketing authorisation for dexamethasone restricts it use to the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant); or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.
- None of the dexamethasone RCTs in the CS are specific to any of the populations specified in the EU marketing authorisation for dexamethasone;
- Absence of direct comparative data from RCTs comparing the EU licensed dosing regimen for dexamethasone with any of the comparators specified by NICE in the decision problem;
- The results of the MEAD studies that provide the majority of evidence for dexamethasone within the CS are potentially flawed due to the high discontinuation rates across the trial arms and the use of a LOCF analysis to account for the missing data;
- High levels of clinical and statistical heterogeneity in the NMA and so the ERG has strong reservations about how robust any conclusion based on them might be;
- Absence of data for some outcomes for some of the comparators in the decision problem, particularly the absence of outcome data for the relevant populations for this STA i.e. those specified in the EU marketing authorisation for dexamethasone;
- Limited long term data on the safety and clinical benefit of dexamethasone in DMO.

Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes; the company carried out deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
Abbreviations used in the table: CEACs, cost-effectiveness acceptability curves; DEX700, dexamethasone 700 µg; DMO, diabetic macular oedema; ERG, evidence review group; HRQL, health-related quality of life; NEI-VFQ, National Eye Institute Visual Functioning Questionnaire-25; NICE, National Institute for Health and Care Excellence; OWSA, one-way sensitivity analysis; QALYs, quality-adjusted life yeas; TTO, time trade-off; VFQ-UI, Visual Functioning Questionnaire Utility Index.		

Table 45. Philips checklist[100]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated
S2: Statement of scope/perspective	Clearly stated (UK NHS)
S3: Rationale for structure	Clearly stated; the company described in detail clinician input derived at the advisory board meetings (CS; Appendix 14).
S4: Structural assumptions	The structural assumptions were transparent. The ERG had concerns about the validity of the following structural assumptions: • The baseline distributions of BSE and WSE across BCVA states were independent from each other (CS, pg336) • movements were restricted to improving or worsening by a maximum of one visual acuity state per cycle (CS; pg337) • patients were only at risk of FEI by the end of Year 1 or Year 2 (CS; pg351) During clarification the ERG asked the company to perform an analysis where the movements between health states were unrestricted using the actual 3-year MEAD trial data. The ERG also explored the impact of increasing the risk of FEI beyond year 2. The results from these analyses are presented in Section 6.1.2.2.
S5: Strategies/ comparators	The main comparators in the base case for DMO patients who are considered unstable for or insufficiently responsive to non-corticosteroid therapy and for DMO patients who are pseduophakic were watch and wait and ranibizumab, respectively. Fluocinolone acetonide was only included as a comparator in a scenario analysis for the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy; laser and bevacizumab were only included as comparators in scenario analysis for the population of DMO patients who are pseudophakic. The company assumed a maximum duration of treatment of 3 years in the base case. The ERG is concerned that the company has underestimated the duration of treatment in UK clinical practice if treatment continues until a patient is no longer responsive. The company provided a scenario analysis extending the duration to 5 years, but restrictions on the

	Legal blindness if BSE				20/40 in BSE is the legal threshold for driving	
Abbreviations used in table: BSE, better-seeing eye; ETDRS, Early Treatment Diabetic Retinopathy Study. Source: Gregori *et al.* (2010)[102]						

The model assumes a maximum duration of treatment of 3 years in the base case; the company's rationale for this assumption and the ERG critique of it are discussed in Section 5.4.4.2. At any time during treatment patients within the cohort may discontinue from treatment for one of two independent reasons:

- Lack (or loss) of efficacy of treatment;
- Adverse events and other non-efficacy related reasons (e.g. withdrawal of consent, lost to follow-up, protocol violation, personal reasons, etc.).

Discontinuation from treatment was modelled to reflect the high discontinuation rates that were observed within the MEAD trials (where 22.5% of patients in the pooled dexamethasone arms discontinued from the study due to adverse events and other non-efficacy related reasons, 4.3% discontinued due to lack or loss of efficacy of treatment and 9.8% were censored due to receipt of an off-protocol treatment). People discontinuing from treatment cannot be assumed to receive the costs and efficacy of treatment within the economic model. The economic model therefore assumed that, following discontinuation, patients receive no further treatment and subsequently their affected eye(s) transition(s) through the BCVA states at a rate consistent with the natural history of vision in patients with DMO. The company expressed the opinion that modelling an explicit next line of treatment following discontinuation would address a different decision problem, i.e. assessment of an optimal sequence of treatments for DMO; therefore, it was decided the assumption of no treatment received following discontinuation was most appropriate for the decision problem addressed by their economic analysis.

The model also considered five key adverse events of interest that may require medical or surgical intervention, comprising cataract, raised increased ocular pressure (IOP), retinal detachment, endophthalmitis and vitreous haemorrhage. Incorporation of adverse events in the model is discussed further in Section 5.4.8 of this report.

Visual acuity health states were based on a 10-letter change in BCVA on the ETDRS eye chart because, according to the company, this 10-letter change is often used as a measure of visual acuity in clinical trials of interventions for DMO. It was argued that a gain or loss of 10 letters may be

probabilities over the whole 3-year duration of treatment in the model as a significant data extrapolation.

The NMA that informed the economic model synthesised data on three mutually exclusive outcomes of gaining vision, losing vision or maintaining stable vision. The company used one multinomial likelihood model "to estimate all three outcomes to ensure that correlation between the three outcomes would be accounted for" (company submission, pg334). The NMA outputs used in the economic analysis were the relative risks of each treatment versus dexamethasone (baseline) for each outcome. However, the ERG notes that correlations across mutually exclusive outcomes are "essentially within-trial, negative correlations between outcomes, applying in each arm of each trial. They arise because the occurrence of outcome events is a stochastic process, and if more patients should by chance reach one outcome, then fewer must reach the others" (NICE TSU document 2, page 23).[89] So the correlations characterise mutually exclusive outcomes (absolute effects) of every treatment, and not multiple relative outcomes between treatments. Therefore, by applying relative risks for each of the mutually exclusive outcomes in the economic model, the correlation between absolute outcomes was not maintained.

However, retaining the underlying correlations across the absolute outcomes was essential in the economic model in order to keep the sum of the probabilities of each of the mutually exclusive outcomes equal to 1. To force the sum of outcome probabilities to equal 1, the company described a method of 'normalisation' at the application of each of the 3 relative risks of every treatment versus dexamethasone associated with each of the 3 mutually exclusive outcomes, respectively, as described earlier. The ERG used the baseline transition probabilities for dexamethasone from baseline to month 3 (shown in Table 59) and the non-normalised and normalised transition probability matrices for watch and wait from baseline to month 3 (shown in Table 62 and Table 63, respectively) for all DMO patients, to calculate the relative risks of watch and wait versus dexamethasone before and after normalisation, in order to explore the impact of normalisation on resulting relative risks. The ERG used the relevant data directly from the electronic version of the economic model (rather than from the tables in the CS), to avoid errors due to the use of rounded figures in the tables. The ERG calculations are shown on Table 64 and Table 65, respectively. The formula used to estimate relative risks (RRs) for every outcome in every cell of the transition matrix is:

$$RR = probWW / probDEX700$$

where probWW is the transition probability of watch and wait in every cell in the matrix and probDEX700 is the baseline probability of dexamethasone in every cell in the matrix.

The relative risks of watch and wait versus dexamethasone that were calculated by the ERG before normalisation took place (Table 64), should replicate the relative risks derived from the NMA that are

presented in Table 61. Indeed, the relative risks for improving vision, retaining stable vision and worsening vision equal [redacted], [redacted] and [redacted], respectively, across all BCVA states.

Table 64. Relative risks of watch and wait versus dexamethasone: baseline to Month 3; all DMO patients, derived from the NMA (calculated by ERG, using dexamethasone baseline transition probabilities from Table 59 and watch and wait transition probabilities, as estimated by the company, from Table 62)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0..00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	0.00	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group; NMA, network meta-analysis.

The relative risks calculated after normalisation are effectively the relative risks that were (implicitly) utilised in the model. The ERG notes that the relative risks estimated following normalisation, although of the same direction, are quite different in magnitude from those estimated from the NMA. Relative risks for all 3 outcomes are higher than the figures derived from the NMA, and overall increase as health states become milder (the exception is the relative risk of worsening vision, which is not constantly increasing with milder health states, but this is probably due to the speculated error in the transition matrix for watch and wait prior to normalisation). The relative risk for improving vision after normalisation ranges from [redacted] to [redacted] (the respective figure derived from the NMA was

[redacted]). The relative risk for retaining stable vision after normalisation ranges from [redacted] to [redacted] (the respective figure derived from the NMA was [redacted]). The relative risk for worsening vision after normalisation ranges from [redacted] to [redacted] (the respective figure derived from the NMA was [redacted]).

Table 65. Relative risks of watch and wait versus dexamethasone, following normalisation: baseline to Month 3; all DMO patients (calculated by ERG, using dexamethasone baseline transition probabilities from Table 59 and normalised watch and wait transition probabilities, as estimated from the company, from Table 63)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	0.00	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group.

By looking at the relative risks estimated by the ERG after normalisation took place, one might think that normalisation resulted in higher relative risks, which overestimated all vision-related relative effects (improving, worsening, or maintaining stable vision), especially at milder health states. In order to investigate whether this is true, the ERG used data from the Excel file DMO_NICE_Oct2014_All DMO and calculated the relative risks for watch and wait versus dexamethasone following normalisation from two more cycles: from 21 to 24 months, and from 33 to 36 months. The findings of these calculations, shown in Table 66 and Table 67, indicate that there is no clear pattern in the change of magnitude of the relative risks that were effectively utilised in the model following normalisation. Nevertheless, these findings demonstrate that normalisation has affected, to some degree, all relative efficacy outcomes of the economic analysis (improving, worsening and retaining stable vision), and therefore is very likely to have affected the results of the economic analysis. To what direction and at what degree cannot be determined by simply looking at the ERG calculations.

Table 66. Relative risks of watch and wait versus dexamethasone, following normalisation: Month 21 to Month 24; all DMO patients (calculated by ERG, using dexamethasone baseline transition probabilities and normalised watch and wait transition probabilities from the Excel file DMO_NICE_Oct2014_All DMO)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	[redacted]	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group.

Table 67. Relative risks of watch and wait versus dexamethasone, following normalisation: Month 33 to Month 36; all DMO patients (calculated by ERG, using dexamethasone baseline transition probabilities and normalised watch and wait transition probabilities from the Excel file DMO_NICE_Oct2014_All DMO)

		To					
		Health State 1	**Health State 2**	**Health State 3**	**Health State 4**	**Health State 5**	**Health State 6**
From	**Health State 1**	[redacted]	[redacted]	0.00	0.00	0.00	0.00
	Health State 2	[redacted]	[redacted]	[redacted]	0.00	0.00	0.00
	Health State 3	0.00	[redacted]	[redacted]	[redacted]	0.00	0.00
	Health State 4	0.00	0.00	[redacted]	[redacted]	[redacted]	0.00
	Health State 5	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]
	Health State 6	0.00	0.00	0.00	0.00	[redacted]	[redacted]

Abbreviations used in table: DMO, diabetic macular oedema; ERG, evidence review group.

Given the limitation of the assumption that relative effects remain stable over time and the impact of normalisation on relative risks across all 3 outcomes of the analysis, the ERG requested that the company run the base case economic analysis for people that are unsuitable for, or insufficiently responsive to non-corticosteroids using the actual data for dexamethasone (as in the economic model submitted by the company) but also for watch and wait from the pooled MEAD trials. This analysis would effectively use the actual relative effects between dexamethasone and sham as observed over

Related to the above, the ERG wishes to note that the European Medicines Agency (EMA) assessment report on dexamethasone for the treatment of DMO states that "the total incidence of cataract adverse events was 67.9%, 64.1%, and 20.4% in the DEX 700, DEX 350, and Sham groups, respectively" (page 46).[105] The total incidence of cataract of 67.9% in the dexamethasone group over three years is even higher than the incidence estimated by the ERG (▇▇▇▇▇) using the data provided by the company; this is because the latter figure refers only to the proportion of phakic patients who had had cataract surgery in the study eye.

Another issue to consider is that the economic model has assumed that eyes are either phakic or pseudophakic in all patients. Therefore, the model appears to assume that once cataract has been removed, there is no additional risk for cataract in the other eye. This assumption seems to be reasonable for patients with unilateral DMO, as the non-affected eyes can be assumed to have the same risk for cataract across cohorts, which is independent of treatment received, and therefore the assumption does not have any substantial impact on the results of economic analysis. However, in patients with bilateral DMO at baseline or following FEI, this assumption results in the risk for cataract in the second DMO eye becoming zero, once cataract formation and extraction has occurred in the first eye. Due to time constraints, the ERG did not have the opportunity to check whether this assumption holds in the economic model, but if it does, it considerably reduces the actual risk of cataract formation and extraction (and associated costs) in patients with bilateral DMO, and has therefore underestimated the costs of dexamethasone and fluocinolone acetonide relative to watch and wait, as both treatments, as corticosteroids, are characterised by high risk of cataract.

Regarding the proportions of patients with raised IOP that were treated with medical or surgical intervention in the economic model, clinical experts confirmed that the proportion of medical versus surgical treatment is affected by type of treatment. It was agreed that increased IOP caused by corticosteroids has a higher probability of being treated surgically, although the large discrepancy in the respective figures (27.42% for dexamethasone versus 88.89% for fluocinolone acetonide was questioned by one of the ERG's clinical experts (but was considered reasonable by two other clinical experts, due to the higher risk of raised IOP with fluocinolone acetonide).

For non-corticosteroids, the ERG was informed that between 0 and 10% of patients with raised IOP would require surgical treatment; this suggests that the ▇▇ figure for patients with laser requiring surgery is probably high; nevertheless, given the low risk of raised IOP with laser (less than ▇ in any year), the ▇▇ figure is unlikely to have affected the results of the economic analysis.

In conclusion, the adverse event data used in the economic analysis appear to be overall reasonable. The ERG ran an additional economic analysis following the corrections in the cataract data for

Table 106. Scenario analyses performed, relevant to all populations under consideration unless stated (taken from CS, Table 116, pgs 417-425)

Scenario number	Base case assumption	Scenario considered	Justification
1*	List price for RAN, FA not included in base case analyses for all DMO patients	Variable discount between 0% (list price) and 50%	A confidential PAS is available to the NHS for RAN and FA. This analysis will allow the committee to select the most plausible ICER.
2**	RAN is the only comparator for DMO patients who are pseudophakic	Comparators are RAN, laser, BEV and watch and wait	RAN is the most appropriate comparator in this population as it is the most commonly used 1st line treatment; however there is minimal use of laser and BEV in practice so these have been included as a scenario analysis. Watch and wait has been included for completeness.
3	Utility regression equation derived from VFQ-UI collected in MEAD	Utility regression equation derived from EQ-5D collected in MEAD	EQ-5D meets the NICE reference case but has been shown not to be sensitive to changes in vision; EQ-5D was collected at baseline only in the MEAD studies whereas NEI VFQ-25 was collected throughout, giving more data from which to derive the base case utility regression.
4	No age-adjusted utilities	Age-adjustment included using a coefficient of -0.00029 per year from Sullivan *et al.,* 2011[143]	The regression equation does not include a coefficient for age; therefore a sensitivity analysis including an age-adjustment has been included.
5	Maximum duration of treatment 3 years	Maximum 5 years of treatment, including 1 maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide treatment), applying LOCF to efficacy outcomes	The base case analysis is 3 years to avoid the need for extrapolating beyond the longest study duration. However, the duration of treatment for DMO is uncertain, so a scenario has been included to extend the duration to 5 years, with two alternative assumptions for the efficacy beyond the MEAD study duration due to the uncertainty as to what these outcomes should be.
6		Maximum 5 years of treatment, including 1 maintenance treatment per year (or a maximum of 1 additional fluocinolone acetonide treatment), assuming stable vision following this	
7	No change in vision upon development of fellow eye DMO	Vision decline equal to 1 cycle of natural history of vision with DMO (Mitchell *et al*., 2012)[31]	Base case assumption is no change in vision as it is assumed given the frequent visit schedule for DMO patients this would be caught early. Scenario of 1 cycle of natural history of vision with DMO to reflect that in practice treatment often is not initiated until some vision loss occurs.
8	Natural history of DMO applied	Stable vision (identity matrix) applied following	Base case assumption is that DMO is a chronic condition and that

**Not applicable to the population of DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£11,630	5.7491	-	-	-
DEX	£14,042	5.7947	£2,411	0.0456	£52,858
Abbreviations used in the table: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; WSE, worst seeing eye.					

Out of those four scenarios, there were three in which dexamethasone was no longer considered cost-effective compared with watch and wait at a willingness-to-pay (WTP) threshold of £20,000 per QALY gained. These included shorter time horizons of 1 and 5 years, and the scenario in which treatment was assumed to be administered only to patients affected in their WSE.

In the scenario where the time horizon was reduced to 10 years dexamethasone no longer dominated watch and wait, however it remained cost-effective at a WTP threshold of £20,000 per QALY with an ICER of £6,365 per QALY gained.

All remaining scenario analyses conducted by the company in the population of DMO patients who are considered unsuitable for non-corticosteroid therapy had minimal impact on the results. However for the population of DMO patients who are considered insufficiently responsive to non-corticosteroid therapy, scenario 1 considered fluocinolone acetonide as a comparator. In addition, the price of fluocinolone acetonide was varied using a 10%, 20%, 30%, 40% and 50% discount to reflect the potential PAS discount available to the NHS.

Regarding scenario 1, dexamethasone was cost-effective if no discount was applied to fluocinolone acetonide i.e. using its list price. When a 10% discount price was applied to fluocinolone acetonide, dexamethasone became less costly and less effective than fluocinolone acetonide. For all higher discounted assessed, fluocinolone acetonide dominated dexamethasone i.e. it was less costly and more effective. The results of scenario analysis 1 for each discount are presented in Table 109. The ERG noted that the company used an average of 1.5 appointments for bilateral treatment with fluocinolone acetonide, instead of 1.75, which was the correct figure. The ERG was unable to provide the correct figures in Table 109 due to time constraints, but notes that the impact on the results is only minor.

Table 109**.** Results of Scenario 1 - Inclusion of fluocinolone acetonide; variation of price of fluocinolone acetonide (adapted from CS; Tables 163-168, pgs 468-70)

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER	ICER vs Baseline
List price for fluocinolone acetonide						
Dexamethasone	£20,413	5.7420	-	-	-	-
Watch and wait	£21,877	5.6765	£1,464	-0.0655	Dexamethasone dominates	Dexamethasone dominates
Fluocinolone	£22,365	5.8214	£1,953	0.0794	£24,591*	£24,591*
10% discount to price for fluocinolone acetonide						
Dexamethasone	£20,413	5.7420	-	-	-	-

In all populations shortening the time horizon of the analysis had a large influence on the results. The company stated that "this is because treatment costs are incurred upfront, whereas the costs of blindness are either incurred or avoided over the longer term" (CS; pg490). The ERG agrees with the company but does not consider shortening the time horizon to less than 10-15 years to be appropriate, as a short time horizon would not allow the long-term impact of treatment on outcomes to be taken into account. On the other hand, in order to consider a time horizon of 15 years, the company had to make a number of assumptions on the natural progression of DMO and on the visual functioning in non-DMO affected eyes, due to lack of relevant data and the complexity of the model that would be otherwise required. It is noted that, although the base case analysis assumed 3 years of treatment according to the duration of key trials that informed the model, the duration of treatment is likely to extend beyond 3 years in UK clinical practice as discussed previously in Section 5.4.4.2. The ERG also notes that increasing the time horizon to 20 years did not have any impact on the results.

Treatment according to DMO status (i.e. unilateral treatment of the BSE or WSE or bilateral treatment) appeared to be an important driver of cost-effectiveness in all populations. The company stated that "this is because patients who are treated in their BSE only and patients who are treated bilaterally have a greater capacity for improvements in utility than patients treated in their WSE" (CS; pg 490). However the ERG notes that when 100% unilateral treatment in the WSE was assumed in DMO patients who are considered unsuitable for or insufficiently responsive to non-corticosteroid therapy, dexamethasone demonstrated lower QALY gains compared with base case analysis, but also was no longer less costly than watch and wait. The ERG checked the detailed cost components associated with each intervention in the electronic copy of the model, and found that this result was due to a smaller difference in costs associated with severe vision loss between dexamethasone and watch and wait (i.e. a smaller difference in patients residing in the lowest health state 1 over the model duration) compared with the base case analysis, which was not adequate to fully offset the dexamethasone acquisition cost (in the base case analysis the cost-savings from prevention of severe vision loss associated with dexamethasone relative to watch and wait offset dexamethasone the acquisition cost, leading to dexamethasone being overall less costly than watch and wait).

For the population of DMO patients who are insufficiently responsive to non-corticosteroid therapy, the results were sensitive to the inclusion of fluocinolone acetonide within the analysis, particularly when a discount was applied to its list price. Results of this analysis indicate that dexamethasone is not cost-effective in DMO patients who are insufficiently responsive to non-corticosteroid therapy, if fluocinolone acetonide is available at a discounted price to the NHS (even at 10%). However, as discussed previously in Section 5.4.6.2, the analysis including fluocinolone acetonide is characterised by important limitations, so the respective results should be interpreted with caution.

was to both correct a number of potential model errors, and to test the robustness of model results to changes in parameters. An outline of the additional analyses carried out by the company following ERG request is provided in Section 5.5.1; an outline of the additional analyses carried out by ERG is presented in Section 5.5.2. Section 6 presents the results of each of these analyses.

5.5.1 Additional analyses carried out by the company, following ERG requests at clarification

The company carried out the following analyses in response to ERG requests at clarification:

- **Analysis A1:** This analysis was not requested directly by the ERG. During clarification, the ERG asked the company to clarify why the baseline BCVA distribution of BSE and WSE in bilateral DMO appeared to be taken from respective DMO eyes in unilateral DMO and was not determined directly from data on the sub-group of patients with bilateral DMO (ERG clarification question B5b). The company's response was that the baseline distribution of vision in the BSE and WSE for bilateral DMO patients was taken from data from the study eye of MEAD, dependent on whether the study eye was the BSE or the WSE (which could include both unilaterally and bilaterally affected patients). However, at clarification the company provided the baseline BCVA distributions observed in dexamethasone patients with unilateral as well as bilateral DMO (shown in Table 53 and Table 54 of this report, respectively); based on these distributions, the company reported alternative results (company's response to clarification, pgs 35-41).
- **Analysis A2:** this analysis used the outputs of the updated NMA, as requested by the ERG at clarification (Priority question B4, pg 31).
- **Analysis A3**: at clarification, the ERG requested an analysis that would utilise 3-month transition probabilities for watch and wait (as well as for dexamethasone) directly from the pooled MEAD trials (i.e. without utilising the NMA outputs), using the assumption that improvement or deterioration of vision by at least 10-letters is restricted to moving up or down by one health state, respectively (which was the assumption used in the original model submitted) (Priority question B1a, pg 11). The rationale for this analysis was the ERG's concern about the validity of the company's assumption, which was central to the model design, that the 12-month relative risks derived from the network meta-analyses remained constant from baseline to year 3; using this assumption, the company applied the 12-month relative risks derived from the NMA onto 3-month baseline transition probabilities over the whole 3-year duration of the model. The ERG believes that this assumption is incorrect, because clinical data demonstrate that the relative effect of dexamethasone versus sham is not stable over 3 years in the MEAD trials, at least not for the whole DMO population. Moreover, normalisation of resulting transition probabilities introduced bias in the submitted analyses, although the direction and magnitude of bias is not known and cannot be predicted. The ERG felt that this method of analysis (use of efficacy data directly from the MEAD trials) was more appropriate and reflective of the relative effects of dexamethasone versus sham (which was used as a proxy for watch and wait).

decreased. This finding was rather unexpected, as it implied that patients who discontinue treatment (either dexamethasone or sham, which was used as a proxy for watch and wait) have higher benefits and incur lower costs compared with those who continue treatment, in particular those receiving sham. This is at odds with the company's claim that the watch and wait arm in the MEAD trials consisted of 'super-responders', due to the high discontinuation rates imposed by the study protocol, who are "not likely to represent what we would expect to observe with no active treatment in clinical practice" and who "potentially overestimate the effect of sham treatment" (company's argument provided in Box 30). The ERG is not clear what the cause of this finding might be. It could be potentially an error in the model programming, but the ERG could not identify such an error. A potential alternative explanation could be that the overall effects of both dexamethasone and watch and wait in the MEAD trials were worse than the 'effect' of natural progression on patients with DMO. In any case, these results indicate that the patient group in sham/watch and wait in the MEAD trials may not consist of 'super responders' and the company's argument that the MEAD trials have overestimated the effect of sham (and thus the effect of watch and wait) and, consequently, have underestimated the relative treatment effect of dexamethasone, may not appear robust.

Table 127. Comparison of the results of the base case analysis and Analysis C3 undertaken by the ERG in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroids

Analysis	Total cost		Incremental cost per patient	Total QALYs		Incremental QALYs per patient	ICER
	DEX700	Watch & wait		DEX700	Watch & wait		
Base case	£20,413	£21,882	£1,469	5.7420	5.6764	-0.0656	Watch & wait dominated
C3: zero discontinuation	£21,511	£25,178	£3,667	5.7394	5.6536	-0.0858	Watch & wait dominated
Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure.							

Further to analyses C1-C13, the results for analysis C14 (use of utility data from Czoski Murray *et al*.[99] and transition probabilities derived directly from the MEAD trials, assuming unrestricted transitions) are reported in Table 128. It can be seen that use of alternative utility data from Czoski-Murray et al.[99] considerably favoured dexamethasone by increasing the incremental QALYs versus watch and wait, resulting in an ICER of £383,512/QALY; this ICER is greatly reduced compared with analysis A4, which also utilised exclusively MEAD trial data, did not impose restrictions in transitions, and utilised the VFQ-UI regression model for the estimation of QALYs. The ICER in

analysis A4 was £1,411,676/QALY. However, the ERG notes that the utility values reported in Czoski-Murray et al.[99] are likely less relevant (and thus less appropriate to use) than those reported by the company, which were based on the VFQ-UI and obtained directly from patients with DMO.

Table 128. Results of revised base-case analysis by ERG: patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids; efficacy data based on MEAD trials, no restrictions on movements by one health state up or down imposed

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Watch and wait	£13,607	5.9558			
DEX	£21,241	5.9757	£7,635	0.0199	£383,512
Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

6.1.2.3 ERG base case ICER

Based upon the model corrections and a selection of the scenario analyses outlined in Sections 6.1.2.1 and 6.1.2.2, respectively, the ERG has estimated a revised base case ICER for the comparison of dexamethasone versus watch and wait in patients with DMO who are considered unsuitable for, or insufficiently responsive to non-corticosteroid therapy. The revised base case ICER has been estimated after combining all model corrections undertaken by the ERG (analyses B1-B5) and additional scenarios considered in the analyses C5-C12 performed by the ERG.

The ERG considers the derivation of efficacy data from watch and wait directly from the pooled MEAD trials as the most robust, due to the severe limitations associated with the application of the NMA outputs in the model, including the assumption that the 12-month relative risks estimated in the NMA are stable and can be applied from initiation of treatment to 3 years of treatment duration, the effect of normalisation on the transition probabilities, and the restriction of transitions by one health state up or down in every cycle of the model. This issue has been discussed in more detail in Section 6.1.1, under Analysis A4 (pgs 159-162). The revised base case analysis by the ERG, for patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids, when the efficacy of watch and wait was based on patient-level data from the pooled MEAD sham arms, resulted in an ICER of £1,166,271/QALY, as shown in Table 129.

Table 129. Results of revised base case analysis by ERG: patients with DMO who are considered to be unsuitable for, or insufficiently responsive to non-corticosteroids; efficacy data based on MEAD trials, no restrictions on movements by one health state up or down imposed

Intervention	Total cost	Total QALYs	Incremental	Incremental	ICER

Table 133. Results of revised scenario analysis by ERG: patients with DMO who are pseudophakic; scenario including laser, bevacizumab and watch and wait

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER	ICER vs baseline (laser)
Laser	£6,831	5.1369				
Bevacizumab	£7,915	5.2359	£1,084	0.0990	£10,945*	£10,945
DEX	£12,841	5.0894	£4,926	-0.1465	Bevacizumab dominates	-£126,595
Ranibizumab (50% discount)	£13,556	5.2054	£5,640	-0.0305	Bevacizumab dominates	£98,134
Watch and wait	£14,799	4.9847	£6,883	-0.2512	Bevacizumab dominates	-£52,356

Abbreviations used in the table: DEX, dexamethasone; DMO, diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
*Bevacizumab vs laser

Nevertheless, the ERG wishes to emphasise the fact that results based on the NMA are characterised by severe flaws (including the assumption that relative risks between all treatments of improving vision, stable vision and worsening vision are equal to 12-month relative risks and stable over the whole 3-year duration of treatment and the normalisation approach) and therefore results obtained from these analyses should be interpreted with great caution.

7 OVERALL CONCLUSIONS

7.1 Summary of clinical effectiveness issues

The EU marketing authorisation for dexamethasone restricts it use to the treatment of adult patients with visual impairment due to DMO, who are pseudophakic (have an artificial lens implant, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. However, the ERG considers that in terms of the actual populations in the six RCTs presented in the CS for dexamethasone, none of them directly addressed the populations covered by the EU marketing authorisation for dexamethasone. All six RCTs had inclusion criteria designed to assess broader populations to the one of interest. The ERG thus considers that the results presented in the CS are limited in their specificity for addressing the populations for whom dexamethasone has EU marketing authorisation.

The ERG notes that two of the RCTs reported in the CS used treatment regimens that are not approved for use in the UK (BEVORDEX and 024). These two studies both allowed re-treatment with dexamethasone more frequently than the 6-month minimum re-treatment period specified in the EU licence. The ERG thus does not consider these trials of relevance to the decision problem.

C5	Not relevant	Not relevant
C6	Inp_MRU	Cell C29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Dex_6m_Y1,4) Cell D29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y2,4) Cell E29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y3,4)
C7	Inp_MRU	Cells 'Inp_MRU'!C32:G32 amended from 2 to =IF('ERG analysis'!$E$9=TRUE,0,2)
C8	Inp_Costs	Cell C94 amended from 52282.93 to =IF('ERG analysis'!$E$10=TRUE,(532*(365.25/7)),52282.93)
C9	Inp_Costs	Cell C104 amended from 517.24 to =IF('ERG analysis'!$E$11=TRUE,2252,517.24)
C10	Inp_Costs	Cell C134 amended from 12.48 to =IF('ERG analysis'!$E$20=TRUE,1.18,12.48) Cell F138 amended from =AVERAGEIF(F133:F137,">0",F133:F137) to =IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))
C11	Inp_Costs	Cell C120 amended from 1421.92 to =IF('ERG analysis'!$E$15=TRUE,(1123*0.5)+(1422*0.5),1421.92) Cell C126 amended from =SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125) to =IF('ERG analysis'!$E$15=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125))
C12	Inp_Costs	Additional cell to account for extra 6 visits: C138 =IF('ERG analysis'!E22=TRUE,6*Cost_Resource_4,0) F138 amended further to =C138+(IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))) C126 amended further to: =C138+(IF('ERG analysis'!$E$21=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125)))
C13	Inp_Efficacy	[redacted]

C5	Not relevant	Not relevant
C6	Inp_MRU	Cell C29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Dex_6m_Y1,4) Cell D29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y2,4) Cell E29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y3,4) Cell C73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Tx2_Y1,4) Cell D73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Tx2_Y2,4) Cell E73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Tx2_Y3,4)
C7	Inp_MRU	Cells 'Inp_MRU'!C32:G32 amended from 2 to =IF('ERG analysis'!$E$9=TRUE,0,2)
C8	Inp_Costs	Cell C94 amended from 52282.93 to =IF('ERG analysis'!$E$10=TRUE,(532*(365.25/7)), 52282.93)
C9	Inp_Costs	Cell C104 amended from 517.24 to =IF('ERG analysis'!$E$11=TRUE,2252,517.24)
C10	Inp_Costs	Cell C134 amended from 12.48 to =IF('ERG analysis'!$E$14=TRUE,1.18,12.48) Cell F138 amended from =AVERAGEIF(F133:F137,">0",F133:F137) to =IF('ERG analysis'!$E$14=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))
C11	Inp_Costs	Cell C120 amended from 1421.92 to =IF('ERG analysis'!$E$15=TRUE,(1123*0.5)+(1422*0.5),1421.92) Cell C126 amended from =SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125) to =IF('ERG analysis'!$E$15=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125))
C12	Inp_Costs	Additional cell to account for extra 6 visits: C138 =IF('ERG analysis'!E22=TRUE,6*Cost_Resource_4,0) F138 amended further to =C138+(IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))) C126 amended further to: =C138+(IF('ERG analysis'!$E$21=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125)))

C5	Inp_Treatment	Cells E25 & E26 amended from 1.5 to =IF('ERG analysis'!$E$15=TRUE,1.25,1.5)
C6	Inp_MRU	Cell C29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Doses_Dex_6m_Y1,4) Cell D29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y2,4) Cell E29 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Doses_Dex_6m_Y3,4) Cell C73 amended from 12 to =IF('ERG analysis'!$E$16=TRUE,13-p_Doses_Tx2_Y1,12) Cell D73 amended from 10 to =IF('ERG analysis'!$E$16=TRUE,8-p_Doses_Tx2_Y2,10) Cell E73 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,6-p_Doses_Tx2_Y3,4) Cell C84 amended from 12 to =IF('ERG analysis'!$E$16=TRUE,13-p_Doses_Tx3_Y1,12) Cell D84 amended from 10 to =IF('ERG analysis'!$E$16=TRUE,8-p_Doses_Tx3_Y2,10) Cell E84 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,6-p_Doses_Tx3_Y3,4) Cell C95 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,5-p_Laser_Tx4_Y1,4) Cell D95 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Laser_Tx4_Y2,4) Cell E95 amended from 4 to =IF('ERG analysis'!$E$16=TRUE,4-p_Laser_Tx4_Y3,4)
C7	Inp_MRU	Cells 'Inp_MRU'!C32:G32 amended from 2 to =IF('ERG analysis'!$E$9=TRUE,0,2)
C8	Inp_Costs	Cell C94 amended from 52282.93 to =IF('ERG analysis'!$E$10=TRUE,(532*(365.25/7)),52282.93)
C9	Inp_Costs	Cell C104 amended from 517.24 to =IF('ERG analysis'!$E$11=TRUE,2252,517.24)
C10	Inp_Costs	Cell C134 amended from 12.48 to =IF('ERG analysis'!$E$14=TRUE,1.18,12.48) Cell F138 amended from =AVERAGEIF(F133:F137,">0",F133:F137) to =IF('ERG analysis'!$E$14=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))
C11	Inp_Costs	Sheet 'Inp_Costs' cell C120 amended from 1421.92 to =IF('ERG analysis'!$E$15=TRUE,(1123*0.5)+(1422*0.5),1421.92) Sheet 'Inp_Costs' cell C126 amended from =SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125) to =IF('ERG analysis'!$E$15=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_6)/COUNTA(C120:C125))
C12	Inp_Costs	Additional cell to account for extra 6 visits: C138 =IF('ERG analysis'!E22=TRUE,6*Cost_Resource_4,0) F138 amended further to =C138+(IF('ERG analysis'!$E$20=TRUE, (0.7*F134)+(0.1*F133)+(0.2*AVERAGE(F135:F137)), AVERAGEIF(F133:F137,">0",F133:F137))) C126 amended further to: =C138+(IF('ERG analysis'!$E$21=TRUE,C120, SUM(p_Cost_IOP_Proc_1,p_Cost_IOP_Proc_2,p_Cost_IOP_Proc_3,p_Cost_IOP_Proc_4,p_Cost_IOP_Proc_5,p_Cost_IOP_Proc_

DMO_NICE_OCT2014_ALL DMO_NO MTC_ALL MOVEMENTS_ERG

Same calculation sheet as in DMO_NICE_OCT2014_ALL DMO_ERG

DMO_NICE_OCT2014_ALL DMO_NO MTC_All MOVEMENTS_UTILITY UPDATE_ERG

Analysis number	Model worksheet affected	Description of ERG changes
C14	Inp_Utility	[redacted]

C13: NA	-	-	-	-	-	-

Abbreviations used in the table: Abbreviations used in table: DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.

Table 170. Patients with DMO who are pseudophakic – all comparators considered by the company for this population

All calculations below based on list price for ranibizumab

Analysis	Treatment	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Base case (CS, Table 201)	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,041	0.1010	£10,310
	DEX700	£15,720	5.0886	£6,318	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
Model corrections						
B1: FEI rate set to 23.77%	laser	£8,289	5.1369			
	bevacizumab	£9,340	5.2359	£1,052	0.0990	£10,618
	DEX700	£15,573	5.0894	£6,232	-0.1465	Dominated
	watch and wait	£21,506	4.9847	£12,166	-0.2512	Dominated
	ranibizumab	£21,564	5.2054	£12,223	-0.0305	Dominated
B2: NA	-	-	-	-	-	-
B3: NA	-	-	-	-	-	-
B4: Cost of fluorescein angiography at £144	laser	£8,553	5.1368	-	-	-
	bevacizumab	£9,586	5.2377	£1,033	0.1010	£10,228
	DEX700	£15,913	5.0886	£6,327	-0.1491	Dominated
	ranibizumab	£21,910	5.2066	£12,325	-0.0312	Dominated
	watch and wait	£22,052	4.9824	£12,466	-0.2553	Dominated
B5: Vitreous haemorrhage cost at £989 & retinal detachment cost at £1,080	laser	£8,083	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,319	0.1010	£13,061
	DEX700	£15,614	5.0886	£6,212	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
All model corrections	laser	£8,207	5.1369			
	bevacizumab	£9,524	5.2359	£1,317	0.0990	£13,301
	DEX700	£15,661	5.0894	£6,137	-0.1465	Dominated
	watch and wait	£21,735	4.9847	£12,211	-0.2512	Dominated
	ranibizumab	£21,750	5.2054	£12,226	-0.0305	Dominated
Additional scenario analyses						
C1: Annual probability	laser	£8,887	5.1357	-	-	-
	bevacizumab	£9,814	5.2500	£927	0.1143	£8,106

of FEI of 55.28%	DEX700	£16,763	5.0830	£6,950	-0.1670	Dominated
	ranibizumab	£22,847	5.2143	£13,033	-0.0357	Dominated
	watch and wait	£24,006	4.9664	£14,193	-0.2836	Dominated
C2: Probability of deterioration of vision increased to 5.5%; improvement 3.5% and stable 91%	laser	£9,288	5.1248	-	-	-
	bevacizumab	£9,677	5.2260	£389	0.1012	£3,842
	DEX700	£17,001	5.0774	£7,325	-0.1487	Dominated
	ranibizumab	£22,144	5.1948	£12,468	-0.0312	Dominated
	watch and wait	£23,756	4.9739	£14,080	-0.2522	Dominated
C3: Discontinuation set at zero	laser	£7,640	5.1527	-	-	-
	bevacizumab	£9,483	5.2421	£1,843	0.0894	£20,621
	DEX700	£16,025	5.0979	£6,542	-0.1442	Dominated
	ranibizumab	£22,641	5.2176	£13,157	-0.0244	Dominated
	watch and wait	£23,728	4.9706	£14,245	-0.2715	Dominated
C4: HR of mortality 3.5 for DMO vs. general population	laser	£7,339	4.5665	-	-	-
	bevacizumab	£8,792	4.6572	£1,453	0.0907	£16,028
	DEX700	£14,225	4.5238	£5,433	-0.1334	Dominated
	watch and wait	£18,861	4.4300	£10,068	-0.2272	Dominated
	ranibizumab	£20,871	4.6288	£12,079	-0.0284	Dominated
C5: Bilateral treatment with anti-VEGF 75% 1 admin visit	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,191	5.2377	£830	0.1010	£8,219
	DEX700	£15,720	5.0886	£6,529	-0.1491	Dominated
	ranibizumab	£21,549	5.2066	£12,358	-0.0312	Dominated
	watch and wait	£21,822	4.9824	£12,632	-0.2553	Dominated
C6: Monitoring visits are incorporated into treatment visits	bevacizumab	£8,110	5.2377	-	-	-
	laser	£8,157	5.1368	£48	-0.1010	Dominated
	DEX700	£15,522	5.0886	£7,413	-0.1491	Dominated
	ranibizumab	£20,683	5.2066	£12,574	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£13,713	-0.2553	Dominated
C7: IOP checks removed from model	laser	£8,361	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,041	0.1010	£10,310
	DEX700 PRN	£15,322	5.0886	£5,920	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,421	-0.2553	Dominated
C8: Private residential care at £532 per week	laser	£6,996	5.1368	-	-	-
	bevacizumab	£9,208	5.2377	£2,213	0.1010	£21,915
	DEX700	£13,107	5.0886	£3,899	-0.1491	Dominated
	watch and wait	£14,043	4.9824	£4,835	-0.2553	Dominated
	ranibizumab	£21,347	5.2066	£12,139	-0.0312	Dominated
C9: Cost of	laser	£8,487	5.1368	-	-	-

depression at £2252	bevacizumab	£9,420	5.2377	£933	0.1010	£9,243
	DEX700	£15,960	5.0886	£6,541	-0.1491	Dominated
	ranibizumab	£21,759	5.2066	£12,339	-0.0312	Dominated
	watch and wait	£22,538	4.9824	£13,118	-0.2553	Dominated
C10: Mean cost of raised IOP (medication) at £88.77	laser	£8,352	5.1368	-	-	-
	bevacizumab	£9,377	5.2377	£1,024	0.1010	£10,147
	DEX700	£15,684	5.0886	£6,307	-0.1491	Dominated
	ranibizumab	£21,722	5.2066	£12,345	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,446	-0.2553	Dominated
C11: Mean cost of raised IOP (surgical) at £1273	laser	£8,364	5.1368	-	-	-
	bevacizumab	£9,402	5.2377	£1,038	0.1010	£10,285
	DEX700	£15,724	5.0886	£6,322	-0.1491	Dominated
	ranibizumab	£21,724	5.2066	£12,322	-0.0312	Dominated
	watch and wait	£21,823	4.9824	12,421	-0.2553	Dominated
C12: Add 6 extra IOP visits for those with raised IOP	laser	£8,410	5.1368	-	-	-
	bevacizumab	£9,472	5.2377	£1,062	0.1010	£10,518
	DEX700	£15,858	5.0886	£6,386	-0.1491	Dominated
	ranibizumab	£21,730	5.2066	£12,258	-0.0312	Dominated
	watch and wait	£21,823	4.9824	£12,350	-0.2553	Dominated
C13: NA	-	-	-	-	-	-
Abbreviations used in the table: Abbreviations used in table: CS, company submission; DEX700, dexamethasone 700µg; DMO, diabetic macular oedema; ERG, Evidence Review Group; FEI, fellow eye involvement; ICER, incremental cost-effectiveness ratio; IOP, intraocular pressure; NA, not applicable.						