NICE STA of OZURDEX® (dexamethasone intravitreal implant)

Additional Analyses requested following Appraisal Consultation (1)

Allergan, March 2011

Executive Summary

OZURDEX® (dexamethasone intravitreal implant) is the first EMA licensed pharmacotherapy for macular oedema following retinal vein occlusion (RVO) and is currently undergoing a NICE Single Technology Assessment for this indication.

The Evidence Review Group (ERG) and NICE Appraisal Committee C have identified important questions regarding the relative clinical and cost effectiveness of OZURDEX from the perspective of the UK NHS which this document sets out to address.

As in any HTA process, identification of the correct comparator for a new technology is a pivotal consideration; providing a meaningful reference point for standard care for a given disease condition and informing any comparative analyses of efficacy and costs.

In the absence of an approved treatment option, there has been experimental use within the NHS of unlicensed therapies in an attempt to manage macular oedema following RVO, highlighting the unmet medical need associated with this condition. In light of this, the Appraisal Committee have requested comparative analyses to explore the relative efficiency of OZURDEX when compared to bevacizumab.

There is little evidence to suggest that bevacizumab constitutes “routine” or “usual” care within the UK NHS and indeed a formal survey commissioned from the School or Health and Related Research at the University of Sheffield (ScHARR) suggests that the majority of centres surveyed regard bevacizumab as an occasional or exceptional treatment for this condition. In the majority of cases, individual funding requests are sent to primary care trusts for exceptional approval in order to fund the use of bevacizumab in this indication. This is in accordance with guidelines provided by the Royal College of Ophthalmologists (RCO) and guidance provided by the MHRA on the unlicensed nature of bevacizumab when used in the eye.

The use of an unlicensed treatment, not intended for this route of administration raises a number of important legislative considerations and exceptional processes for providers, prescribers and patients which are difficult to adequately capture within the confines of a standard economic analysis. In addition, the absence of controlled trials to quantify the efficacy and safety of bevacizumab in this indication hamper attempts to conduct a rigorous comparative analysis by usual means.

In addressing the committees concerns it has therefore been necessary to use exploratory techniques to i) illustrate the feasibility of a network model approach to effect a mixed treatment comparison ii) consider a cost minimisation evaluation of OZURDEX relative to bevacizumab and iii) use data from another anti-VEGF (ranibizumab) to provide a proxy of the “best” possible efficacy and safety profile anticipated for bevacizumab.

The economic analyses described in detail in **Section 1** are subject to critique and cannot be considered an appropriate and valid, scientific approach to evaluation. However in the absence of Grade A-C evidence these are provided in full to support assessment of the boundaries of a comparative assessment of OZURDEX relative to an unlicensed treatment

occasionally used in NHS practice. These are provided as scenario analyses utilising a different modelling framework from the core OZURDEX submission as patient level data sets are not available for the comparator arms and the core model relies upon a granular assessment of individual patient transitions to make maximum use of available data in a robust analysis.

In essence, the analyses provided in Section 1 illustrate that relative to anti-VEGF treatment (bevacizumab or ranibizumab)

1. OZURDEX is a cost saving strategy, with the potential to save the UK NHS between £4,463 and £14,994 per treated patient.
2. OZURDEX also has the potential to save NHS capacity as significantly fewer treatment and follow-up sessions are required each year.
3. OZURDEX is a cost effective treatment option (at a threshold of £20,000) when compared to treatment with bevacizumab for macular oedema following BRVO, based on a cost utility analysis utilising Mixed Treatment Comparison (MTC) MTC results. Probabilistic sensitivity analysis shows that treatment with OZURDEX is cost effective on 93% of occasions when compared to bevacizumab using a conservative MTC approach
4. OZURDEX is a cost effective treatment option (at a threshold of £20,000/QALY) when compared to either ranibizumab or bevacizumab, based on a crude, unadjusted indirect comparison between OZURDEX and data from the CRUISE study of ranibizumab in macular oedema following CRVO evaluating net monetary benefit (NMB)

The Appraisal Committee also requested that a number of assumptions within the core economic model evaluating OZURDEX vs. Observation (standard of care) be adjusted to form a revised basecase. Each of these areas is discussed in detail in **Section 2** and further evidence-based justification for the decisions taken in addressing these points is provided, referencing external, independent literature wherever possible.

In summary, the changes requested to the basecase:

- change the ratio of Outpatient vs. Day case procedures for intravitreal injections to reflect the clinical reality of the UK where different centres have adopted different practice based on available resources and expertise.
- adjust the way that the costs of vision loss (COVL) are applied to better seeing eye (BSE) patients whose BCVA in their affected eye falls below <20/200; this revision now takes full account of the BCVA status of the fellow eye and avoids inappropriate application of costs to patients with residual vision in their fellow eye sufficient to enable them not to require the specialist resources considered within the COVL for severe visual impairment

Once these changes are incorporated into a revised basecase (see Table 1), OZURDEX remains a cost effective treatment option compared to standard of care (at a threshold of £20,000/QALY) for patients with CRVO and those with BRVO who are unsuitable for laser

photocoagulation ranging from £6,361/QALY in BRVO Prior Laser to £18,472 in BRVO Macular Haemorrhage.

The Appraisal Committee asked that different intensities of re-treatment be evaluated through scenario analysis to identify the impact of this assumption on the cost effectiveness of OZURDEX vs. observation. These analyses are provided in **Section 3** and illustrate that this is an important driver of overall cost effectiveness. Even in the most extreme scenario, whereby all patients continue to be re-treated at the rate observed at day 180 in GENEVA throughout a 2.5-3yr treatment period, which is considered unlikely in practice, OZURDEX remains cost effective at a threshold of £30,000/QALY in CRVO and at a threshold of £20,000/QALY in BRVO patients who have previously received laser photocoagulation.

The survey conducted by ScHARR provides important information regarding the time to discharge currently observed in UK NHS practice for both BRVO and CRVO which would suggest that the assumptions used in the base case of the economic evaluation are more likely to mirror the actual management of these conditions in UK practice.

The Appraisal Committee also requested the provision of further information regarding the definition of the BRVO Macular Haemorrhage subgroup within the evaluation, and the meaningfulness of this subgroup in UK practice. This is explored in **Section 4 .** This subgroup represents an important population of patients for whom today there are no licensed therapeutic alternatives. The absence of proven pharmacotherapies underpins the current treatment strategy of “watch and wait” for patients with extensive macular haemorrhage, even though data across a wide range of studies have consistently demonstrated the importance of early treatment for optimal vision gain.

Therefore, Allergan believe that OZURDEX represents a significant advance for the preservation and improvement of vision in patients with macular oedema following RVO. The analyses provided demonstrate that OZURDEX is a cost (and capacity) saving strategy compared to the experimental use of anti-VEGF treatments in UK practice, and is cost effective compared to standard of care (observation).

Introduction

OZURDEX (0.7mg Dexamethasone intravitreal implant) is currently undergoing a NICE Single Technology Appraisal examining clinical and cost effectiveness in the treatment of macular oedema following retinal vein occlusion (RVO). Following an Appraisal Committee meeting held in January 2011 an Appraisal Consultation Document was issued which requested that the manufacturer (Allergan) conduct and provide a number of additional analyses to support an understanding of the relative clinical and cost effectiveness of OZURDEX from the perspective of the UK NHS.

This document addresses each of the points raised, providing a number of unique analyses and outlining and justifying the assumptions that underpin these.

The ACD formally requests the following analyses/information:

1. The clinical and cost effectiveness of OZURDEX compared with bevacizumab. The cost-effectiveness analysis should include varying vial sharing assumptions for treatment with bevacizumab.
2. A revised base case for the cost effectiveness of OZURDEX, incorporating the following assumptions:
    - the costs of OZURDEX treatment based on a day case, with outpatient appointment costs as a sensitivity analysis
    - the extrapolation of data from the observation arm of the model based on all of the 0- to 6-month data from the randomised controlled trial
    - modelling of the fellow eye involvement, ensuring that costs of blindness are applied only to patients in whom both eyes fall into the worst health state (severe visual impairment).

3. Alternative scenario analyses for the re-treatment rate that reflects clinical practice in the UK, including:
    - an analysis in which proportions re-treated are as at day 180 for the five injections after the first injection in people with CRVO
    - an analysis in which proportions re-treated are as at day 180 for the four injections after the first injection in people with BRVO
    - alternative analyses in which proportions re-treated are varied between the two extremes of the base case and the randomised controlled trial.
4. The Committee requires further clarification of the location and extent of macular haemorrhage for the subgroup of patients for whom laser treatment was not considered appropriate because of macular haemorrhage.

Section 1: Comparing OZURDEX vs. Bevacizumab

It is stated in section 4.25 of the ACD states that *'....The Committee concluded that a comparison of OZURDEX with bevacizumab in the economic model was required to address the decision problem of most relevance to the NHS.'*

Is bevacizumab routinely used in the UK NHS for treatment of macular oedema following RVO?

A key point of emphasis within the ACD relates to the feasibility of a valid comparison between OZURDEX and Bevacizumab. This is a difficult area to resolve in the absence of suitable data or reliable estimates of efficacy or safety to incorporate in a robust economic model.

In support of the assumptions made in this response, and in an effort to systematically evaluate whether Bevacizumab can be justified as a comparator in this specific indication, a formal survey of UK retinal centres was commissioned, conducted by the University of Sheffield School of Health and Related Research (ScHARR). The detailed findings of the survey are provided in Appendix A and are referenced throughout this response to provide additional qualitative and quantitative support for key assumptions made. In short, the survey supports the view that Bevacizumab is not used 'routinely' in clinical practice for the management/treatment of RVO. This conclusion is based on responses from 8 tertiary treatment centres across the UK.

It is important to note throughout that Bevacizumab is not licensed for use in the eye and that a number of different policy statements and guidelines would bring the use of Bevacizumab in the treatment of macular oedema following RVO into question. These include MHRA guidance issued in April 2009[1] which comments that:

"The responsibility that falls on healthcare professionals when prescribing an unlicensed medicine or a medicine off-label may be greater than when prescribing a licensed medicine within the terms of its licence. Prescribers should pay particular attention to the risks associated with using unlicensed medicines or using a licensed medicine off-label. These risks may include: adverse reactions; product quality; or discrepant product information or labelling (e. g, absence of information for some unlicensed medicines, information in a foreign language for unlicensed imports, and potential confusion for patients or carers when the Patient Information Leaflet is inconsistent with a medicine's off-label use)."

This guidance document goes on to comment on the use of Bevacizumab in the eye as a specific example of the off-licence use of a medicine, stating that

"Off-label intravitreal use of Bevacizumab (Avastin, licensed for treatment of various solid cancers) has been associated with reports of severe eye inflammation and sterile

endophthalmitis. The production methods, formulation, and doses for Bevacizumab were developed for use in oncology. Its use in the ophthalmology setting has not been authorised." [1]

NICE have raised key questions regarding safety monitoring and risk management for Bevacizumab in the eye as it is not licensed for this route of administration

This issue was explored by NICE as part of a pre-scoping exploratory analysis of the potential appraisability of Bevacizumab for eye conditions held on 13th July 2010[2]. A report issued summarising the proceedings of this meeting stated that:

"Patients, clinicians and healthcare commissioning groups would benefit from an appraisal, or appraisals, of the clinical and cost effectiveness of intravitreal Bevacizumab in eye conditions. However, there are concerns that recommendations on the clinical and cost effectiveness of intravitreal Bevacizumab may be interpreted as a guarantee of safety, and without a specific regulatory review of quality and safety of the product this may be misleading." This salient point stems from the facts that there is no license for Bevacizumab for the treatment of any eye condition, nor is there any Grade A evidence from which to confidentially extract safety and efficacy information regarding the use of Bevacizumab

"Furthermore, since an unlicensed product would not have the support of a manufacturer or sponsor, alternative arrangements for risk management / pharmacovigilance would be likely to have to be put in place in order to monitor the safe usage of the product.

Stakeholders discussed the challenges and considered that an appraisal, or appraisals, of the clinical and cost effectiveness of Bevacizumab in eye conditions could be feasible if the safety and quality of the product also are, or have been, adequately assessed."

This point is particularly relevant when cost comparisons are made as the overall cost to the UK NHS of a safety registry for Bevacizumab, and responsibility for its implementation needs to be considered. It is also one of the hardest components to model as standard health economic models would not usually need to consider incremental expenses such as a safety registry. Due to uncertainty around the costs and responsibility for such a requirement, this has not been incorporated into the submitted analyses which should therefore be interpreted as a conservative assumption.

Whilst the proceedings indicate a desire to conduct an evaluation of the clinical and cost effectiveness of Bevacizumab in eye conditions they also highlight key areas of concern, and uncertainty, that arguably would need to be addressed before Bevacizumab could robustly be considered to be an appropriate comparator for HTA.

Recognising however that this has been stated to be an important consideration for the Appraisal Committee, Allergan have thoroughly reviewed the available evidence with

support from expert methodologists to establish whether sufficient information exists to conduct an indirect comparison vs. Bevacizumab. Firstly, there are no randomised controlled pivotal clinical trials of Bevacizumab in RVO from which to draw reliable conclusions on safety and efficacy.

In the absence of this Grade A medical evidence, we have looked to other sources of information. However the "case series data and information from prospective and retrospective studies" referred to by the ERG provide minimal information and may not yield reliable estimates of efficacy or safety for Bevacizumab.

Allergan believe the scientific validity in selecting reliable estimates from the available evidence is questionable, subject to considerable uncertainty and subjectivity and does not meet the requirements of the NICE reference case for a robust economic evaluation.

As OZURDEX is the only licensed treatment available in the UK for this condition, it is important to consider that any decision not to recommend it's usage, based on analyses comparing to Bevacizumab could imply a recommendation for an unlicensed treatment with only Grade D evidence to support its efficacy and safety in this specific patient population.

Addressing the requests raised in the Appraisal Consultation Document

Recognising all the limitations and issues described above, in order to try to address the committee's request and to provide meaningful information to address the question of cost effectiveness in comparison to Bevacizumab three different methodologies have been deployed

I) Cost minimisation

II) An indirect comparison utilizing a Mixed Treatment Comparison (MTC) methodology to bridge between OZURDEX and bevacizumab for macular oedema following BRVO

III) An indirect comparison based on a proxy estimate of anti-VEGF effectiveness and safety, leading to a crude indirect cost utility evaluation for macular oedema following CRVO

In preparing these analyses, Allergan commissioned a thorough systematic review of all available literature regarding the use of Bevacizumab in macular oedema following RVO. The following randomised controlled studies were identified as potential sources of comparator data for completing an evidence network to compare bevacizumab with OZURDEX; Russo (2009)[3], which compared treatment with bevacizumab with macular laser grid photocoagulation in BRVO, and the Branch vein occlusion study group report (1984)[4]

which compared macular laser grid photocoagulation with observation. A description of the methodology and results of the MTC are provided in section 1.2.1 and Appendix B.

Given the weakness of the available evidence base, these analytical approaches are open to significant debate and criticism and should be interpreted with appropriate caution.

1.1 Cost minimisation:

Given the lack of data to support the effectiveness of treatment with Bevacizumab and the detailed, trial based transition approach used in the Dexamethasone intravitreal implant health economic model, it has not been possible to include Bevacizumab in the existing model prepared for the original STA submission. A new analysis has therefore been performed to estimate the relative cost effectiveness of OZURDEX treatment relative to anti-VEGF treatment from the perspective of the UK NHS.

Without evidence from which to draw reliable estimates of comparative efficacy and safety between Bevacizumab and OZURDEX, an assumption of equal efficacy has been made, and hence a cost minimisation methodology employed. Differences between OZURDEX and Bevacizumab are modelled in treatment related adverse event rates, but this is only assumed to impact relative costs.

There is uncertainty surrounding the appropriate cost of acquiring bevacizumab in NHS practice due to the lack of dosage recommendations or licence for this indication

The BNF states that the cost of a 100mg vial of Bevacizumab is £242.66[5]. The dose assumed to be required for treatment of macular oedema following RVO however is substantially smaller than this (although not based on evidence) and therefore this approach would be subject to a large amount of wastage.

A survey of UK retinal centres conducted by the University of Sheffield School of Health and Related Research (ScHARR) confirmed that the UK centres utilising Bevacizumab in NHS practice predominantly source pre-filled syringes from one of two "specials" manufacturers in the UK. The cost of a pre-filled syringe of Bevacizumab sourced from one of these manufacturers was therefore applied within the base case analysis of costs. Moorfields Pharmacy sell Bevacizumab at a unit cost per pre-filled syringe of £105.00 (excl VAT)[6]. As in the original STA submission, the cost of OZURDEX is taken as £870 per unit (excl. VAT).

Scenario analysis was performed as requested by the Appraisal Committee to examine the possibility of vial sharing; however it should be recognised that this potentially contravenes good clinical practice regarding the handling of injectable medicines. An alert issued by the National Patient Safety Agency (NPSA) in March 2007[7] states that in relation to injectable medicines, single use products should only be used to prepare single doses. This alert goes on to describe that:

> *"It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied. The NPSA suggests that NHS organisations should work with the pharmaceutical industry to identify new products and formulations that could make practice safer.*

Frequently, an unlicensed injectable medicine has to be prepared from a licensed product in clinical areas before the prescribed medicine can be administered to the patient. Where these products have been assessed as high or moderate-risk, they should be prepared and/or supplied by a pharmacy or alternative risk reduction methods should be used to improve patient safety. Ready-to-use and ready-to-administer products that cannot be prepared in the hospital pharmacy department should be sourced from NHS manufacturing units or commercial 'specials' manufacturers. It is essential that the quality of these medicines is assessed and approved by an appropriate quality assurance pharmacist before being purchased."

Sensitivity analysis examining the impact of varying "vial sharing" assumptions as requested by the Appraisal Committee are provided in Appendix C are provided for completeness but are not considered to be appropriate in view of the points raised above and so are not presented in the revised basecase.

The setting of care assumed for the procedure is a major driver of total costs

There is also uncertainty as to the appropriate setting for treatment with both Bevacizumab and OZURDEX. The ACD noted in section 4.28 that *'...the Committee concluded that the costs of treatment based on an outpatient appointment had been underestimated in the model and that the base-case model should include day-case costs, with outpatient costs included in a sensitivity analysis'.*

In order to address this uncertainty in a transparent manner we have referred to previous HTA analyses and NICE costing recommendations on the management of intravitreal injections[8]. An estimated rate (a point between an outpatient consultation and a day case admission) has been applied to each treatment administration for both OZURDEX and Bevacizumab. This equates to £523.50 per treatment administration: 75% of the cost of a Day Case procedure and 25% of the cost of an Outpatient procedure. This also reflects the reality of variable access to specialist facilities, including the availability of a "clean room" vs. a theatre in different settings of care across the UK. In order to reflect the findings from the ScHARR survey, Appendix C also contains a sensitivity analysis in which 50% of the cost of an outpatient procedure and 50% of the cost of a day case procedure are used, This results in a per treatment administration cost of £399.

Frequency of Bevacizumab administration assumed to mirror data from the only large controlled trial programme of anti-VEGF treatments in RVO

Within the cost minimisation model, the annual number of doses of OZURDEX reflects published data (as reported from the GENEVA Trial programme) and used in the main economic submission. There are few data reporting the appropriate number of annual doses of Bevacizumab in a longitudinal manner and therefore it is assumed that the protocol of Bevacizumab usage mirrors that of the only large RCT of an anti-VEGF treatment in macular

oedema following CRVO[1] (Ranibizumab, CRUISE). Assumed doses are shown in Appendix C, Table 1.

The number of assumed treatment administrations, consultations, including treatment visits and routine outpatient reviews is captured for each arm and are shown in Appendix C, Tables 1 to 4.

The adverse event profile for OZURDEX includes an increased rate of cataract and non-cataract events and reflects the assumptions used in the main economic submission. The only data available from the CRUISE trial of Ranibizumab detailed the rate of cataracts, reported over a six month period. These were converted to an annual rate and included in the model. In the absence of any Level 1 evidence upon which to base assumptions, no other adverse events were assumed for Bevacizumab; this is considered conservative particularly in light of recent database analyses published by Curtis et al[15] The costs assumed for the treatment of captured adverse events are summarised in Table 5 of Appendix C.

It is assumed that treatment with either strategy is for a period of 3 years and that after that time that all costs and effects are equal. Costs are discounted at an annual rate of 3.5%

Results

The base case results for the cost minimisation analysis are shown in Table 1. In summary despite the higher OZURDEX drug acquisition cost, the greater number of doses required for treatment with Bevacizumab and associated administration costs means that treatment with OZURDEX reduces overall costs to the NHS, saving £4,463 per patient over 3 years. A comparison with Ranibizumab is included in the results for completeness and shows that treatment with OZURDEX is cost reducing, saving £14,994 per patient over 3 years.

Table 1*: Base case Cost Minimisation Results: CRVO*

	Ranibizumab	**Bevacizumab**	**OZURDEX**
Drug cost	£12,216	£1,685	£3,231
Cost of drug administration	£8,401	£8,401	£1,944
Cost of additional follow-up appointments	£455	£455	£344
Cost of cataracts	£72	£72	£243
Cost of other adverse events	£0	£0	£389
Total cost	£21,145	£10,614	£6,151
Marginal Cost (Dexamethasone vs.)	**-£14,994**	**-£4,463**	**--**

Further detail is available in Appendix C

[1] This cost minimisation has been performed to compare treatment strategies in CRVO alone to mirror the approach taken later in formulating an indirect cost effectiveness evaluation. Data relating to the specific subgroups of BRVO discussed in the OZURDEX STA are not available from the published BRAVO study of ranibizumab in BRVO and protocols differed substantially in terms of the inclusion of laser photocoagulation in BRAVO as an adjunctive treatment option and so a comparison cannot be attempted.

Sensitivity analyses have been performed examining the effect of removing adverse events, assuming vial usage rather than pre-filled syringes, vial sharing, assumptions on the mix of day case and outpatient visit required for administration and the annual number of doses required. The results of these analyses are shown in Table 6, Appendix C and show that in all cases, except a scenario where all administrations are performed in an outpatient setting (considered by the Appraisal Committee to be inappropriate), treatment with OZURDEX saves the NHS money compared to either Bevacizumab or Ranibizumab treatments.

A separate request from the Appraisal Committee explores the uncertainty around re-treatment rates with OZURDEX by assuming that all patients continue to receive treatment at the rates observed in the GENEVA study until year 3. The results of this analysis for OZURDEX are described in Section 3. As similar uncertainty exists regarding the dosing frequency required for anti-VEGF treatments the same approach has been taken here, to explore the potential cost savings associated with OZURDEX treatment relative to either Bevacizumab or Ranibizumab under these conditions. In this sensitivity analysis the proportions of patients receiving Ranibizumab, Bevacizumab and Dexamethasone treatments in the cost minimisation analysis are as at day 180 for the remaining treatments out until year 3. The results are shown in Table 2.

Table 2: *Scenario analysis Cost Minimisation Results: CRVO*

	Ranibizumab	**Bevacizumab**	**OZURDEX**
Total cost	£27,447	£13,582	£8,151
Marginal Cost (OZURDEX vs.)	**-£19,296**	**-£5,431**	**-**

Conclusion

The presented analyses demonstrate that the use of Bevacizumab, an unlicensed treatment option used in NHS practice in the absence of an approved option, based on NHS acquisition and administration costs would not save money when compared to an OZURDEX treatment strategy. Sensitivity analyses (shown in Appendix C) demonstrate that this conclusion is robust to uncertainty in the protocol for drug acquisition (vial sharing and pre-filled syringes), as it is the cost of administration that drives the economic case rather that the cost of drug acquisition. The model is no longer cost saving in the extreme assumption where all administrations are assumed to be performed as outpatient visits, however given the results of the ScHARR survey (see appendix A) which reports that 50% of intravitreal injections are given as day cases, and the assumptions underpinning the NICE costing tool for anti-VEGF treatments in wAMD[8] which assumes that 75% of treatments are given in the day case setting, this is considered unlikely. For retinal centres to perform intravitreal injections as outpatient procedures access to clean rooms and other specialist equipment

are required that may only be available in some centres to day-case patients. This is reflected in the current capacity issues in ophthalmology where there are constraints on the availability of trained specialists, access to clean rooms and theatre time which impact on waiting times thereafter. The introduction of OZURDEX, which reduces the number of required administrations compared to bevacizumab will therefore not only reduce the cost to the NHS, but will also have the potential to reduce the growing burden on ophthalmology services and improve patient access to effective treatment.

Potentially greater savings in practice

The cost minimisation results provided in Table 1 are considered to be conservative given that the costs of providing the: "*risk management / pharmacovigilance that would be likely to have to be put in place in order to monitor the safe usage of the product"*[2] *a*re not considered within this analysis. Additionally the limited data available for Bevacizumab in this specific patient population and indication do not allow a thorough assessment of the likely safety considerations and adverse event profile that might imply additional costs within the Bevacizumab arm. When qualitatively considering these factors, OZURDEX becomes an even more cost saving strategy compared to the use of this unlicensed treatment option.

GMC guidance to doctors[9] regarding the prescription of unlicensed medicines suggests the following:

1. *You can prescribe unlicensed medicines but, if you decide to do so, you must:*
    a. *a. Be satisfied that an alternative, licensed medicine would not meet the patient's needs*
    b. *b. Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy*
    c. *c. Take responsibility for prescribing the unlicensed medicine and for overseeing the patient's care, including monitoring and any follow up treatment*
    d. *d. Record the medicine prescribed and, where you are not following common practice, the reasons for choosing this medicine in the patient's notes.*

It is expected that as a result of GMC guidance, treating a patient with bevacizumab will necessitate additional administrative activities as there may be a requirement for the consultant to spend extra time with the patient filling in exceptional paper work. A sensitivity analysis has been performed to demonstrate the impact of this where it is estimated that an additional 15 minutes per patient will be required to fully counsel and consent. This has been costed at £36.50 based on the PSSRU [10]cost of £146 per patient hour

for a medical consultant (not including qualifications). The result of this analysis is shown in Table 3.

Table 3*: Sensitivity analysis assuming an additional 15 minutes consultant time for completing exceptional paperwork when treating with Bevacizumab*

	Ranibizumab	**Bevacizumab**	**OZURDEX**
Total cost	£21,145	£11,199	£6,151
Marginal Cost (Dexamethasone vs.)	**-£14,994**	**-£5,049**	-

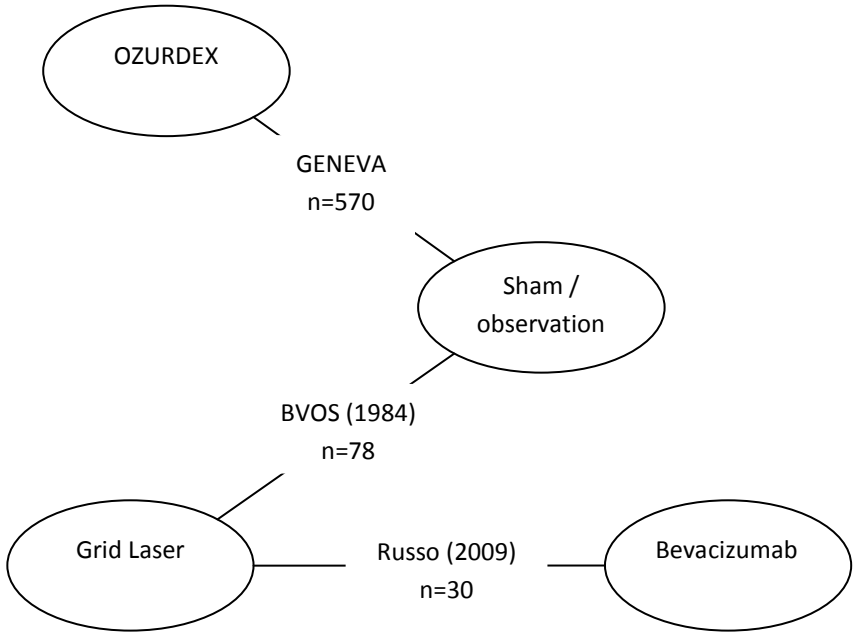
1.2 Indirect cost-effectiveness

1.2.1 Mixed Treatment Comparison

In response to the request from NICE in the ACD to compare treatment with OZURDEX to bevacizumab, an MTC has been attempted to synthesise the available data across studies. A thorough systematic review of all available literature regarding the use of Bevacizumab in macular oedema following RVO has been performed. The identified randomised controlled trials were then examined to determine whether an evidence network could be established to bridge from bevacizumab through to OZURDEX. Trials were required to report change in BCVA for inclusion in the analysis.

A network was established specifically for macular oedema following BRVO using the following studies; Russo (2009)[11], which compared treatment with bevacizumab with macular laser grid photocoagulation in the treatment of macular oedema following BRVO, and the Branch Vein Occlusion Study (BVOS) group report (1984)[4] which compared macular laser grid photocoagulation with observation in the treatment of macular oedema following BRVO. The study by Russo et al[11] was the only randomised controlled study which examined bevacizumab. Evidence for OZURDEX was based on the BRVO subgroup of the GENEVA clinical studies. Analyses were run using OZURDEX efficacy values at day 60 (as a sensitivity analysis), where OZURDEX efficacy is at its peak and at day 180 (as a basecase) where efficacy has waned and a second treatment may be required for a proportion of patients. This is a conservative approach given the differences in pharmacokinetic profiles between the two comparator arms. The network analysis assumes that the sham arm of the GENEVA trials and the observation arm of the CVOS study are equivalent. The evidence network is shown in Figure 1.

Figure 1: Network of included trials

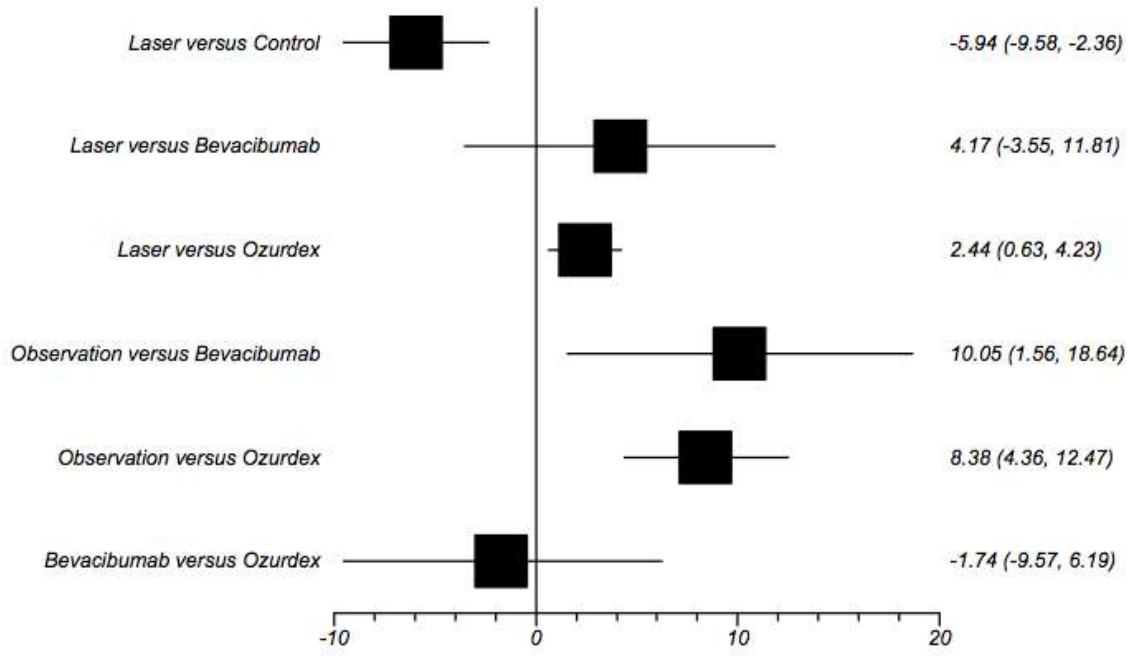


The results of the MTC are shown in Figures 2 and 3. These demonstrate that treatment with OZURDEX (efficacy assessed at day 180) is directionally less effective than bevacizumab, with a difference in BCVA of -1.74 letters (95% CI -9.57 to 6.19) although not statistically significantly. When valued at day 60 however, OZURDEX is directionally better than bevacizumab with an difference in BCVA of +2.55 letters (95% CI -5.28 to 10.48) though also not statistically significant. OZURDEX is also shown to be significantly better than observation and laser.

These analyses show that treatment with OZURDEX is directionally better than bevacizumab when efficacy is valued at day 60 and directionally worse when assessed at day 180 due to the differences in pharmacokinetic profiles between the two comparators. The uncertainty surrounding these analyses however means that no significant differences in improvement in BCVA can be determined and that estimates require cautious interpretation.

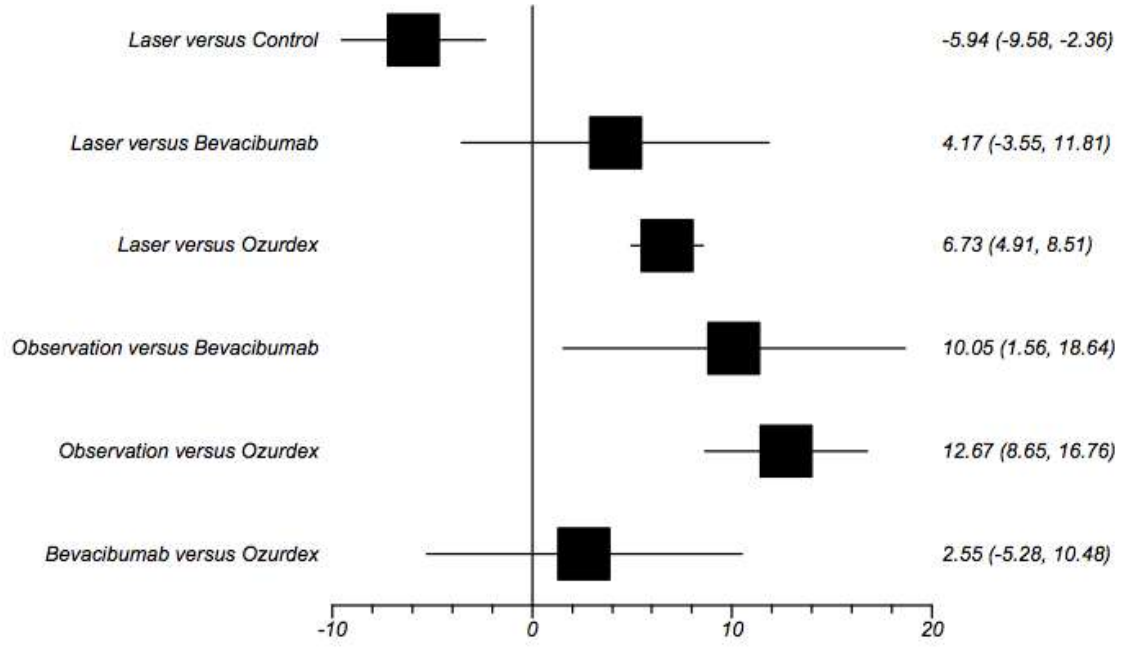
Full details of the MTC are provided in Appendix B.

Figure 2: Results from the MTC showing difference in Best Corrected Visual Acuity (95% CI)[a,b] for OZURDEX assessed at day 180.



[a] *Results to the left of the vertical line favour treatments listed first, and to the right of the line favour the treatment listed second in the descriptor*

Figure 3: Results from the MTC showing difference in Best Corrected Visual Acuity (95% CI)[a,b] for OZURDEX assessed at day 60.



[a] *Results to the left of the vertical line favour treatments listed first, and to the right of the line favour the treatment listed second in the descriptor*

1.2.2 Cost Utility Model based on Mixed Treatment Comparison (MTC)

Methodology

The approach to modelling costs and adverse events used in the cost minimisation approach in section

1.1 above were retained in this cost utility analysis, apart from cost data were updated for BRVO (see Appendix D for details). The results of the MTC were used to estimate the incremental mean number of letters gained for Bevacizumab compared to OZURDEX at month 6, reported as 1.74 letters (non-significant). The utility algorithm used in the main submission was then used to convert this difference in BCVA into QALY gains (see Appendix H for details). The algorithm for the NEI-VFQ-UI requires that the effect is quantified in either the better-seeing eye (BSE) or the worse-seeing eye (WSE) and so the base case values of 10% and 90% respectively were used for this estimation in both arms. The day 60 results which report a 2.55 letter gain for OZURDEX relative to bevacizumab are used in sensitivity analysis.

The model was run over a lifetime horizon with an initial 3 year treatment period. After this period it is assumed that all costs are equal on both treatment arms. The benefit from treatment with Bevacizumab is conservatively assumed to be maintained over the patient's lifetime. This assumption is varied in sensitivity analysis. Retreatment rates are assumed to be in accordance with those of the main submission, and adjusted accordingly to estimate equivalent re-treatment rates between arms (Appendix D). This is likely to be a conservative assumption as it is anticipated based on data from other retinal conditions that anti-VEGF therapy might need to be maintained at a higher rate of intensity. Reductions in efficacy as measured by BCVA were also observed in the CRUISE and BRAVO studies when treatment intervals were extended[19,12,13.] The FDA reflected this in their labelling of ranibizumab for the treatment of macular oedema following RVO recommending that treatment should continue monthly (beyond the initial 6 months). As bevacizumab is not licensed in this indication, it is not possible to refer to label or protocol recommendations regarding dosage intervals and retreatment intensity.

Patients enter the model aged 68 and are assumed to experience mortality based on standard UK all-cause mortality curves.

Results

The base case results for this analysis are shown in Table 4 below. The results show that treatment with OZURDEX versus treatment with Bevacizumab results in a reduction in overall cost of £2,829 with a relative loss in quality of life of 0.03 QALYs given the difference in mean BCVA at 6 months in the MTC. Given the negative marginal costs and QALYs, the resulting ICER must be interpreted with care. An analysis of net marginal benefit (NMB) at a threshold of £20,000 and £30,000 has therefore been performed to facilitate this. Where the NMB is > 0, treatment with OZURDEX is considered cost effective. **The analysis shows that at a £20,000 threshold treatment with OZURDEX is cost effective compared to treatment with Bevacizumab.** This is explained in further detail in Appendix I.

Table 4: *Base case results for cost utility analysis based on MTC*

Discounted Costs	Marginal	Marginal	NMB at	NMB at

OZURDEX	Bevacizumab	Discounted Costs	Discounted QALYs*	£30,000/ QALY	£20,000/ QALY
£3,693	£6,523	-£2,829	-0.030	£1,927	£2,228

**Absolute QALY values not shown as only marginal values are calculated using the utility algorithm*

Probabilistic sensitivity analysis (PSA) was also performed to examine the effect of the uncertainty around the estimate of treatment effect. 10,000 Monte Carlo simulations were performed to sample plausible efficacy values. This analysis demonstrates that treatment with OZURDEX is cost effective when compared to bevacizumab on 93% of occasions.

Sensitivity analyses have been performed examining the effect of removing adverse events, assumptions on the mix of day case and outpatient visits required for administration and the effect of varying the assumption of length of treatment benefit. The results of these analyses are shown in Appendix D.

The sensitivity analyses show that treatment with OZURDEX remains cost effective at a £20,000 threshold in all scenarios except those where 100% of administrations are assumed to be performed as outpatient visits which as detailed in section 2.1 is considered highly unlikely in UK practice.

A separate request from the Appraisal Committee explores the uncertainty around re-treatment rates with OZURDEX by assuming that all patients continue to receive treatment at the rates observed in the GENEVA study until year 3. The results of this analysis for OZURDEX are described in Section 3. As similar uncertainty exists regarding the dosing frequency required for anti-VEGF treatments the same approach has been taken here, to explore the potential cost savings associated with OZURDEX treatment relative to either Bevacizumab b under these conditions. In this sensitivity analysis the proportions of patients receiving Bevacizumab and Dexamethasone treatments in the cost effectiveness analysis are as at day 180 for the remaining treatments out until year 3. The results are shown in Table 5.

Table 5: *Scenario results for cost utility analysis (based on MTC) where retreatment levels are held constant at day 180 rates for 3 years*

Discounted Costs		Marginal Discounted Costs	Marginal Discounted QALYs*	NMB at £30,000/ QALY	NMB at £20,000/ QALY
OZURDEX	**Bevacizumab**				
£6,615	£10,694	-£4,079	-0.030	£3,177	£3,478

**Absolute QALY values not shown as only marginal values are calculated using the utility algorithm*

The base case comparison in this scenario assumes that mean change in BCVA is assessed at 6 months. This is likely to bias against OZURDEX which releases dexamethasone into the vitreous for up to six months. A sensitivity analysis has therefore been performed which examines the effect of using the mean letter gain at day 60 (5.3 letters) which results in a mean letter gain for OZURDEX compared to bevacizumab of 2.55 letters based on the MTC analysis. The results of this analysis are shown in Table 6 and show that in this scenario treatment with OZURDEX dominates Bevacizumab with a cost saving of £2,829 and an increase in quality of life of 0.044 QALYs

Table 6: *Sensitivity analysis results for the cost utility analysis assuming OZURDEX efficacy is assessed at day 60.*

Discounted Costs		Marginal Discounted Costs	Marginal Discounted QALYs*	ICER	NMB at £30,000/ QALY	NMB at £20,000/ QALY
OZURDEX	**Bevacizumab**					
£3,693	£6,523	-£2,829	0.044	Dominant	£4,151	£3,711

**Absolute QALY values not shown as only marginal values are calculated using the utility algorithm*

A sensitivity analysis is performed which examine the effect of assuming that the proportion of patients treated as daycases is 50% as reported in the ScHARR survey, rather than the 75% assumed in the basecase. The results of this analysis are shown in Table 7 and demonstrate that treatment with Ozurdex is a cost effective option at both a £30,000 and a £20,000 threshold.

Table 7: *Sensitivity analysis results for the cost utility analysis assuming 50% of patients are treated as daycases.*

Discounted Costs		Marginal Discounted Costs	Marginal Discounted QALYs*	NMB at £30,000/ QALY	NMB at £20,000/ QALY
OZURDEX	**Bevacizumab**				
£3,418	£5,294	-£1,876	-0.030	£974	£1,275

A final sensitivity analysis is performed which includes the potential cost of completing exceptional paperwork as discussed in section

1.1. The results of this analysis are shown in Table 8.

Table 8: *Sensitivity analysis assuming an additional 15 minutes consultant time for completing exceptional paperwork when treating with Bevacizumab*

Discounted Costs		Marginal Discounted Costs	Marginal Discounted QALYs*	NMB at £30,000/ QALY	NMB at £20,000/ QALY
OZURDEX	Bevacizumab				
£3,693	£6,883	-£3,190	-0.030	£2,287	£2,588

**Absolute QALY values not shown as only marginal values are calculated using the utility algorithm*

Conclusion

Using the results of the MTC to estimate the comparative efficacy of OZURDEX versus Bevacizumab, treatment with OZURDEX can be demonstrated to be cost saving but based on a conservative analysis has a lower gain in quality of life due to differences in mean BCVA observed at month 6.

An analysis of NMB demonstrates that treatment with OZURDEX is cost effective compared to treatment with Bevacizumab and is robust to sensitivity analyses. As discussed above, the 1.74 letter gain for Bevacizumab is highly conservative as this is based on the 6 month comparison of a "peak" Bevacizumab effect with a waning effect for the first cycle of OZURDEX treatment, at which stage the treatment difference is likely to be at its greatest and furthermore is not adjusted for baseline population differences. Additionally, the assumption that this benefit then remains for the patient's lifetime biases heavily against OZURDEX and the analysis has been shown to be sensitive to this assumption. When the peak point of treatment with OZURDEX is used within this analysis then treatment with OZURDEX dominates Bevacizumab.

It is likely therefore that the base case cost effectiveness results presented significantly underestimate the cost effectiveness of treatment with OZURDEX relative to Bevacizumab. With all limitations recognised, even under these conservative conditions, OZURDEX is demonstrated to be a cost-effective alternative to Bevacizumab in the management of macular oedema following RVO.

1.2.3 Indirect comparison based on a proxy estimate of anti-VEGF effectiveness and safety

In order to estimate the maximum anticipated efficacy of an anti-VEGF treatment in ME following CRVO, an alternate approach to the MTC analysis described above was devised. Here we use evidence from the only large, randomised study of an anti-VEGF in macular oedema following CRVO, the CRUISE study for Ranibizumab [20]and assume that this is an appropriate proxy for the efficacy and safety of Bevacizumab.

This analysis has only been conducted for macular oedema following CRVO (rather than both BRVO and CRVO) for the following reasons:

- Published data from the BRAVO trial of Ranibizumab in the treatment of macular oedema following BRVO does not permit a like-for-like comparison against the specific BRVO subgroups described in the OZURDEX STA submission
- There were substantial differences in baseline populations and treatment protocols which would potentially confound any analysis. Importantly in BRAVO patients could receive "rescue laser" from month 3 onwards therefore it is not possible from the published data available to quantify the differential effects of these two active treatments.

Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE) refers to a phase III multicenter trial in which patients with macular oedema following CRVO were randomized to receive monthly intraocular injections of 0.3 mg or 0.5 mg Ranibizumab or sham injections. The CRUISE study was a 6 month RCT study with an additional six months of follow up (12 months in total) during which patients could continue to receive monthly injections of Ranibizumab if they met pre-specified functional and anatomical criteria. The primary efficacy outcome was mean change in BCVA in the study eye.

The approach described, where data from the CRUISE study is used as a proxy for efficacy and safety anticipated with Bevacizumab is associated with significant limitations, primarily because it is not appropriate to assume that two different products are associated with identical efficacy and safety profiles. Ranibizumab and Bevacizumab have not been compared in a head to head analysis within macular oedema following RVO and so any cross-utilisation of efficacy or safety data is heavily assumptive and open to criticism. A large US Medicare claims cohort analysis performed by Duke University suggests that differences in stroke rates and all-cause mortality may exist between ranibizumab and bevacizumab[14]. A health economic analysis presented at the 2nd World Congress on Controversies in Ophthalmology (COPHy) in March 2011[15]) concludes that "the perceived cost effectiveness of bevacizumab vs. ranibizumab may be overstated if potential safety differences are considered". In the absence of Level 1 evidence to establish the safety of bevacizumab in

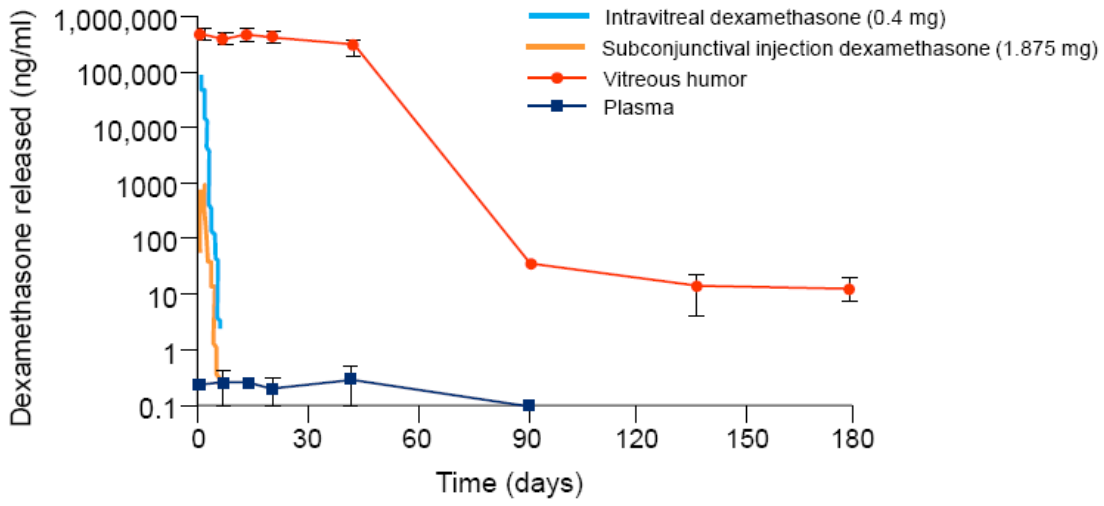
Retinal Vein Occlusion, no additional adverse events have been considered within this analysis. Based on the report described above this may be conservative.

The benefit of treatment measured by mean change in best corrected visual acuity (BCVA) is converted to a utility value and a cost-utility model then used to estimate the cost effectiveness of an OZURDEX treatment strategy compared to either Bevacizumab or Ranibizumab.

This crude, unadjusted analysis is confounded by a number of critical factors

This indirect comparison approach between CRUISE and GENEVA[17-21] is highly conservative given the difference in treatment protocols for the two arms: the estimates of mean BCVA change are based on month 6 data, the point at which the OZURDEX treatment effect is diminished (due to the potential need for a second treatment in a proportion of patients) compared to a monthly schedule of anti-VEGF treatment. OZURDEX releases dexamethasone into the vitreous for up to, but not exceeding, six months.

Figure 3: *OZURDEX releases Dexamethasone into the vitreous for up to six months*

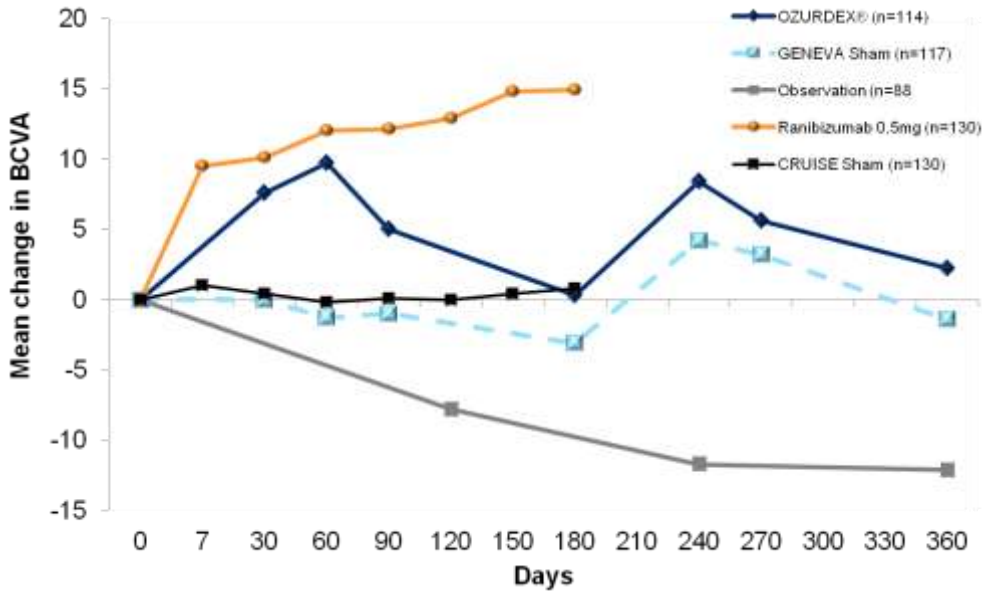


Welty DF *et al*. Abstract 6794. WOC 2008

Due to the monthly dosing schedule for anti-VEGFs compared to the six-monthly dosing schedule for OZURDEX, at month 6 this crude indirect comparison provides the most pessimistic comparison, biasing the analysis significantly against OZURDEX treatment. It is also limited on the basis of the publicly available data from CRUISE which doesn't permit an assessment of differences that could be expected when utilising patient level data rather than mean estimates. The direction of bias from having only a "mean change" approach is

unclear but does not account for potentially important differences within the distributions and confound interpretation beyond a measure of central tendency.

Figure 4: *Without head-to-head data, comparisons across studies are misleading*



1. Allergan Data on File 2. Brown DM, et a*l. Ophthalmology* 2010;117:1124–33

The estimate of relative benefit is further confounded by significant differences in baseline populations particularly pertaining to the duration of ME and baseline BCVA as can be seen in Table 9 provided below.

Table 9: *Baseline characteristics of patients in the GENEVA and CRUISE trials.*

	GENEVA-CRVO[17-2016171819]		**CRUISE**[20]	
	Dexamethasone 0.7mg	**Sham**	**Ranibizumab 0.5mg**	**Sham**
N	136	147	130	130
Age (years)	65.2	62.7	67.6	65.4
Duration of ME				
<90 days (%)	15.4	14.3	72.3	70.0
>90 - <180 days (%)	57.4	54.4	13.1	20.8
>180 days	27.1	31.3	14.6	9.3
Mean (months)	4.8	4.9	3.3	2.9
Mean BCVA	54.3	54.8	48.1	49.2
CRT (nm)	648	620	689	687
Phakic status (%)	85	88	83	88

Key factors affecting the interpretation of the efficacy results from the GENEVA and CRUISE trials include the baseline mean BCVA and duration of ME. Patients with a lower BCVA at baseline have a greater chance of improvement with treatment. The mean BCVA of the CRUISE patient population at baseline was 6.2 letters lower than the GENEVA population, which is more than one line on the ETDRS.

Additionally, the duration of ME prior to treatment is shown to affect a patient's responsiveness to treatment. Patients with a longer duration of ME are less likely to respond to treatment. The effect of delayed treatment has been observed across major randomised controlled studies of the treatment of retinal vein occlusion including Geneva and CRUISE (see Appendix G). At baseline, there were significant differences in the duration of ME in the GENEVA and CRUISE populations, with 15% versus 70% of the study populations having a mean duration of ME < 90 days. Therefore, it is unlikely that the GENEVA patient population would demonstrate similar gains in BCVA compared to the CRUISE population. Taking into consideration both of these factors, this unadjusted analysis should be considered a conservative estimate of the relative efficacy of OZURDEX versus anti-VEGF therapy at month six.

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

[redacted]

Sensitivity analyses have been performed examining the effect of removing adverse events, varying assumptions on the mix of day case and outpatient visits required for administration, the effect of varying the assumption of length of treatment benefit, retreatment rates, OZURDEX efficacy assessed at day 60 and additional time required for Bevacizumab administration. The results of these analyses are shown in Appendix E.

Conclusion

Crudely compared to an anti-VEGF based treatment strategy, treatment with OZURDEX for macular oedema following CRVO can be demonstrated to be cost saving but based on a conservative analysis has a lower gain in quality of life due to differences in mean BCVA observed at month 6.

An analysis of NMB demonstrates that treatment with OZURDEX is cost effective compared to treatment with Bevacizumab and is robust to sensitivity analyses. [redacted]

It is likely therefore that the base case cost effectiveness results presented significantly underestimate the cost effectiveness of treatment with OZURDEX relative to anti-VEGF treatments. With all limitations recognised, even under these highly conservative conditions, OZURDEX is demonstrated to be a cost-effective alternative to anti-VEGF treatments in the management of macular oedema following RVO.

Section 2: Changes to base-case assumptions within the OZURDEX cost effectiveness Model

NICE have requested that Allergan remodel the cost effectiveness of OZURDEX based on revised assumptions core to the structure of the cost utility model provided as part of the original submission. Each set of assumptions is first varied individually and then in composite to demonstrate the impact on the estimated cost effectiveness of OZURDEX relative to observation.

2.1 The costs of Dexamethasone treatment based on a day case, with outpatient appointment costs as a sensitivity analysis

The original model provided to NICE costed the administration of OZURDEX as a day case procedure and highlighted that this was likely to be a conservative approach, as treatment would be expected to transition into the outpatient area over time. The ERG subsequently requested that Allergan re-model these costs as outpatient costs; these analyses were provided to the Appraisal Committee in November 2010.

There was substantial discussion around this point at the Appraisal Committee, with clear perspective differences between commissioners and providers of care.

In exploring this point further with UK clinical experts Allergan remain convinced that treatment may begin in the day case setting as clinicians build familiarity with the technique required for administration but will ultimately transition increasingly to the outpatient area in some centres where adequate facilities exist (see Appendix A). We therefore believe that the most appropriate methodology to use is that utilised by NICE in their evaluation of wet AMD, which assumed a mix of outpatient and day case administration with a ratio of 3:1 (i.e. 75% of administrations were day cases).The results of this analysis are shown in Table 11 below.

Additional sensitivity analysis are provided in Appendix F, which show the 'book ends' of the assumptions where all administrations are provided either as day cases or outpatient visits.

Table 11: *Analysis assuming 75% of administrations are day case (assumption 2.1)*

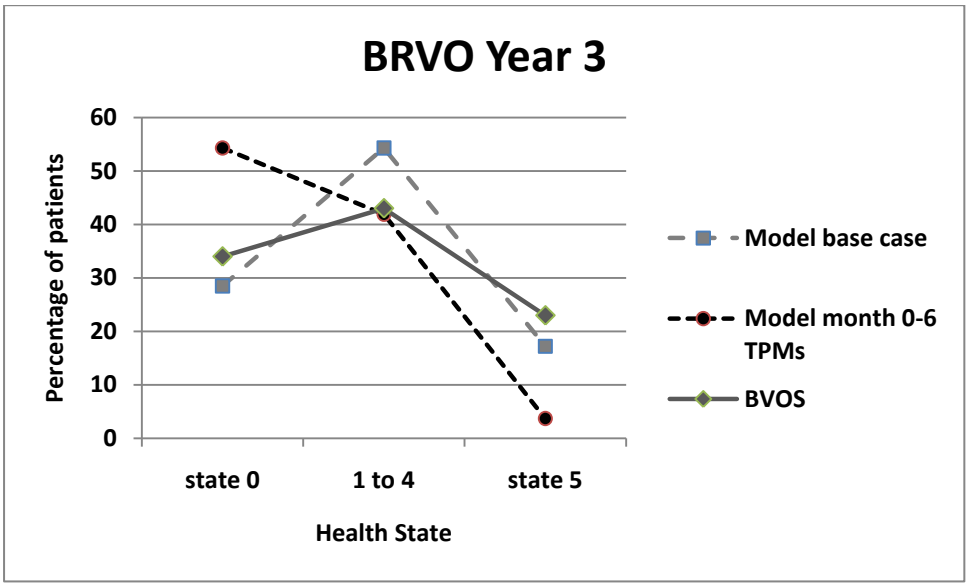
Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Original Base Case ICER
All RVO						
Observation	£7,873	11.04				
Dexamethasone	£10,669	11.25	£2,797	0.21	£13,278	£7,616
CRVO						
Observation	£9,868	10.89				
Dexamethasone	£13,190	11.18	£3,322	0.29	£11,601	£6,221
BRVO						
Observation	£6,822	11.11				
Dexamethasone	£9,342	11.28	£2,520	0.17	£14,759	£8,848
BRVO- Macular Haemorrhage						
Observation	£6,952	11.11				
Dexamethasone	£9,422	11.28	£2,471	0.18	£14,054	£8,313
BRVO- Prior Laser						
Observation	£10,077	10.83				
Dexamethasone	£10,797	11.12	£720	0.29	£2,465	Dominant

2.2 The extrapolation of data from the observation arm of the model based on all of the 0- to 6-month data from the randomised controlled trial

The use of 3-6mnth Transition Probability Matrices (TPMs) in the original model was based on a number of factors which it is important to reiterate and explore. Macular oedema following BRVO is recognised in the literature to spontaneously resolve in 26% of patients[21]. The likelihood of spontaneous resolution is highest during the early months following an occlusion, particularly in BRVO. Using 0-6m observation TPMs through the extrapolation phase of the model can be demonstrated to produce predicted results in BCVA change which are at odds with published estimates of disease resolution in untreated patients – predicting that 54% of patients spontaneously improve to BCVA 20/40 or better, rather than the 26% recognised in published literature

The ERG report recognised that the choice of TPMs for the extrapolation of the observation arm of the model is an important determinant of cost effectiveness; however the decision taken to utilise transitions observed between 3-6m was based on a sound interpretation of the available evidence and validated vs. external sources and published estimates of the trajectory of BCVA improvements in untreated cohorts

Figure 5: *Graph showing proportions of BRVO observation arm patients in each health state in year 3 for the base case of the model, the model using month 0-6 transition matrices and the BVOS study group.*



Based on this scientific analysis and external validation Allergan refute the assertion that 0-6m TPMs should be considered in the base case estimate of OZURDEX cost effectiveness. This would not be in accordance with published references regarding the natural history of untreated disease and is considered to unfairly bias the analysis against OZURDEX. The use of 3-6m TPMs has therefore been retained in the base case analysis. The rationale for this is presented below.

The predicted BCVA of untreated patients within the economic model utilising 3-6m Transition Probability Matrices in extrapolation is in full accordance with published data on natural history of BCVA decline in these populations

In support of this position, tables supplied below capture a comparison of where untreated CRVO and BRVO patients respectively are projected to be at time points up to 3 years (within the model) compared to benchmarks available from published literature. It can be seen from review of these tables that the projections within the model have face validity when compared to natural history cohorts reported in independent studies. Healthstates within the OZURDEX model have been collapsed to replicate reported categories in the available literature.

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

[redacted]

Table 12 clearly demonstrates that the modelled projections of BCVA decline in untreated patients with CRVO have face validity when compared to the published literature and support that the application of 3-6m transition probability matrices is an appropriate strategy to model the natural history of untreated disease. As the submitted economic model assumes stability in BCVA beyond year 3, the distributions shown above are highly relevant to interpretation of the results.

[redacted]

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

[redacted]

Table 13 clearly demonstrates that the modelled projections of BCVA decline in untreated patients with BRVO are actually slightly conservative when compared to the published

literature and support that the application of 3-6m transition probability matrices is an appropriate strategy to model the natural history of untreated disease. This is particularly important in BRVO where it is recognised that the majority of spontaneous resolutions happen early, close to the initial occlusion.

Utilising 0-6m Transition Probability Matrices to extrapolate the BCVA of untreated groups overstates the likelihood of spontaneous improvement in BRVO patients and does not reflect published literature on the natural history of untreated disease

The results of the analysis requested are presented below in Table 14 only as a sensitivity analysis. These results are clearly not clinically plausible as they show that the untreated observation patients achieve a higher quality of life than treated patients in the BRVO-MH and prior laser populations, driven by healthstate movements within the model that would infer that 54.3% of BRVO patients recover BCVA >20/40 by day 1080 which is at odds with literature estimates and considered clinically implausible.

Table 14: *Sensitivity analysis assuming use of day 0 – 180 TPM to extrapolate observation arm (assumption 2.2)*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Original Base Case ICER
All RVO						
Observation	£7,000	11.14				
Dexamethasone	£9,477	11.25	£2,477	0.11	£23,314	£7,616
CRVO						
Observation	£9,913	10.84				
Dexamethasone	£11,649	11.18	£1,736	0.34	£5,161	£6,221
BRVO						
Observation	£5,466	11.30			-£191,763	
Dexamethasone	£8,333	11.28	£2,867	-0.01	(Dominated)	£8,848
BRVO- Macular Haemorrhage						
Observation	£5,485	11.29			-£213,784	
Dexamethasone	£8,413	11.28	£2,928	-0.01	(Dominated)	£8,313
BRVO- Prior Laser						
Observation	£5,754	11.26			-£29,703	
Dexamethasone	£9,788	11.12	£4,034	-0.14	(Dominated)	Dominant

As described above, these results are not credible as they suggest, contrary to the published literature and clinical opinion, that the majority of untreated patients with BRVO will spontaneously improve. This is because the higher rate of spontaneous resolution in months 0-3 within the economic model is artificially applied to the entire extrapolation period of 3 years through the application of 0-6m TPMs. It can be observed above that the effect on the CRVO ICER is much less; this is because CRVO rarely spontaneously improves and in fact the

rate of BCVA decline over the early months following an occlusion is steeper than is observed in the longer term. The application of 3-6m TPMs within the observation basecase adjusts for each of these issues and has face validity when benchmarked against published natural history cohorts.

2.3 Request that in the modelling of the fellow eye involvement the costs of blindness are applied only to patients in whom both eyes fall into the worst health state (severe visual impairment).

The ERG raised an important concern regarding the handling of assumptions relating to the costs and mortality applied to patients assumed to have bilateral BCVA corresponding to the worst health state (HS05 <20/200) in the original model submitted. The original model applied specific costs and a mortality multiplier to those patients affected in their BSE at baseline (or at a later point due to fellow eye occurrence) who fell into HS05 either with observation or treatment. This approach was taken in accordance with the methods used to estimate cost effectiveness of other retinal therapies in e.g. wAMD whereby the BSE was determined to be the driver of overall BCVA and therefore relative health status.

The ERG highlighted however, that there may be a proportion of BSE patients (either index or fellow eye involved) who have a BCVA in their other eye (defined as WSE at baseline/entry to the model) that is above the threshold for HS05. This would mean that some patients would not technically meet the criteria of bilateral visual impairment sufficient to justify the application of costs and mortality multipliers associated with severe visual impairment (<20/200, HS05).

It is important to note that the original approach adopted within the model has some important limitations which may render original estimates less optimistic than is implied by the ERG requested analyses:

- The model only accounts for lifetime evolution of BCVA in either eye due to RVO alone (index or subsequent events)**.** It therefore fails to capture the changing dynamics of bilateral vision due to other diseases associated with an ageing population (such as cataract, AMD, Glaucoma, retinopathy) or trauma
- This emphasises still further the importance of valuing sight retention in a single eye – as the relative risk of experiencing a second eye event, not limited to RVO, over lifetime lead to an unacceptable risk of blindness (principle of all eyes being equal)
- The original model only applied Costs of Vision Loss (COVL) to the worst health state (<20/200), whilst in reality it is recognised that increased costs of care and social support may be incurred in more moderate states of visual impairment

- The application of COVL within the model excluded potential one-off costs such as blind registration due to the memory-less structure of a Markovian model, thereby potentially failing to capture some PSSRU costs relevant to the population described
- Adjustments made to the COVL applied at the request of the ERG are likely to underestimate the costs of residential care for patients with severe visual impairment; the rate of self-pay included within the analysis is based on general census data for patients in residential care facilities and is not adjusted to reflect the cause of admission to a specialist facility. There are no UK data available to accurately quantify the proportion of patients with severe visual impairment who self-fund their own residential care but it is likely to be less than the general population
- Therefore the COVL applied within the original model are likely to underestimate the actual costs of severe bilateral visual impairment
- The original model only applied mortality multipliers to the worst health state, whilst Christ et al recognise that moderate visual acuity defined health states can also be associated with increased mortality and reduced life expectancy

Changes were made to the economic model to permit exploration of the balance of binocular vision and the application of costs of vision loss

In order to explore this point in greater depth the main economic model has been amended to allow the model to simulate the impact of assuming that only a proportion of patients that enter HS05 are considered to be bilaterally severely visually impaired (<20/200) and thus incur the costs of vision loss. As patients age over time, this proportion is expected to increase due to age related deterioration and the development of other sight-reducing conditions. An annual adjustment factor has been applied to capture this changing dynamic over time.

The annual cost of vision loss in HS05 was amended in the model so that different costs could be applied annually. This enabled different assumptions to be made each year as to the proportion of patients in HS05 that were bilaterally severely visually impaired

Based on clinical opinion it was assumed that in the first year of treatment 25% of patients affected in their BSE at baseline had a WSE BCVA below <20/200 (i.e. had severe visual impairment in both eyes)

The costs of vision loss applied to BSE patients falling into HS05 was reduced by this percentage to adjust for the proportion of patients with residual sight in their fellow eye

sufficient to keep them above the threshold of bilateral “legal blindness” and to avoid the inappropriate application of COVL or mortality multipliers

This was then varied through the course of the model to increase the proportionate COVL applied at a rate of 10% per year representing the changing proportion of patients assumed to be “bilaterally” in HS05 as they become affected by sight-reducing conditions in their fellow eye

This approach generated ICERs ranging from £2,905 for BRVO-prior laser to £12,001 for BRVO-MH and are shown in Table 15 below

To explore this further, a scenario whereby the annual rate of fellow eye decline is adjusted to 5% is captured in Table 16 to demonstrate the relative sensitivity of the model to this assumption.

Table 15*: Analysis assuming 25% of BSE patients (either index or fellow eye involved) have a BCVA in their other eye (defined as WSE at baseline) that is below the threshold for HS05, with a 10% annual increase in this figure (Assumption 2.3)*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Original Base case ICER
All RVO						
Observation	£6,207	11.04				
Dexamethasone	£8,712	11.25	£2,505	0.21	£11,896	£7,616
CRVO						
Observation	£7,600	10.89				
Dexamethasone	£10,791	11.18	£3,191	0.29	£11,142	£6,221
BRVO						
Observation	£5,473	11.11				
Dexamethasone	£7,618	11.28	£2,144	0.17	£12,561	£8,848
BRVO- Macular Haemorrhage						
Observation	£5,558	11.11				
Dexamethasone	£7,668	11.28	£2,110	0.18	£12,001	£8,313
BRVO- Prior Laser						
Observation	£7,684	10.83				
Dexamethasone	£8,533	11.12	£848	0.29	£2,905	Dominant

Table 16: <u>Scenario Analysis</u> *assuming 25% of BSE patients (either index or fellow eye involved) have a BCVA in their other eye (defined as WSE at baseline) that is below the threshold for HS05, with a 5% annual increase in this figure.*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Original Base case ICER
All RVO						
Observation	£5,278	11.04				
Dexamethasone	£8,355	11.25	£3,078	0.21	£14,613	£7,616
CRVO						
Observation	£6,382	10.89				
Dexamethasone	£10,372	11.18	£3,990	0.29	£13,932	£6,221
BRVO						
Observation	£4,696	11.11				
Dexamethasone	£7,294	11.28	£2,598	0.17	£15,216	£8,848
BRVO- Macular Haemorrhage						
Observation	£4,758	11.11				
Dexamethasone	£7,330	11.28	£2,573	0.18	£14,634	£8,313
BRVO- Prior Laser						
Observation	£6,293	10.83				
Dexamethasone	£7,964	11.12	£1,672	0.29	£5,724	Dominant

The risk of a patient developing a subsequent sight-threatening condition increases with age. Therefore, patient who experience ME following BRVO or CRVO are at risk for developing other conditions that may affect their visual outcomes such as wet age-related macular degeneration (AMD), dry AMD, diabetic retinopathy (DR), diabetic macular oedema (DME), and cataracts. The incidence and prevalence of AMD was shown to increase exponentially with age. The 10-year incidence of AMD in the population over the age of 40 is estimated to be 2.1% (.21% annual incidence)[22]. The overall prevalence for all persons ranged from 0.85% for those aged 60–80 years to 8% for those aged over 65 years[22]. It is reasonable to assume that patients with RVO would also be at risk for developing AMD similar to the general aging population.

Similarly, in DR and DME, the risk of developing these complications increases with the duration of diabetes. Approximately 14% (336,000) of people with diabetes have DME and prevalence increases to 29% (696,000) for people with diabetes who use insulin for more than 20 years[23]. The incidence of DR increases up to 85% in type II diabetes with a duration of disease of 15 years[24]. As diabetes is a risk factor for the development of RVO, the risk of developing DR or DME increases within the population. The Eye Disease Case-Control Study

found a greater risk of any type of CRVO in patients with diabetes mellitus[25] and according to the Beaver Dam Eye Study, diabetes was associated with increased incidence of CRVO (OR, 6.35; 95% CI, 1.90–21.27). Approximately 14%–34% of patients with CRVO also have diabetes mellitus[26], which is a greater prevalence when compared with the national survey controls[27].

RVO patients are at significant risk for developing other sight-threatening conditions. The current model underestimates the total risk of severe, bilateral vision loss by not taking account of the risk of developing other conditions related to aging or other risk factors associated with RVO. Furthermore, the above discussion does not include all risks to vision.

When predicting the proportion of patients who would have severe bilateral vision in HS5 at baseline and the subsequent risk of additional patients falling into HS5 bilaterally over time it is important to try to account for risk of sight loss associated with other conditions. Based on, the epidemiological evidence discussed above, we believe that the assumption that 25% of patients have severe bilateral vision impairment sufficient to fall into HS5 at baseline with a 10% annual risk of patients bilateral vision progressing to this level in an already suppressed second eye (defined as WSE at baseline) is a reasonable estimate to account for the risk of vision loss in this patient population.

In conclusion it should be recognised that the application of the costs of vision loss remain conservative as a contributing factor to the overall cost effectiveness of OZURDEX in ME following RVO because:

- The costs applied are considered to underestimate the true costs incurred by NHS and social services in providing support to individuals living with severe visual impairment
- There are limited data available to predict the dynamic nature of bilateral vision as individuals age but it is recognised that the ageing process is associated with increased incidence of other sight reducing conditions
- The importance of treating the first eye affected is recognised by the NICE Appraisal Committee in conjunction with the points raised above

Revised basecase

The assumptions included in the revised basecase are summarised in Table 17 and reflect the changes requested by NICE. The results of this analysis are presented in Table 18. Allergan however, believe that these results should still be regarded as potentially conservative for the reasons stated within each section.

Table 17: *Assumptions made in the revised base case which differ from assumptions in the original submission.*

Structural component	Revised base-case assumption	Rationale
Treatment administration procedure	75% of intravitreal injections will be administered as a day case procedure; 25% of intravitreal injections will be administered as an outpatient procedure.	This approach was utilised by NICE in their evaluation of wet AMD. It is believed that treatment may begin in a day case setting whilst clinicians gain familiarity with the administration technique, but will increasingly transition to outpatient procedures in centres where adequate facilities exist. Therefore it is plausible to assume a mixture of both day case and outpatient visits as it is recognised that even in the long run not all centres will have the facilities to accommodate outpatient procedures of this kind.
Severe visual impairment	25% of patients in HS05 who are affected in the BSE at baseline have their WSE BCVA below 20/200 (i.e. have severe visual impairment in both eyes); 10% annual increase in this number, up to a maximum of 100% of patients affected in their BSE	It is agreed that only a proportion of patients in the worst health state (HS05) will be considered bilaterally severely visually impaired, and thus incur the cost of vision loss. This proportion is assumed to increase over time, due to age related deterioration and other sight reducing conditions.

Table 18: *NICE revised base case results (incorporating assumptions 2.1 and 2.3)*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Original Base Case ICER
All RVO						
Observation	£6,207	11.04				
Dexamethasone	£9,905	11.25	£3,698	0.21	£17,558	£7,616
CRVO						
Observation	£7,600	10.89				
Dexamethasone	£12,332	11.18	£4,732	0.29	£16,522	£6,221
BRVO						
Observation	£5,473	11.11				
Dexamethasone	£8,627	11.28	£3,153	0.17	£18,472	£8,848
BRVO- Macular Haemmorhage						
Observation	£5,558	11.11				
Dexamethasone	£8,677	11.28	£3,119	0.18	£17,741	£8,313
BRVO- Prior Laser						
Observation	£7,684	10.83				
Dexamethasone	£9,542	11.12	£1,857	0.29	£6,361	Dominant

Section 3: Scenario analyses examining re-treatment rates

NICE have requested that Allergan provide additional analysis regarding the retreatment rates that reflect clinical practice in the UK. These are shown in Table 19 and Table 20 below and include assumption 2.1 and 2.3 from the revised base case. The analyses should be treated with caution as they are intended to reflect UK treatment patterns and yet there is little UK experience from which it is possible to draw assumptions regarding UK practice. The ScHARR survey of UK clinicians suggested that currently time to discharge in UK practice is 2 years (ranges: 1-3 years BRVO, 1-5 years CRVO).

NICE have requested an analysis in which '*proportions re-treated are as at day 180 for the five injections after the first injection in people with CRVO'* and *'an analysis in which proportions re-treated are as at day 180 for the four injections after the first injection in people with BRVO'.* The results of these analyses are shown in Table 19**Error! Reference source not found.**.

All analyses in Section 3 are run using the revised basecase specified in Table 18.

Table 19: *Sensitivity analysis investigating the effect on cost effectiveness of treatment with Dexamethasone of varying the retreatment assumptions based on those retreated at day 180 (incorporating assumptions 2.1 and 2.3)*[ab]

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Revised Base Case ICER
All RVO						
Observation	£6,500	11.037				
Dexamethasone	£14,541	11.2685	£8,041	0.23	£34,682	£17,558
CRVO						
Observation	£7,648	10.895				
Dexamethasone	£15,194	11.2367	£7,546	0.34	£22,083	£16,522
BRVO						
Observation	£5,895	11.1113				
Dexamethasone	£14,197	11.2853	£8,301	0.17	£47,708	£18,472
BRVO- Macular Haemorrhage						
Observation	£5,980	11.11				
Dexamethasone	£14,278	11.29	£8,298	0.18	£45,878	£17,741
BRVO- Prior Laser						
Observation	£8,106	10.83				
Dexamethasone	£14,394	11.21	£6,288	0.38	£16,548	£6,361

[a] *For CRVO patients the proportion re-treated are as at day 180 for the five injections after the first injection*

b For BRVO patients the proportion re-treated are as at day 180 for the four injections after the first injection

NICE have also requested an analysis '*in which proportions re-treated are varied between the two extremes of the base case and the randomised controlled trial'.* The base case results, incorporating assumptions 2.1 and 2.3 are shown in Table 18 and repeated below in **Error! Reference source not found.**. Further sensitivity analyses which set the proportion of patients retreated to be at the midpoint between the basecase and as at day 180 and the interquartile ranges for BRVO and CRVO patients are shown in Figure 6 and Figure 7.

Table 20: *Sensitivity analysis in which the proportions of patient retreated are based on the observed retreatment rates from the GENEVA trial and extrapolated based on expert opinion (retreatment assumptions match the original basecase)*

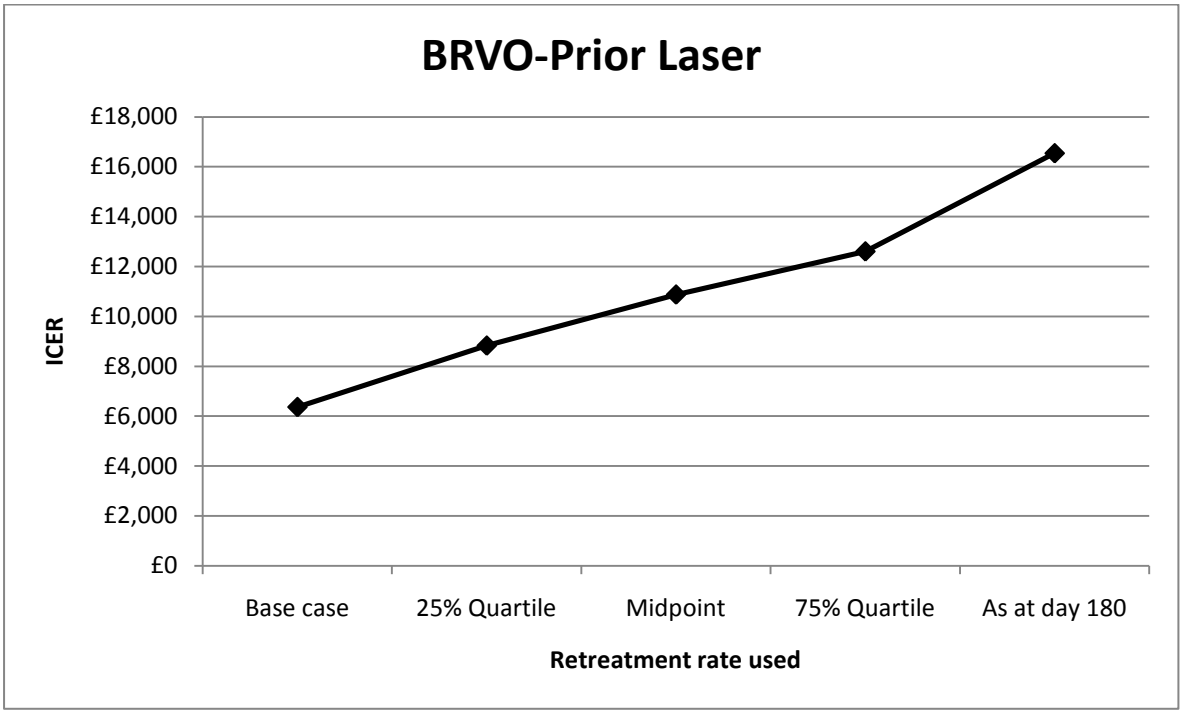
Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
All RVO					
Observation	£6,207	11.04			
Dexamethasone	£9,905	11.25	£3,698	0.21	£17,558
CRVO					
Observation	£7,600	10.89			
Dexamethasone	£12,332	11.18	£4,732	0.29	£16,522
BRVO					
Observation	£5,473	11.11			
Dexamethasone	£8,627	11.28	£3,153	0.17	£18,472
BRVO- Macular Haemorrhage					
Observation	£5,558	11.11			
Dexamethasone	£8,677	11.28	£3,119	0.18	£17,741
BRVO- Prior Laser					
Observation	£7,684	10.83			
Dexamethasone	£9,542	11.12	£1,857	0.29	£6,361

As requested by NICE, Table 21 provides an analysis where the midpoint ranges between expert option (shown in Error! Reference source not found.) and an analysis whereby *proportions re-treated are as at day 180 for the five injections after the first injection in people with CRVO'* and *'an analysis in which proportions re-treated are as at day 180 for the four injections after the first injection in people with BRVO'.*

Table 21: *Sensitivity Analysis in which the proportions of patient retreated are based on the midpoints between observed retreatment rates from the GENEVA trial and the retreatment assumptions at day 180 shown in Table 19.*

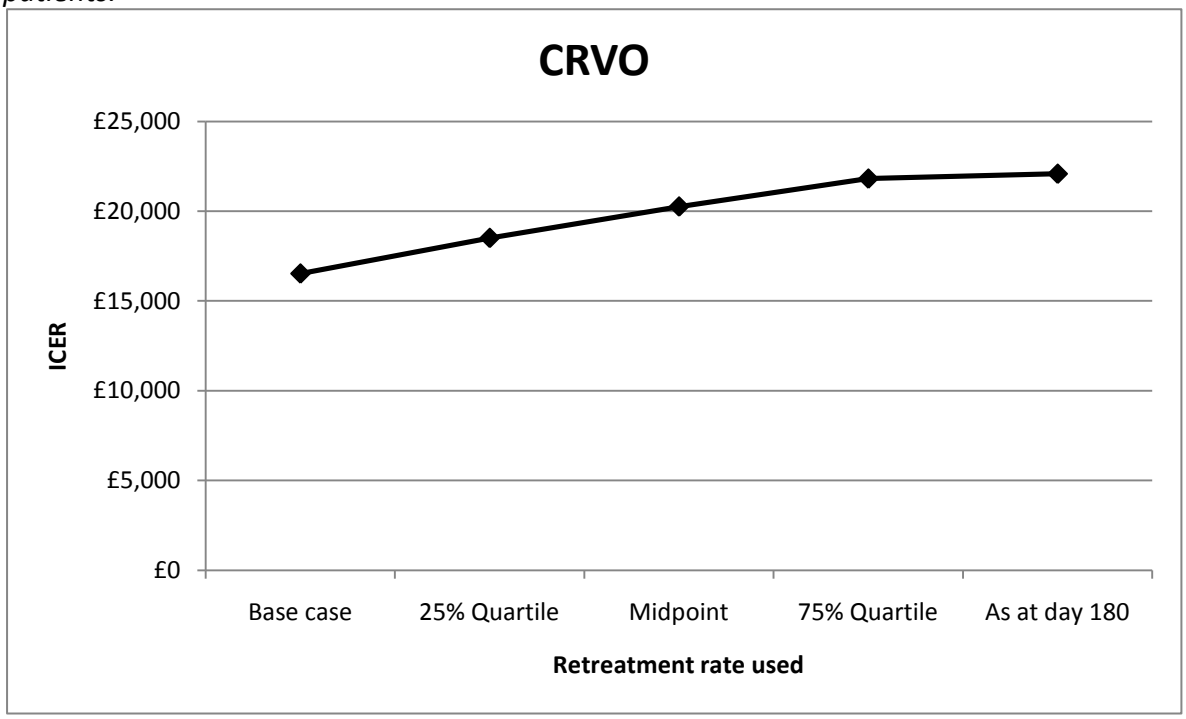
Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Revised Base Case ICER
All RVO						
Observation	£6,207	11.04				£17,558
Dexamethasone	£12,144	11.26	£5,937	0.23	£26,332	
CRVO						
Observation	£7,600	10.89				
Dexamethasone	£14,181	11.22	£6,581	0.32	£20,257	£16,522
BRVO						
Observation	£5,473	11.11				
Dexamethasone	£11,072	11.28	£5,599	0.17	£32,332	£18,472
BRVO- Macular Haemorrhage						
Observation	£5,558	11.11				
Dexamethasone	£11,143	11.28	£5,585	0.18	£31,123	£17,741
BRVO- Prior Laser						
Observation	£7,684	10.83				
Dexamethasone	£11,504	11.18	£3,819	0.35	£10,876	£6,361

Figure 6: *Sensitivity analysis examining the effect of varying the retreatment rate for BRVO patients who have received prior laser.*[a]



[a]*Re-treatment rates are varied between the rates from the GENEVA trial (used in the basecase) and the retreatment assumptions at day 180 (shown in* **Error! Reference source not found.***)*

Figure 7: *Sensitivity analysis examining the effect of varying the retreatment rate for CRVO patients.*[b]



[b] *Re-treatment rates are varied between the rates from the GENEVA trial (used in the basecase) and the retreatment assumptions at day 180 (shown in* **Error! Reference source not found.***)*

NICE have emphasised the importance of treating "first eye" and "second eye" patients due to the ongoing risk to a patient's second eye (section 4.17 ACD)

In the ACD it is recognised that patients should be offered treatment whether presenting with an occlusion in their first or second eye. The submitted economic analysis allows for a detailed consideration of whether an individual is affected in their better or worse seeing eye and allows for clearer interpretation of the resulting impact on HRQoL and ultimately cost effectiveness. However the valuation of HRQoL change based on the balance of BSE/WSE patients is potentially at odds with the Appraisal Committee's position regarding the treatment of all eligible patients.

To explore the impact of this, Table 22 repeats the requested scenario analysis whereby all patients continue to be retreated at the rates observed at day 180 in the GENEVA studies, representing the most intensive treatment scenario, but values resulting change in HRQoL as if all patients were affected in their better seeing eye. The changes made to the basecase in section 2 still apply, therefore the costs of vision loss and mortality multipliers are only applied to the proportion of BSE patients who are projected to be in a bilateral state of severe visual impairment. This analysis is repeated in Table 23 for the revised basecase (shown in Table 18).

As can be clearly seen in Tables 22 and 23 the decision to “value” HRQoL using utility estimates informed by best/worse seeing eye (effectively first or second eye) has a significant effect on the resulting ICERs. This is potentially important given the stated intention of NICE to ensure that patients receive treatment whether affected in their first or second eye due to the ongoing risk to vision in the second eye.

Table 22: *Analysis including constant retreatment assumptions (as at day 180)* **Error! Reference source not found.***, but using BSE utilities to value HRQoL gains (based on revised basecase, incorporating assumptions 2.1 and 2.3).*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER valued using BSE	ICER valued using BSE 10% and WSE 90% Error! Reference source not found.
All RVO						
Observation	£6,500	9.45				
Dexamethasone	£14,541	9.89	£8,041	0.44	£18,335	£34,682
CRVO						
Observation	£7,648	9.10				
Dexamethasone	£15,194	9.80	£7,546	0.71	£10,682	£22,083
BRVO						
Observation	£5,895	9.64				
Dexamethasone	£14,197	9.93	£8,301	0.30	£27,902	£47,708
BRVO- Macular Haemorrhage						
Observation	£5,980	9.62				
Dexamethasone	£14,278	9.94	£8,298	0.31	£26,474	£45,878
BRVO- Prior Laser						
Observation	£8,106	9.05				
Dexamethasone	£14,394	9.76	£6,288	0.72	£8,787	£16,548

Table 23: *Revised basecase* Error! Reference source not found. *(incorporating assumptions 2.1 and 2.3), but using BSE utilities to value HRQoL gains.*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER valued using BSE	ICER valued using BSE 10% and WSE 90% Error! Reference source not found.
All RVO						
Observation	£6,207	9.45				
Dexamethasone	£9,905	9.85	£3,698	0.40	£9,172	£17,558
CRVO						
Observation	£7,600	9.10				
Dexamethasone	£12,332	9.68	£4,732	0.58	£8,160	£16,552
BRVO						
Observation	£5,473	9.64				
Dexamethasone	£8,627	9.95	£3,153	0.31	£10,168	£18,472
BRVO- Macular Haemmorhage						
Observation	£5,558	9.62				
Dexamethasone	£8,677	9.95	£3,119	0.32	£9,718	£17,741
BRVO- Prior Laser						
Observation	£7,684	9.05				
Dexamethasone	£9,542	9.60	£1,857	0.55	£3,347	£6,361

Section 4: BRVO with Macular Haemorrhage

The Committee requires further clarification of the location and extent of macular haemorrhage for the subgroup of patients for whom laser treatment was not considered appropriate because of macular haemorrhage.

In the phase 3 OZURDEX™ 206207-008 and 206207-009 trials, Macular haemorrhage was assessed by use of standardized fundus photographs that were evaluated by trained and masked graders at the University of Wisconsin Fundus Photo Reading Centre using a standardized grading protocol. The grading procedure is based on the Early Treatment for Diabetic Retinopathy Study (ETDRS) Macular Edema Grading Protocol.

All assessment of the location and extent of retinal haemorrhage were based on standardized stereoscopic fundus photography, completed as an array of seven or three standard photographic fields as part of the GENEVA study protocol. Slide transparencies were mounted in a plastic sheet in approximate anatomic position and examined on a light box with aid of a magnifying viewer. A set of printed grids (i.e., opaque figures printed on transparent film) were used to determine the proximity of an abnormality such as retina haemorrhage to the centre of the macula.

Retinal haemorrhage was defined as patches of blood within the retina. The presence of haemorrhages in the macula, was assessed by a question that asks for presence of retinal haemorrhage in the grid (macular area), using following scale:

- Absent
- Questionable
- Definite
- Cannot grade

An answer of “definite” was defined in the procedure manual to mean that the grader was at least 90% certain that the abnormality (in this case retina haemorrhage) was preset in the grid (i.e. macular area). It included both superficial and deep haemorrhages. In the

OZURDEX™ 0.7mg BRVO subgroup, macular haemorrhage was graded as “definite” for 88.5% (255/288) of the OZURDEX™ 0.7mg treatment group and 94.9% (262/276) of the observation group at the qualification or baseline visit.

Patients with significant haemorrhage (in any retinal layer) were excluded from the BVOS study which first demonstrated that grid laser was beneficial, and thus this practice has continued since then. The rationale is two-fold: (1) if there is too much haemorrhage, it is not possible to assess if there is dramatic non-perfusion (a type of patient who did not benefit from laser) or exactly where the leakage is coming from (treatment protocol dictates treating the leaking areas) ; (2) haemorrhage takes up laser energy, so if there is a lot of haemorrhage in the way, there will be more energy take up in the inner retina and inner retinal damage as well as less energy getting to the RPE which is the desired target. Thus, physicians generally do not treat patients with laser until there is sufficient clearance of haemorrhage (typically present in multiple retinal layers), either spontaneuously or facilitated by pharmacotherapies.

OZURDEX potentially allows patients with macular haemorrhage to be treated at the time of presentation rather than waiting for this haemorrhage to disperse and clear. The importance of prompt treatment was explored in post-hoc analyses of the GENEVA trial population. In BRVO and CRVO, the longer the duration of ME, the less likely it is to resolve spontaneously. There are no clear indicators at baseline to suggest which patients are more likely to experience spontaneous improvements; therefore it is important to treat ME early. In patients with chronic ME (> 8 months duration)[28], permanent retinal damage and vision loss may occur[29].

Haemorrhages into the vitreous from neovascularisations are more likely to affect eyes with chronic ME and often result in poor final VA and a less favourable prognosis[30]. As such, the longer the duration of ME, the more challenging the treatment[31]. In order to achieve optimal improvements in VA or to prevent further vision loss, it is important to treat ME promptly.

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For the subgroup of BRVO patients with macular haemorrhage which prevents prompt laser photocoagulation, OZURDEX represents the first approved treatment option and addresses an unmet medical need.

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