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Appendix A: Report on the UK Survey of Ophthalmologists

Survey of the practice and management of retinal vein occlusion (RVO) in treatment of macular oedema in the NHS in England

Report to Allergan Ltd

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Acknowledgements

We wish to thank the Consultant Opthalmologists who, at short notice, contributed their time to respond to this survey, and also BresMed Health Solutions for providing drafts of questions which formed the basis of the questionnaire.

Background

The National Institute for Health and Clinical Excellence (NICE) is conducting a Single Technology Assessment of OZURDEX (dexamethasone intravitreal impact) in the treatment of macular oedema following retinal vein occlusion (RVO). Pending consultations, the preliminary decision of the NICE Appraisals Committee (AC), is minded not to recommend dexamethasone for the treatment of macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).
http://www.nice.org.uk/guidance/index.jsp?action=article&o=52886
The AC requested the manufacturer, Allergan to provide further information to be available for consideration at the next AC meeting in March. The information requested included a comparison with bevacizumab which, although requested in the scope, had not been included in the manufacturers' submission. In view of the questions raised, Allergan wished to gather information on the current management of macular oedema following RVO and access to different therapies in NHS clinics in the UK. As part of this process, the University of Sheffield was commissioned to design and conduct a survey of current specialist practice in the NHS.

Aims and objectives

The aims and objectives of the survey were to provide a snapshot of current practice in the management of RVO in NHS clinics in different areas of the UK. The information sought was to be based on the best estimates of clinical experts in the field rather than documented records.

Methods

Given the short timeframe, the University felt that the most efficient method to collect the data would be a questionnaire that could be sent electronically direct to specialists to complete and return by email, backed up if necessary by an email or telephone reminder. The advantages of using electronic methods over telephone, paper-based and face-to-face approaches to gather information are that they:

- allow the views of a group of experts to be collected systematically, quickly, and relatively economically. They facilitate the possibility of getting access with the appropriate person more or less instantly. They reduce the costs of printing, paper, mail, telephone, and human costs. Delivery or non-delivery is more secure and is known by the sender almost immediately.
- enable each specialist to consider his or her responses in their own time and space.
- reduce the potential bias in face-to-face meetings where powerful individuals may sway the discussions in one direction or another.
- enable specialists in different geographic areas to be consulted with a minimum of disruption to their daily routines and clinical responsibilities.

A series of questions provided by BresMed Health Solutions was formatted into a questionnaire and submitted to Allergan for approval. A list of 40 Consultant Opthalmologists in England was drawn up by a stratified process which identified:

1) the main ophthalmology NHS Trust providers in England;

2) in each Trust, experts whose clinical profiles indicated a special interest in macular oedema following RVO, and

3) supplementary searches to obtain current email addresses and other contact details.

Following minor modifications, the questionnaire was approved by Allergan, (Appendix 1) and on the same day it was mailed to each potential participant individually. The covering email explained the background to the approach and requested the specialists to complete and return the questionnaire within the next four days. The names of the potential participants were substituted by code numbers. Neither the manufacturers nor their technology was referred to by name in any of the documentation. Subsequently, an email reminder was sent to those experts who had not responded extending the deadline by a further two days.

Results

Four emails and questionnaires were returned as undeliverable due to incorrect addresses. We received eleven responses. Two specialists declined to take part due to time pressures. Another indicated that he did not specialise in the management of macular oedema following RVO routinely. Eight experts completed and returned the questionnaire. The responders were based in NHS Trusts in the Wirral, Liverpool, Birmingham, Oxford, Lincolnshire, Leicester, Derby, and Sheffield. A summary of the responses received to each question is shown in table 1.

Ques 1 Opinion on the frequency of spontaneous resolution in branch retinal vein occlusion (BRVO) covered the spectrum from 'uncommon' (expressed by two experts) to 'fairly common'.

Ques 2 There was closer agreement in respect of the average time for BRVO (range of responses 1-3 years) than for CRVO patients (range of responses 1-5 years) to achieve stability or be discharged following treatment. Two years was the most frequent estimate for both BRVO and CRVO.

Ques 3 The recurring characteristics in BRVO patients who the specialists considered are not suitable for laser treatment were extensive haemorrhages and foveal ischaemia. There was an apparent divergence between the specialists in the views expressed about the range of vision. Two considered that a characteristic affecting the suitability of BRVO patients for laser treatment was poor vision <6/96, and 6/60 or less, and another considered vision >6/9 was a factor.

Ques 4 and 5 In respect of bevacizumab, the most frequent response was 'rarely' (n=5). How access is funded was mostly through individual finance requests (n=4). Three reported that funding was through the hospital budget. One responder had no access to bevacizumab.

Ques 6 Six of the eight responders reported that in their clinics bevacizumab was procured in the form of pre-filled syringes.

Ques 7 The responses to the question about how RVO procedures are managed usually divided equally between out-patient (n=4) and day cases (n=4).

Ques 8 The responses to the question asking whether there will be locally commissioned arrangements for RVO treatment were divided almost equally ('No' 4, 'Yes' 3, Possibly 1).

Ques 9 There was some variation in the estimates of the apportionment of costing for managing RVO procedures as day-cases or outpatients between the experts, although a consensus (7 experts to 1) seemed to be towards 50%-100% outpatients. The comments of one specialist who felt

that a 50-50% split was reasonable, suggested that management of BRO as a day case under PbR was due to viability for the Trust and this may change following local negotiations that are ongoing. (Table 1)

Table 1 Summary of responses

Question	**Response**	**Mode**
Ques 1 Estimated frequency of spontaneous resolution in BRVO (VA returning to pre-VO state)	• Unusual for vision to return to the premorbid state - <10% • 'Uncommon' x 2 • 25% of patients spontaneously resolve • 30% of patients spontaneously resolve • 33%, of patients spontaneously resolve • 60% of patients spontaneously resolve • Fairly common if small initially	'Uncommon'
Ques 2 After treatment, average time to discharge/stability for BRVO	• 1-3 years; • Varies with size of BRVO	2 years
After treatment, average time to discharge/stability for CRVO	• 1-5 years	2 years
Ques 3 Characteristics of BRVO patients not considered suitable for laser treatment	• Lots of haemorrhages; • Extensive macular ischaemia, vision 6/60 or less • Poor vision <6/96, • Ischaemia on flourescien angiography; • Foveal ischaemia x 2 • Subfoveal fibrosis • Spontaneous improvement • Vision better than 6/9, foveal ischaemia or FAZ damage, multiple haemorrhages, <3 months duration, resolving oedema; improving vision; central oedema only; • Good va. extensive haemorrhage, not responded to previous laser, gross CMO	
Ques 4 Use of bevacizumab for RVO	• Rarely x 5 • Occasionally x 1	Rarely

in NHS clinic	• Regularly x 2	
Ques 5 Access to bevacizumab in NHS practice	• Hospital budget x 3 • Individual finance request x 4 • No access to bevacizumab x 1	Individual finance request
Ques 6 Procurement form of bevacizumab	• Pre-filled syringes x 6 • Local compounding of larger vials x 1	Pre-filled syringes
Ques 7 Usual treatment for RVO – day-case vs outpatient	• Day-case x 4 • Outpatient x 4	
Ques 8 Locally commissioned arrangements for RVO	• Yes x 3; • Possibly x 1 • No x 4	

Ques 9

Views of costing apportionment for RVO between day-case and outpatient	% Day-case	% Outpatient	Frequency
	75	25	1
	50	50	3
	25	75	1
	0	100	3

Discussion

This survey has been carried out to support the NICE Single Technology Assessment process of dexamethasone that is currently underway. We gathered information about access to different therapies and the current management of macular oedema following RVO relying on the best estimates of specialists working in NHS clinics in different Trusts in England rather than from documented sources. Eight specialists in eight NHS Trusts in different parts of England completed and returned the

questionnaire within the time available. The responses to each question were formatted simply into a table to enable patterns of convergence and divergence in specialist views, and similarities and differences in the management of RVO in NHS clinics in England, to be observed.

The results indicate some variation between different NHS clinics in England in the use of and access to different therapies for treating macular oedema following RVO. One specialist reported having no access to bevacizumab, most reported using bevacizumab 'rarely', and two reported using it 'regularly'. Access to bevacizumab (procured mostly in pre-filled syringes) is mostly by individual funding requests. However in some Trusts bevacizumab is provided through the hospital budget. There are differences in the current management of RVO treatment which, on the basis of this study, indicate a split between outpatients and day-cases. A suggestion in one of the 'additional comments' made by one of the responders is that management of intravitreal injections as day cases is due to viability for the Trust under PbR arrangements rather than clinically indicated. There appears to be an emerging consensus in the specialist views available that a reasonable apportionment of costs for RVO treatment between outpatients and day-cases is in the direction of 50%-100% outpatients.

Strengths and weaknesses of methods

To our best knowledge, thirty-five ophthalmologist specialists in macular oedema following RVO received our invitation to take part in the survey and, in a limited time-frame, eight completed and returned the questionnaire. Eight may be considered a fairly small number. Nevertheless, within the context of this survey of clinical specialists, approached 'cold', given a six day timeframe in which to respond (including a weekend) and without payment, it is a good response. The original list of potential participants included Trusts in London, the South

East, the South West, Cambridgeshire and the North East. It is perhaps disappointing therefore that no specialists in these areas responded. However, effective and reliable utilization of a small sample from a limited number of experts with similar training and subject understanding in a particular field of study, has been reported previously.[1] This evidence suggests that the aggregated results of our survey based on the responses of eight specialists working in what, nationally, is a highly specialised field of medicine with a limited number of experts, will be reasonably stable.

Conclusion

We are confident that the results of this survey provide a reliable snapshot of current views of specialists in the current management of macular oedema following RVO, and access to different therapies available in the NHS in in England.

References

1 Akins R B, Tolson H, Cole B R Stability of response characteristics of a Delphi panel: application of bootstrap data expansion. BMC Medical Research Methodology 2005;5:37 doi:10.1186/1471-2288-5-37

The University Of Sheffield.

Single technology assessment for a new treatment of macular oedema caused by retinal vein occlusion (RVO) : Consultation with clinical experts in ophthalmology

1. In your view, how common is spontaneous resolution (i.e. with VA returning to pre-VO state) in branch retinal vein occlusion (BRVO)?
2. After treatment, what is the average time to discharge/stability?

For BRVO	For CRVO

3. What are the characteristics of BRVO patients with macular oedema who are not considered suitable for laser treatment?

4. How often is Bevacizumab used for RVO procedures in your NHS practice?

Rarely ☐ Occasionally ☐ Regularly ☐ Routinely ☐ Don't know ☐

5. How is access to Bevacizumab funded in your NHS practice?

By individual finance requests ☐ Through the hospital budget ☐ Don't know ☐

If **'Other'**, please specify overleaf

6. What form is Bevacizumab procured in for administration in your clinic?

Pre-filled syringes		Local compounding of larger vials		Don't know	

7. Is RVO treatment usually provided as a day case or an outpatient procedure?

Outpatient		Day case	

8. Will there be locally commissioned arrangements for RVO treatment?

Yes		No	

Information: The NICE costing tool for wAMD uses 75% day case and 25% outpatient procedures

9a) In your view, is this a reasonable apportionment for RVO procedures?

Yes		No	

b) Do you consider that a 50% day case 50% outpatient to be a more reasonable weighting for RVO procedures?

Yes		No	

If 'No' please suggest a % distribution that you consider to be more appropriate

Please use this space to make any additional comments to this consultation that you may wish to make

Additional comments

THANK YOU FOR YOUR HELP

Please save your completed form as a new file and send it as an email attachment to p.coleman@sheffield.ac.uk

Alternatively please send a printed version by FAX to

0114 272 4095 or 0114 222 0749 For the attention of P. Coleman, Research Fellow, School of Health and Related Research (ScHARR).

Appendix B: Detailing the Mixed Treatment Comparison

Report Detailing a Mixed Treatment Comparison Comparing OZURDEX with Bevacizumab in the Treatment of Macular Oedema following Branch Retinal Vein Occlusion.

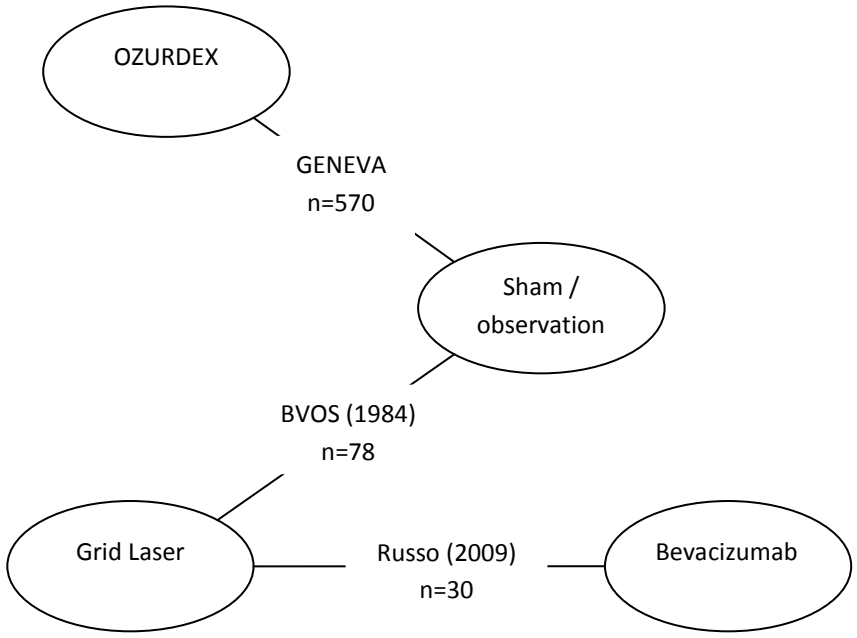
Nic Brereton, BresMed Health Solutions

Prof. Nick Freemantle, Phd, University of Birmingham

Overview

A mixed treatment comparison has been performed to examine the comparative efficacy of OZURDEX and bevacizumab in the treatment of branch retinal vein occlusion (BRVO). The endpoint of interest in the analysis is improvement in best corrected visual acuity (BCVA). A systematic review was performed to identify appropriate randomised controlled studies. These were searched to determine those which could be used to identify change in BCVA or comparative BCVA. A potential network was then established from the data. Bevacizumab is not licensed for treatment of BRVO and therefore randomised controlled trial data (RCT) is sparse.

Figure 1: The network of evidence



Estimated mean effect of treatment on Hb through analysing standardised effect sizes, and back transforming to Hb via weighted average SD. Standardised effect size (SES) calculated for each study group conventionally from the SD and mean Hb. Thus:

$$SES = \frac{Hb}{SD}$$

Where SD is the weighted pooled average from all groups in that trial

$$\hat{SD} = \sqrt{\left(\frac{SD_1^{\,2}(n_1 - 1) + SD_2^{\,2}(n_2 - 1)}{n_1 + n_2 - 2} \right)}$$

Back transformation was based upon the weighted average SD across the trials, calculated similarly. The MTC was calculated using the method developed by Lu and Ades, using published algorithms, modified for the data structure. The code and data used for the final model are supplied in below.

A major limitation of the analysis was the sparseness of the data, particularly in the Russo study linking Bevacizumab to grid laser. Fixed effects models were therefore estimated.

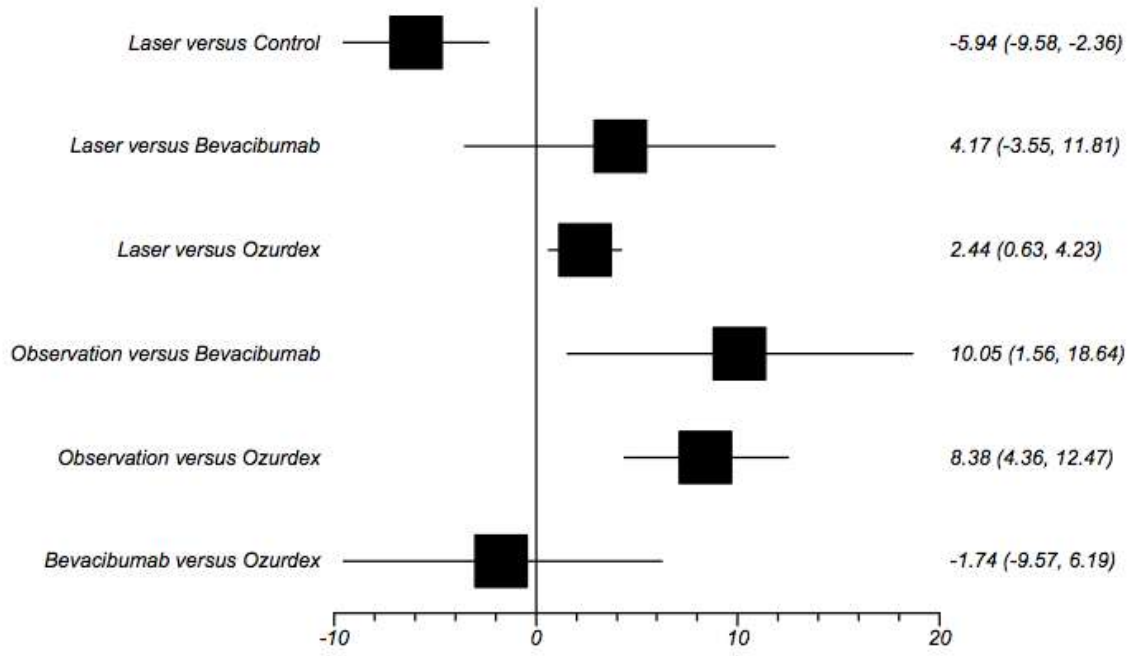
All analyses were conducted using Winbugs 14. Analyses were based upon 10,000 model iteration burn in, and 10,000 iteration estimation runs. Model convergence was assessed through observing convergence plots.

Results

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 decrease in BCVA of 1.74 (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 increase in BCVA of 2.55 (95% CI -5.28 to 10.48) though also not statistically significant. OZURDEX is also shown to be significantly better than observation and laser.

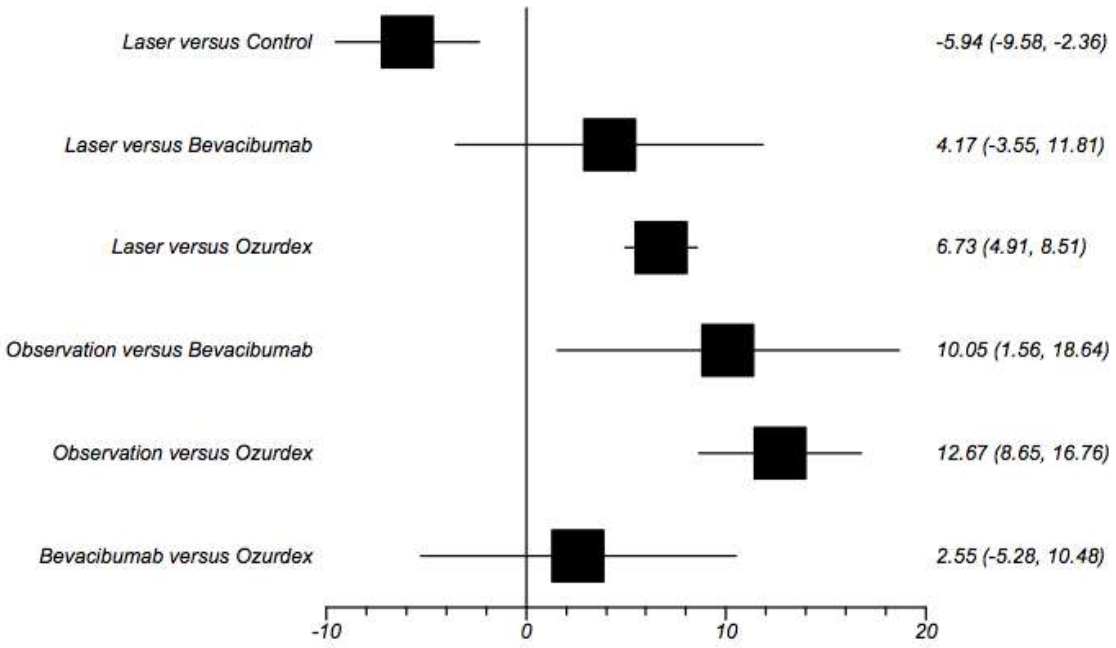
The uncertainty around these estimates is large, mostly due to very small sample in the Russo et al analysis (n=30) estimates require cautious interpretation.

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*

Data Extraction Table

The following data were extracted from the identified studies and used to inform the mixed treatment comparison. Missing confidence intervals were imputed and included in the winbugs code below. BVOS Snellen values were converted to BCVA scores using the midpoint of the score ranges. Given the lack of reported uncertainty, score ranges were assumed to be confidence intervals for estimates. logMAR scores from Russo study were converted to letters gained by dividing by 0.02.

Data extracts from the identified literature

Study	Arm	N	Baseline letters	CI	Endpoint Letters	CI	Change in letters	Mean Diff	CI
BVOS 1984	Laser	35	56.9	-	58.6	(54-63)	1.7		
BVOS 1984	Observation	43	56.4	-	68.5	(64-73)	12.1	10.4	-
Russo 2009	Laser	15	0.89[a]	+/-0.13	0.69	+/-0.13	10		
Russo 2009	Bevacizumab	15	0.87	+/-0.16	0.56	+/-0.16	15.5	5.5	-
Geneva (day 60)	Sham	279							
Geneva (day 60)	OZURDEX	291	-	-	-	-	-	5.3	3.8, 6.7
Geneva (day 180)	Sham	279	-	-	-	-	-		
Geneva (day 180)	OZURDEX	291						2.5	0.6,4.3

[a] *Reported on logMAR scale*

Winbugs Code and data

Fixed effect model

```
model{

for(i in 1:N) { p[i]<-mu[s[i]]+ d[t[i]] - d[b[i]]
 # model
        r[i]~dnorm(p[i],n[i]) }
for(j in 1:NS) { mu[j]~dnorm(0,.0001)}     # vague priors for 3 trial baselines
d[1]<-0
for (k in 2:NT) {d[k] ~ dnorm(0,.0001) }   # vague priors for basic parameters

# pairwise SESs
for (c in 1:(NT-1))
        { for (k in (c+1):NT)
                { SES[c,k] <- d[k] - d[c]
                ACC[c,k] <- SES[c,k]*11.765
# back translation to ACC using weighted pooled SD
                }
        }
}
# sample <ACC> and <SES>
list(N=6, NS=3, NT=4,
s=c(1, 1, 2, 2, 3, 3),
t=c(1, 2, 1, 3, 2, 4 ),
r=c(0.262, 0.157, 0.694, 1.076, 0.298, 0.942 ),
n=c(73, 75, 15, 15, 426, 427),
```

Appendix C: Details of the Cost Minimisation Analysis between OZURDEX and bevacizumab (CRVO Only)

Table 1: Number of Treatment Administrations

It is assumed that each of these treatments requires either a day case or an outpatient administration visit

Treatment	Days 0-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 900-1080	Total
Ranibizumab	5.60	3.30	2.43	2.43	1.41	1.41	16.05
Bevacizumab	5.60	3.30	2.43	2.43	1.41	1.41	16.05
Dexamethasone	1.00	0.86	0.63	0.63	0.37	0.37	3.71

Table 2: Number of patients remaining on treatment at each cycle point

The proportion of patients remaining on treatment is required to determine the number of follow up visits during the period. It is assumed that these retreatment rates apply to both treatment arms.

Proportion of patients remaining on treatment during days:					
0-180	181-360	361-540	541-720	721-900	900-1080
100.0%	85.7%	63.0%	63.0%	36.5%	36.5%

Table 3: Number of follow up visits

Whilst patients are receiving treatment, there is a requirement for them to attend for outpatient consultation and review in addition to treatment visits. These are assumed to be performed in the outpatient setting. These are shown in the table below. When a patient stops treatment (either due to lack of response or resolution) they are assumed to no longer require treatment associated follow-up appointments. These are costed at £73 (NHS Reference costs 2008-9, follow-up ophthalmology - non-admitted face to face contact) to retain consistency with the OZURDEX main health economic model.

Treatment	Total required ophthalmology consultations		Additional observation visits required in addition to treatment administration visit		
	Initial 6 months	Post 6 months	Year 1	Year 2	Year 3
Ranibizumab	6	6	2.24	2.71	0.78
Bevacizumab	6	6	2.24	2.71	0.78
Dexamethasone	3	2	2.86	1.26	0.73

Table 4: Number of additional follow up visits required

The number of additional follow up visits required are calculated from the total number of visits required for patients on treatment (table 3), multiplied by the proportion of patients still on treatment (table 2) minus the number of administrations (Table 1) to avoid potential double counting.

Treatment	Number of additional observation appointments required during days;					
	0-180	181-360	361-540	541-720	721-900	900-1080
Ranibizumab	0.40	1.84	1.35	1.35	0.78	0.78
Bevacizumab	0.40	1.84	1.35	1.35	0.78	0.78
Dexamethasone	2.00	0.86	0.63	0.63	0.37	0.37

Table 5: Cost of treating adverse events

The cost of a cataract extraction was taken from the core economic model (Sheet AE _Cost, cell F91). For Ranibizumab and Bevacizumab, this cost was multiplied by the percentage of patients experiencing cataracts during the CRUISE trial (1.6%), and then multiplied by 2 (as the available CRUISE trial data was for 6 months) to give a yearly cost of £25.25 for patients receiving Ranibizumab or Bevacizumab. For OZURDEX the cost of cataract extraction was multiplied by the percentage of CRVO patients experiencing cataracts in GENEVA studies (8.3%) (Main Submission p.103), giving a per treatment cost for cataract extraction for patients receiving OZURDEX of £65.49.

The costs of non-cataract adverse events were taken from the originally submitted model. This was a sum of all of the costs of non- cataract related adverse events for the first procedure, or for subsequent procedures (summary sheet, cells V34 +V39 + V42 or V36 + V40 + V43). This gave a per treatment cost of non-cataracts adverse events for patients receiving OZURDEX of £105.20 for the first treatment and £104.45 for subsequent treatments. Due to lack of information regarding non-cataracts adverse events for Ranibizumab and Bevacizumab these were not included.

Treatment arm	Adverse Events		
	Cataract Extraction	Non cataracts on 1st treatment	Non cataracts on retreatment
Ranibizumab	£25.25	£0	£0
Bevacizumab	£25.25	£0	£0
Dexamethasone	£65.49	£105.20	£104.45

Table 6: Sensitivity analysis varying the number of patients that can share a vial of bevacizumab.

Number of patients sharing vial (excluding adverse events)	Marginal Cost (dexamethasone vs bevacizumab)
1	-£6,672
2	-£4,725
4	-£3,751
6	-£3,427
8	-£3,265
10	-£3,167
12	-£3,102
14	-£3,056
16	-£3,021
18	-£2,994
20	-£2,973

Table 7: Scenario analysis for cost minimisation comparison between dexamethasone and ranibizumab and bevacizumab

Scenario	**Marginal Cost (dexamethasone vs)**	
	Ranibizumab	**Bevacizumab**
Base Case	-£14,994	-£4,463
Base case excluding adverse events	-£15,554	-£5,023
Base case but bevacizumab administered from whole vial	-£14,994	-£6,672
Base case but bevacizumab administered from whole vial and excluding AE's	-£15,554	-£7,232
Base case but assuming all administrations given as day case	-£16,530	-£5,999
Base case but assuming all administrations given as out patient	-£10,387	£144
Base case but assuming all administrations day case and no adverse events	-£17,090	-£6,558
Base case but assuming all administrations outpatient and no adverse events	-£10,947	-£416
Base case but halving number of treatments for ranibizumab and bevacizumab	-£8,038	-£2,773
Base case but halving number of treatments for ranibizumab and bevacizumab excluding AEs	-£8,283	-£3,017
Base case but assuming 50% of administrations as outpatient and 50% as day case	-£13,458	-£2,927
Base case but assuming 50% of administrations as outpatient and 50% as day case. Excluding AEs	-£14,018	-£3,487

Appendix D: Details of the OZURDEX vs. bevacizumab Cost Utility Analysis based on Mixed Treatment Analysis

Below are the details regarding treatment frequency for the costs incurred, based on the mixed treatment comparison (BRVO only)

Table 1: Number of Treatment Administrations

It is assumed that each of these treatments requires either a day case or an outpatient administration visit

Treatment	Days 0-180	Days 181-360	Days 361-540	Days 541-720	Days 721-900	Days 900-1080	Total
Ranibizumab	5.70	2.70	0.63	0.63	0.30	0.00	9.96
Bevacizumab	5.70	2.70	0.63	0.63	0.30	0.00	9.96
Dexamethasone	1.00	0.79	0.19	0.19	0.08	0.00	2.24

Table 2: Number of patients remaining on treatment at each cycle point

The proportion of patients remaining on treatment is required to determine the number of follow up visits during the period. It is assumed that these retreatment rates apply to both treatment arms.

Proportion of patients remaining on treatment during days:					
0-180	181-360	361-540	541-720	721-900	900-1080
100.0%	78.8%	18.5%	18.5%	8.0%	0.0%

Table 3: Number of follow up visits

Whilst patients are receiving treatment, there is a requirement for them to attend observation consultation. These are assumed to be performed in the outpatient setting. The are shown in the table below. When a patient stops treatment (either due to lack of response or resolution) they are assumed to no longer require treatment associated follow-up appointments. These are costed at £73 (NHS Reference costs 2008-9, follow-up ophthalmology - non-admitted face to face contact) to retain consistency with the OZURDEX main health economic model.

Treatment	Total required ophthalmology consultations		Additional observation visits required in addition to treatment administration visit		
	Initial 6 months	Post 6 months	Year 1	Year 2	Year 3
Bevacizumab	6	6	2.33	0.96	0.18
Dexamethasone	3	2	2.79	0.37	0.08

Table 4: Number of additional follow up visits required

The number of additional follow up visits required are calculated from the total number of visits required for patients on treatment (table 3), multiplied by the proportion of patients still on treatment (table 2) minus the number of administrations (Table 1) to avoid potential double counting.

	Number of additional observation appointments required during days;					
Treatment	**0-180**	**181-360**	**361-540**	**541-720**	**721-900**	**900-1080**
Bevacizumab	0.30	2.03	0.48	0.48	0.18	0.00
Dexamethasone	2.00	0.79	0.19	0.19	0.08	0.00

The results in the table below are shown for OZURDEX vs. bevacizumab. The results are presented as net marginal benefit (MNB) analyses and therefore a NMB of >0 is means that treatment with dexamethasone is cost effective at the threshold

Table 5: Scenario analyses for cost utility approach based on Mixed Treatment Analysis for OZURDEX vs. Bevacizumab.

Scenario	**NMB at £30,000/QALY**	**NMB at £20,000/QALY**
Base Case	£1,927	£2,228
Base case excluding adverse events	£2,232	£2,533
Base case but using the incremental letter gain at day 60 (1.68 letters)	£4,151	£3,711
Base case but using the incremental letter gain at day 60 (1.68 letters). Excluding AEs	£4,456	£4,015
Base case but assuming 50% of administrations are day case procedures	£974	£1,275
Base case but assuming 50% of administrations are day case procedures. Excluding AEs	£1,279	£1,579
Base case but assuming all administrations given as day case	£2,880	£3,181
Base case but assuming all administrations given as day case. Excluding AEs	£3,185	£3,486
Base case but assuming all administrations performed as out patient visits	-£932	-£632
Base case but assuming all administrations performed as out patient visits. Excluding AEs	-£628	-£327
Base case but assuming retreatment rates are as at day 180	£3,177	£3,478

Base case but assuming retreatment rates are as at day 180. Excluding AEs	£3,785	£4,086
Base case but including the cost of completing exceptional paperwork when treating with Bevacizumab	£2,287	£2,588
Base case but including the cost of completing exceptional paperwork when treating with Bevacizumab. Excluding AEs	£2,592	£2,893

A limitation of the basecase analysis is that it assumes that the VA improvement that patients achieve on first dosing is maintained throughout the model. This assumes that the treatment effect continues even after many treatments, or after patient discontinues treatment. A sensitivity analysis was performed which reduced the treatment effect over time. Annually, the mean letter gain from treatment with bevacizumab is reduced by an annual rate ranging from 1% to 20%.

The results of this analysis show that including this effect improves the cost effectiveness and OZURDEX is cost effective treatment at all thresholds.

Table 6: Analysis exploring the effects of an annual percentage reduction in the incremental letters gained post 3 year treatment period.

Annual reduction in incremental letters benefit between Bevacizumab and Dexamethasone	**NMB at £30,000/QALY**	**NMB at £20,000/QALY**
Including Adverse Events		
1%	£1,995	£2,273
5%	£2,196	£2,407
10%	£2,349	£2,509
20%	£2,506	£2,614
Excluding Adverse Events		
1%	£2,300	£2,578
5%	£2,500	£2,712
10%	£2,653	£2,814
20%	£2,811	£2,919

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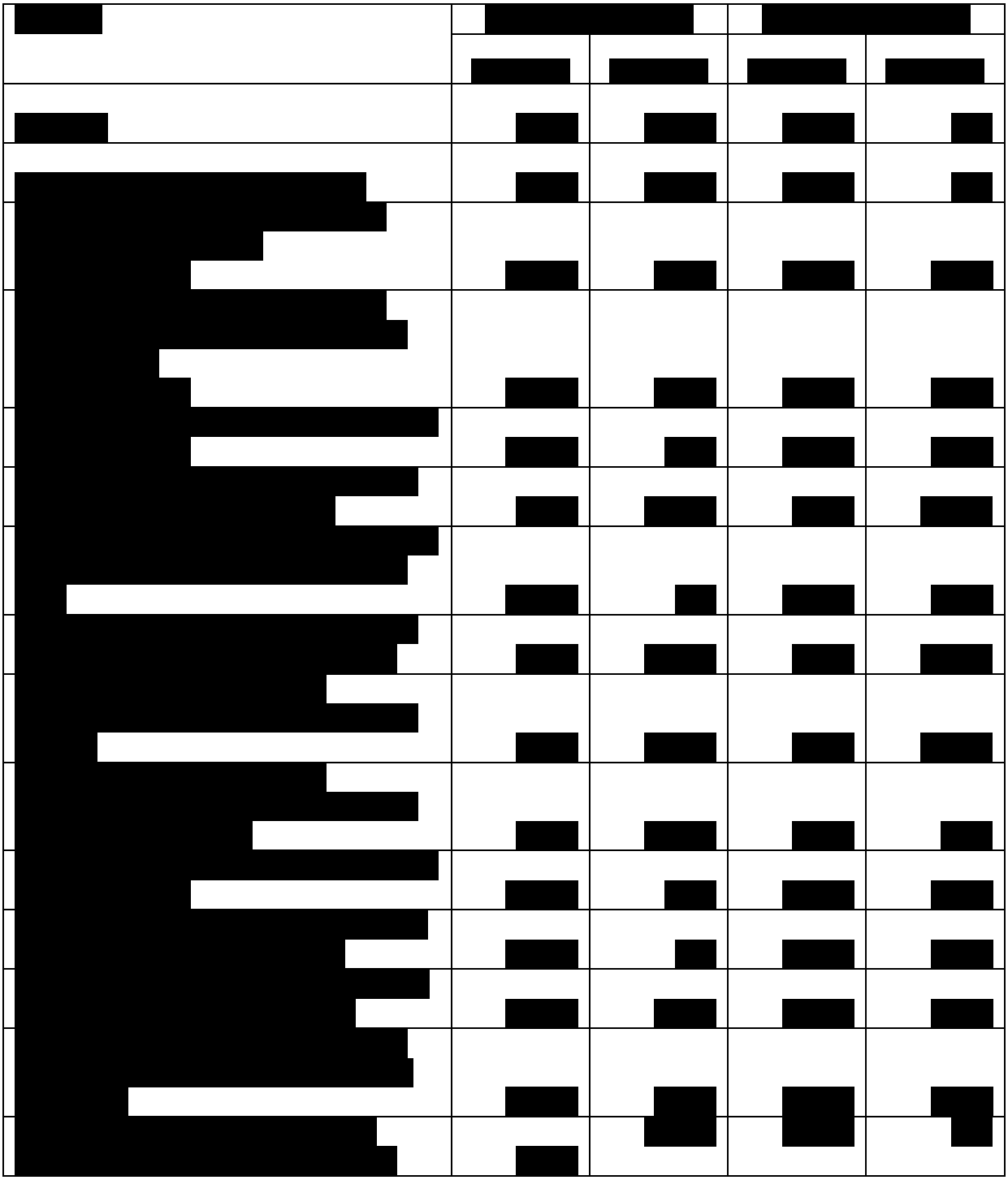

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Appendix F: Predictors of outcomes in RVO

The four main differences in the characteristics between baseline patient populations in CRUISE[i] and GENEVA[ii,iii,iv,v] are baseline BVCA, OCT, duration of macular oedema and delaying treatment (i.e. longer duration of disease) (see table 2 in the main response). These all impact the efficacy of treatment and thus demonstrate that an indirect comparison between these trials is not reasonable.

Baseline BVCA

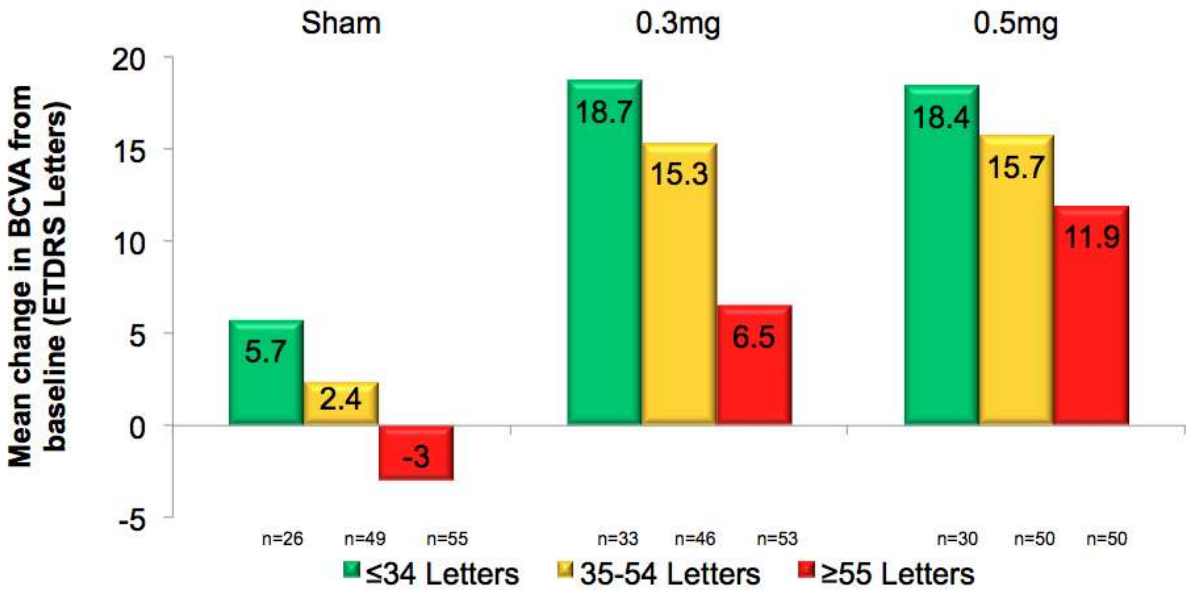
Table 1 shows the difference in baseline BCVA between the GENEVA and CRUISE trials. Patient in the GENEVA trial have a higher BCVA and are therefore less severe than those in CRUISE

Table 1: *Baseline mean BCVA for patients in the GENEVA and CRUISE studies*

	GENEVA-CRVO		CRUISE	
	Dexamethasone	**Sham**	**Ranibizumab**	**Sham**
Mean BCVA	54.3	54.8	48.1	49.2

The effect on mean change in BCVA of baseline BCVA is shown in figure 1. This analysis demonstrates that the lower the baseline BCVA, the greater the mean change in BCVA from baseline. Therefore it is expected that the lower baseline BCVA in ranibizumab patient in the CRUISE study will result in a greater treatment benefit compared to Ozurdex patients treated in the GENEVA trial.

Figure 1: *The effect of baseline BCVA on mean change in BCVA in the CRUISE trial*



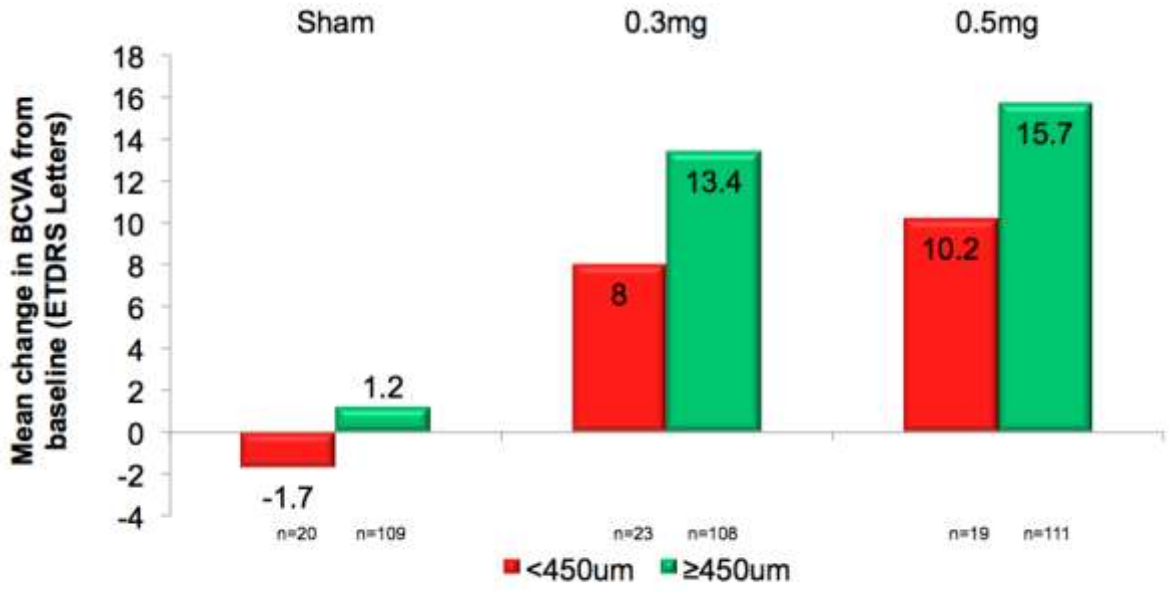
Baseline CRT

Table 2 shows that difference in baseline central retinal thickness (CRT) between patients in the GENEVA and CRUISE trials. Patients in the GENEVA trial have a higher lower CRT than those in the CRUISE trial and figure 2 demonstrates that the higher the CRT level the greater the response from treatment. Therefore as ranibizumab patients in the CRUISE trial have a higher baseline CRT it would be expected that they would achieve a higher mean change in BCVA

Table 2: *Baseline mean CRT for patients in the GENEVA and CRUISE studies*

	GENEVA-CRVO		CRUISE	
	Dexamethasone	**Sham**	**Ranibizumab**	**Sham**
Mean CRT	648	620	689	687

Figure 2: The effect of baseline CRT on mean change in BCVA in the CRUISE trial



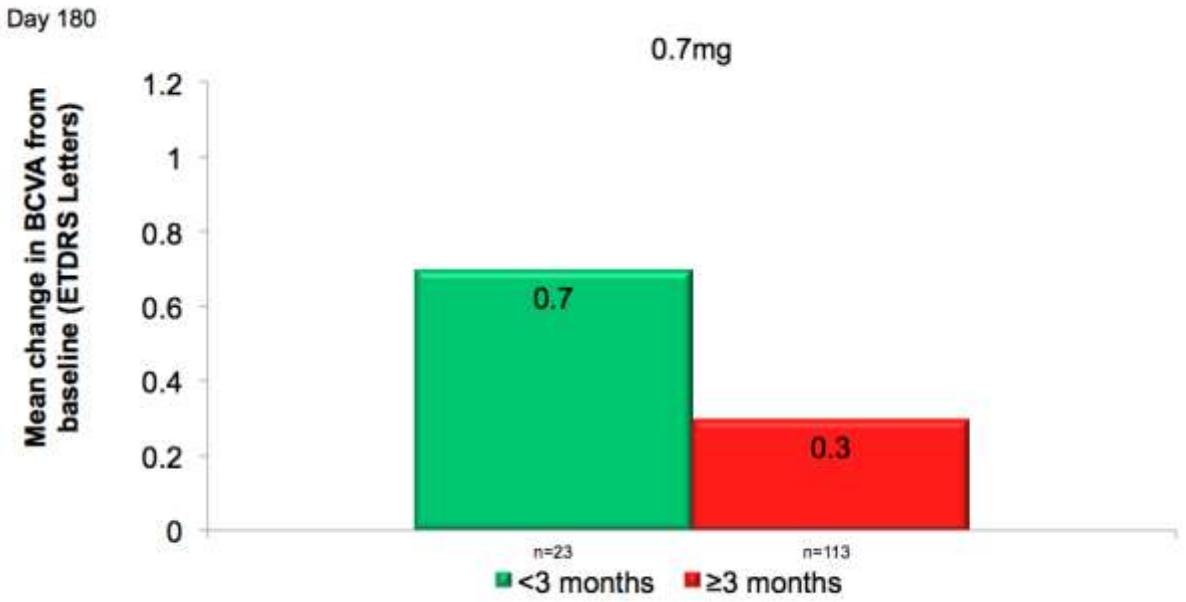
Effect of ME on endpoints

Table 3 shows the difference in the baseline duration of macular oedema between the GENEVA and CRUISE trials. The majority of patients in the CRUISE trial had experienced macular oedema for less than 90 days compared to patients in GENEVA who were mostly >90 days. Figure 3 demonstrates that patients who have ME for less than 3 months have a greater mean change in BCVA compared to those with a ME for > 90 days and therefore the expected treatment effect for patients on ranibizumab would be expected to be higher than those on Ozurdex in the GENEVA trial.

Table 3: *Baseline mean CRT for patients in the GENEVA and CRUISE studies*

	GENEVA-CRVO		CRUISE	
	Dexamethasone	**Sham**	**Ranibizumab**	**Sham**
<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

Figure 3: The effect of duration of ME on mean change in BCVA in the GENEVA trial



Effect of delayed treatment

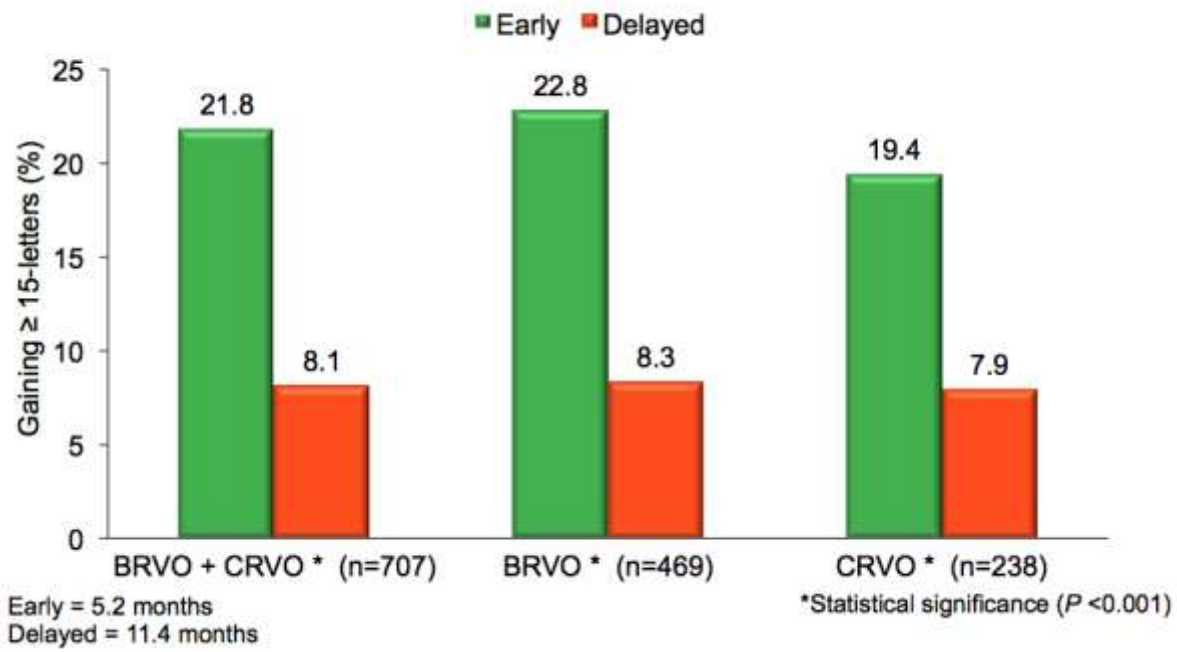
The majority of patients in the CRUISE trial had a duration of macular oedema of less that 3 months at the point of enrolment. The majority of patients in the GENEVA trials had >3 months duration of macular oedema.

Figure 4 shows the effect on the mean BCVA change from baseline for patients with early (5.2 months) and delayed (11.4 months) treatment.

Table 4: Duration of macular oedema due to RVO from diagnosis to treatment.

Duration of Macular Oedema	% of patients	
	GENEVA	CRUISE
≤3 months	16.7	72.3
>3 months ≤ 6 months	51.9	13.1
>6 months ≤ 9 months	22.1	7.7
≥9 months	9.4	6.9

Figure 4: The effect of time to treatment on the percentage of patients the gain ≥ 15 letters.



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[i] Brown D, Campochiaro. PA, Singh. RP, Li. Z, Gray. S, Saroj. N, et al. Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Six-Month Primary End Point Results of a Phase III Study. Ophthalmology. 2010;117(6):1124-33.

[ii] Allergan. Study 206207-008 6 month report: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Data on file. 2008.

[iii] Allergan. Study 206207-009 6 month report: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Data on file. 2008.

[iv] [iv] Allergan. Study 206207-009 12 month report: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Data on file. 2009.

[v] Allergan. Study 206207-008 12 month report: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion. Data on file. 2009.