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Pfizer Global Pharmaceuticals

RE: Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

We are grateful for the opportunity to comment on the Technology Assessment Report (TAR) prepared by the Southampton Health Technology Assessment Centre (SHTAC). We believe this report uses the best-available evidence in the public domain to appraise ranibizumab and pegaptanib.

However, we have a number of concerns with the approaches taken by SHTAC that have the impact of underestimating the incremental cost-effectiveness of pegaptanib and overestimating the benefit for ranibizumab. This response details our major concerns, notably:

1) Risk of vision loss or gain is dependent upon baseline visual acuity

SHTAC have assumed that the risk of vision loss or gain is independent of baseline visual acuity (VA); an assumption not supported by the clinical data and which results in significant underestimation of the incremental benefit for pegaptanib within the clinical trial timeframe and, therefore, the subsequent long-term incremental cost per QALY (IC/QALY).

2) Risk of vision loss or gain is time-dependent

SHTAC have adopted an oversimplified approach for determining the likelihood of vision loss or gain over time. Using patient-level data, Pfizer have demonstrated that the SHTAC model produces conservative estimates for IC/QALY for pegaptanib, whilst potentially overestimating the benefits for ranibizumab.

3) A revised Pfizer model for patients with pre-treatment VA between 6/12 and 6/24, adopting suggested SHTAC monitoring costs, shows the IC/QALY for pegaptanib to be £15,068.

We provide IC/QALY results from a revised analysis based specifically on the data from the chosen population of patients with pre-treatment VA of 6/12 to 6/24. The SHTAC model for patients with pre-treatment VA of 6/12 to 6/24 uses probabilities derived from the full VISION study population (VA of 6/12 to 6/95). We have shown that pre-treatment VA is a statistically significant covariate in analyses and that the IC/QALY for pegaptanib is more favourable than the SHTAC model suggests when treatment is initiated in patients with better pre-treatment VA. Based on this population of patients with pre-treatment VA of 6/12 to 6/24, pegaptanib is below the £20,000 IC/QALY threshold even after all concerns highlighted by SHTAC are fully incorporated into the model.

Furthermore, Pfizer maintain that results from the full trial population should not be restricted and applied to a population with different pre-treatment VA. Pfizer request that IC/QALY results from the full trial population should appear as the base case in the SHTAC model. Pfizer have shown pegaptanib to be cost-effective based on the full population with pre-treatment VA of 6/12 to 6/95 from the VISION study.

4) Results from the ranibizumab models from SHTAC and Novartis are subject to additional uncertainty and provide contradictory conclusions that are not fully addressed

The SHTAC and Novartis models produce widely differing results for ranibizumab. No explanation is provided for the order of magnitude difference between the SHTAC and Novartis model IC/QALY results (the manufacturer's own analyses produce less favourable results). The significant

discrepancy within the ranibizumab IC/QALY results reflect the differing methodologies used for the indirect analysis and selection of utility values. However, the uncertainty with these results is not adequately reflected within the Executive Summary, hence provides a misleading level of confidence for ranibizumab.

5) Recent data on non-selective VEGF safety from ranibizumab randomised trials should be included to inform the risk:benefit ratio.

The recently published data that raise safety concerns for non-selective VEGF inhibition have not been highlighted by SHTAC. Data from randomised trials have shown a significant increase in the risk of stroke and non-ocular haemorrhage for ranibizumab. These findings should inform the risk:benefit ratio.

For the above reasons 1-4, we believe that the SHTAC model produces conservative estimates of the IC/QALY for pegaptanib whilst overestimating the benefits for ranibizumab. The Pfizer model provides a more robust estimate of the IC/QALY for pegaptanib that accounts for both time and VA dependence. We request that the manufacturers' IC/QALY estimates are included within the Executive Summary of the TAR along with a clear explanation of the reasons for the variability. This will provide readers an indication of the potential impact and understanding for the methodological uncertainty around these assumptions.

The following provides full detail on the above concerns and gives a detailed response to all concerns and questions raised by the SHTAC with regards to the Pfizer model (Appendix 4). Given the opportunity, we would be happy to provide any further clarification or justification for our model.

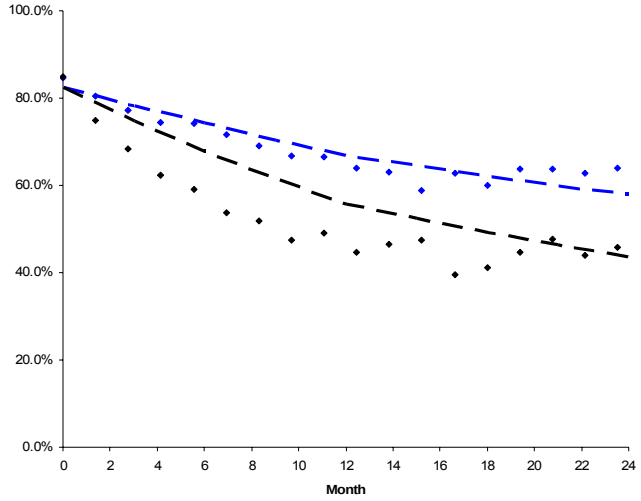
1) Risk of vision loss or gain is dependent upon baseline visual acuity

a)Incremental benefits for pegaptanib are underestimated by the SHTAC model during the two year trial period.

The SHTAC model adopted a simple approach to modelling visual acuity (VA) change using probabilities derived from the number of patients that had lost 3 to 6 lines, lost ≥ 6 lines and gained ≥ 3 lines at year 1 and year 2 in the VISION trial. We rejected this approach early in our development of the pegaptanib model, as validation of model predictions within the first two years with respect to trial data demonstrated substantial discrepancies. The structure of the early Pfizer model was consistent with the SHTAC approach (see Appendix 1 for further detail). The percentage of patients with a VA of >6/60 was calculated from the model and compared with data extracted from the VISION trial dataset.

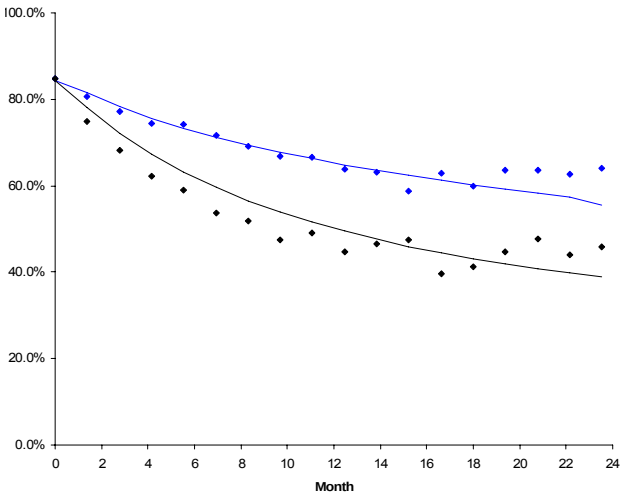
The prediction of this early model, using the probabilities applied in the SHTAC model (reported in Table 4.12 of the TAR), is compared with the VISION trial data in Figure 1. We observed that this approach resulted in very poor prediction of the trial data for the sham cohort.

Figure 1. Percentage of pateints with VA >6/60: VA independent model using SHTAC probabilities
symbols represent VISION trial data, dashed lines represent model prediction using SHTAC probabilities



This approach was abandoned in favour of an approach analogous to that adopted by Smith et al[1] in order to incorporate the time-dependence of VA change, as well as the dependence on pre-treatment VA observed by Smith et al[1]. The prediction of the Pfizer submission model is compared with the VISION trial data in Figure 2.

Figure 2. Percentage of patients with VA >6/60: Pfizer submission model with VA dependence
symbols represent VISION trial data, solid lines represent Pfizer submission model prediction



The QALY estimates produced by the SHTAC model are compared with QALYs calculated directly from the trial data using the same utility weights, Table 1 (see Appendix 2 for further detail). Equivalent estimates generated by the Pfizer submission model are also presented for comparison.

Table 1. QALY estimates over 2 years (Pre-treatment VA 6/12 to 6/24)

	Discounted QALYs in first 2 years		
	Pegaptanib	Sham*	Incremental
SHTAC Model[1]	1.43	1.37	0.06
VISION Trial Data[2]	1.38	1.26	0.13
Pfizer Submission Model[3]	1.32	1.23	0.09

* Best Supportive Care in the Pfizer and SHTAC models

1. Taken from the Technology Assessment Report (Table 4.22, page 136)

2. The percentage of patients at each assessment in each of the 5 VA states defined in the SHTAC and Pfizer submission models was extracted from the VISION trial dataset for patients with a baseline VA between 6/12 and 6/24 (inclusive). QALYs were calculated for each 6-week period using these data by applying the utility weights adopted for the SHTAC base case analysis (Brown et al., 2000), discounted at 3.5%, and summed over the 2-year period. See Appendix 2 for further details.

3. For a population with pre-treatment VA between 6/12 and 6/24; mortality rates set to zero; no treatment discontinuation rules applied.

The incremental QALY estimated in the SHTAC analysis is half of that estimated directly from the trial data (a difference of 0.07 QALYs, 52%).

The Pfizer submission model used probabilities for loss and gain of individual Snellen lines derived from survival curves fitted to the patient-level data of the VISION trial, with pre-treatment Snellen line as a covariate. Thus the dependence of VA change on pre-treatment VA was reflected in the model predictions. This model prediction for QALYs within the first 2 years in each treatment cohort is closer to that calculated from the trial data than that of the SHTAC model. The incremental benefit estimated by the Pfizer submission model is still conservative compared to that generated from the trial data, although less so than the SHTAC model. Incremental QALYs within the first two years are underestimated in the Pfizer submission model by 0.04 QALYs (28%). Furthermore, although it has been recognised by others that VA change is dependent on pre-treatment VA levels[1] (Smith et al., 2004), in the SHTAC base-case analysis, probabilities derived from the VISION trial population with a VA range of 6/12 to 6/95[2] were used to model VA change for patients with a pre-treatment VA of between 6/12 and 6/24.

Although SHTAC currently acknowledge their assumption that the probability of gaining or losing VA is independent of pre-treatment VA in the Executive Summary, a clear statement that this provides a conservative estimate for the IC/QALY of pegaptanib is missing. We request such a statement and clear explanation of the variability are provided in the Executive Summary based on the Pfizer findings that the data is dependent on pre-treatment VA and this leads to a lower IC/QALY.

[1] Time to transition to lower VA level was found to be highly dependent on baseline Snellen ($P = 0.0065$).
[2] 99% of patients in the pegaptanib 0.3mg and sham arms had a baseline VA of 6/12 to 6/95 inclusive.

b) Underestimation of the incremental benefit for pegaptanib during the 2-year trial period results in underestimation of the benefit in subsequent years.

Although the SHTAC model and the Pfizer submission model adopted very different approaches to the extrapolation of outcomes beyond trial follow-up, the two models provide a similar prediction for the proportion of benefit gained during the trial period and during the extrapolation period. Table 2 presents the proportion of the total incremental benefit estimated over the 10 year time horizon that was gained during the 2-year trial period and during the extrapolation period (between year 2 and year 10) in the two analyses. The base-case SHTAC analysis is presented, i.e. the scenario in which no disease-modifying effect was assumed.

Table 2. Incremental QALY estimates during trial follow-up and extrapolation periods (Pre-treatment VA 6/12 to 6/24)

	Discounted incremental QALYs			
	Trial follow-up (2 Years)	Extrapolation (2-10 years)	Total (10 Years)	% during extrapolation
SHTAC Model[1]	0.06	0.20	0.26	77%
Pfizer Submission Model[2]	0.09	0.33	0.42	79%

1. Derived from Technology Assessment Report Table 4.22, page 136 (assumes no disease-modifying effect).
2. For patients with a baseline VA between 6/12 and 6/24 (makes no assumption with regard to disease-modifying effect).

The incremental QALYs estimated during the extrapolation period represented 77% of the total incremental QALYs estimated over 10 years in the SHTAC model, and 79% in the Pfizer submission model. Therefore, these two analyses, although applying very different methods for extrapolation, provide very similar predictions for the extension of benefit after trial follow-up. However, the underestimation of the incremental benefit of pegaptanib during the two year trial period in the SHTAC model is continued into the extrapolation period, resulting in substantial underestimation of pegaptanib's incremental benefit over 10 years.

The Pfizer submission model made best use of available data to model outcomes beyond trial follow-up and after treatment discontinuation. Outcomes in the usual care cohort were modelled using time-dependent probabilities estimated by extending the survival curves fitted to the patient-level data collected in the 2-year trial period. Outcomes in the pegaptanib cohort were modelled in a similar way using survival curves fitted to 1-year follow-up data for patients in the VISION trial that discontinued treatment after 1 year. Thus, no assumptions were made with regard to a "disease-modifying" effect, or continuation of treatment effect after 2 years. Rather, the impact of treatment discontinuation observed in the VISION trial was applied, and uncertainty in the extrapolation was explored as fully as possible.

We propose that since:

a. the SHTAC and Pfizer submission models generated very similar predictions for the incremental benefit in the extrapolation period in proportion to that in the trial follow-up period;

b. the SHTAC model has been demonstrated to underestimate the incremental benefit during the two year trial period; and

c. the Pfizer submission model makes best use of available data and explores the uncertainty in the extrapolation fully without assuming a "disease-modifying" effect;

it is reasonable to conclude that the Pfizer model provides a credible estimate of the incremental benefit of pegaptanib over 10 years.

Pfizer contend that SHTAC should provide within the Executive Summary the lower estimate of IC/QALY from the Pfizer model along with an explanation of the assumptions leading to the variability. Furthermore, the TAR comments should be amended to clarify that the Pfizer extrapolation does not assume a "disease modifying" effect and thereby is not an overestimate of the IC/QALY.

2) Risk of vision loss or gain is time-dependent

Pfizer will demonstrate that the independent methodology applied in the SHTAC model has a differential impact that potentially favours ranibizumab whilst being conservative for pegaptanib.

All three models reported in the TAR apply differing methodologies to account for the time-dependence of the risk of vision loss or gain. Briefly, Pfizer derived time-dependent transition probabilities (TPs) for the loss and gain of individual Snellen lines from parametric survival curves fitted to patient-level data from the VISION trial, following a similar methodology applied by Smith et al.[1] Both Novartis and SHTAC use fixed TPs allocated to particular discrete time intervals. The TPs for the SHTAC model are derived separately for Year 1 and Year2 onwards. The TPs for the Novartis model are derived separately for the first 3 months, the remainder of Year 1, and Year 2 onwards.

Year 1

TPs for the first year in the SHTAC model are derived from the one year results from the relevant trials for both active and control arms. Therefore, an assumption is made that the risk of loss or gain is constant throughout the first year. Figures 3 and 4 show the rate of change of VA for pegaptanib from the VISION trial and ranibizumab from the MARINA trial, respectively. As can be seen the assumption of a linear, constant rate of change is a fair estimate for both active and sham arms from the VISION data (Figure 3A). However, although the sham arm shows a linear rate of change from MARINA, there is a clear period within the first 3 months where the rate of change for ranibizumab 0.5mg is greater than the remainder of the first year. This is in concordance with the time intervals adopted in the Novartis submission which reflect the trial data.

It is unclear whether this assumption of constant TPs for ranibizumab 0.5mg for the first year will overestimate or underestimate the incremental benefit in Year 1.

Figure 3: Rate of change of VA – Pegaptanib VISION trial

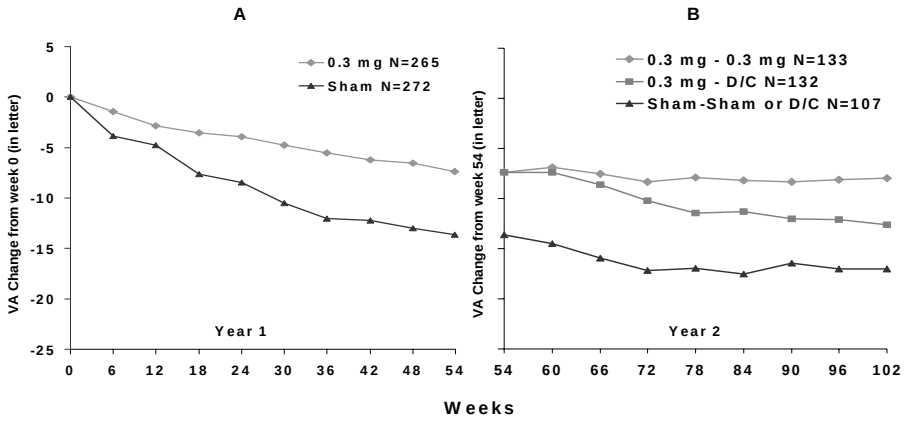
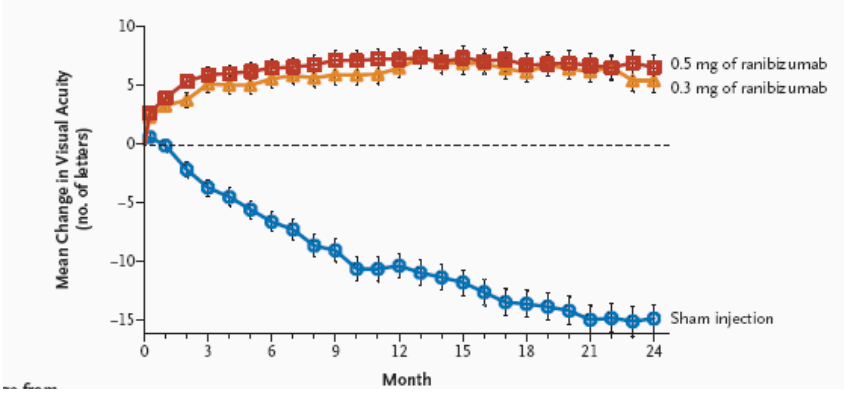


Figure 4: Rate of change of VA – Ranibizumab MARINA trial



Year 2

More importantly than the Year 1 TPs, we believe the SHTAC calculation of the Year 2 TPs will significantly advantage ranibizumab versus pegaptanib. The SHTAC group calculate the Year 2 TPs based upon the trial results taken from baseline (start of trial) to the end of Year 2; i.e. re-inclusion of the Year 1 data. As illustrated in Figures 3 and 4, there is minimal change in VA during Year 2 for both ranibizumab and pegaptanib. Therefore, the TPs for Year 2 should ideally be based solely on data from Year 2. By applying Year 2 TPs that are derived from the full trial period, the benefit observed in Year 1 appears to be "double counted" i.e. for ranibizumab the initial, early gain in vision has been incorporated into the derivation of the Year 2 TPs and will therefore lead to a higher TP for vision gain in Year 2 than indicated from the trial data. Furthermore, the initial, early loss of vision for pegaptanib will be incorporated again into Year 2 TPs.

Pfizer believe this simplification has differential impact for pegaptanib versus ranibizumab due to the inherent differences in the trial data. The methodology is conservative for pegaptanib but favours ranibizumab. This could provide the explanation as to why the Novartis model, which used time intervals that reflect the trial data, produces a less favourable IC/QALY estimate than the SHTAC model.

The inherent uncertainty and potential impact of this key assumption should be included in the Executive Summary and the manufacturers estimates should be provided as alternative estimates for the IC/QALY.

3) A revised Pfizer model for patients with pre-treatment VA between 6/12 and 6/24, adopting suggested SHTAC monitoring costs, shows the IC/QALY for pegaptanib to be £15,068.

The SHTAC analysis focuses on a population with a pre-treatment VA of between 6/12 and 6/24, and the TAR proposes that additional costs associated with monitoring of patients during pegaptanib treatment should be included in the analysis. We have therefore re-estimated the IC/QALY for this population using the Pfizer submission model, and explored the impact of including the additional monitoring costs.

The TAR proposes that the following costs associated with monitoring of patients during pegaptanib treatment should be included in the analysis (TAR page 105):

- Optical coherence tomography (OCT) at every attendance;
- Vision assessment at every attendance;
- Repeat fluorescein angiography (FA) every 3 or 6 months.

OCT and FA are not included in the pegaptanib model as decisions to continue treatment were based on an individual patient's vision which is the desired outcome and more informative than OCT and FA for pegaptanib. However, we recognise that ophthalmologists may prefer to monitor patients receiving pegaptanib particularly early in their experience with the drug, although they may feel able to perform less monitoring as their familiarity and confidence with pegaptanib increases. We have therefore adopted the monitoring costs assumed in the SHTAC model in full in a revised analysis reported below.

In the Pfizer submission model, the cost of vision assessments was assumed to be included within a standard ophthalmology ward attendance. We believe this to be a reasonable assumption since National Reference Costs represent the average cost for such attendances, and vision assessment is expected to be performed in the majority of ophthalmology attendances. However, the costs assumed in the SHTAC model for administration and monitoring have been adopted in full in the revised analysis.

The TAR also questioned the number of administrations estimated by the Pfizer submission model in calculating drug and administration costs. The number of administrations was based on drug usage in the VISION trial and adjusted to account for treatment discontinuation due to death during the treatment period, and also the treatment discontinuation rules applied (for example when VA dropped below a threshold of 6/95 or by 6 or more lines from pre-treatment levels). We therefore believe the number of administrations estimated in the Pfizer submission model to be reasonable. However, the drug costs estimated by the SHTAC analysis have been adopted in full in the revised analysis.

The results of the revised analysis are presented in Table 3. These assume the mean cost of drug, administration and monitoring reported in Table 4.23 of the TAR. For completeness, the costs of managing adverse events and photodynamic therapy (PDT) reported in Table 4.23 were also applied.

Table 3. Results of Pfizer submission model for pre-treatment VA of 6/12 to 6/24; adopting all SHTAC treatment costs

Analysis time-frame	**2 years (no extrapolation)**			**10 years**		
	Pegaptanib	Usual Care	Incremental	Pegaptanib	Usual Care	Incremental
Costs						
Drug	£7,388	-	£7,388	£7,388	-	£7,388
Admiinistration & Monitoring	£4,107	£220	£3,887	£4,107	£220	£3,887
Management of adverse events	£98	-	£98	£98	-	£98
PDT	£404	£590	-£186	£404	£590	-£186
Services for Visually Impaired	£1,098	£2,255	-£1,157	£7,914	£12,772	-£4,858
Excess depression & fracture	£55	£59	-£4	£179	£184	-£5
Total	£13,149	£3,124	£10,026	£20,090	£13,766	£6,324
Outcomes						
Vision Years	1.59	1.34	0.25	4.10	2.85	1.25
QALYs	1.25	1.16	0.09	3.73	3.31	0.42
Incremental cost/QALY gained						
Deterministic mean		£115,035			£15,068	
Probabilistic mean; 95% CIs	£115,481	£92519 to £157706		£15,230	£11,328 to £21,423	
Probability of cost-effectiveness						
£20/000/QALY		0%			94%	
£30/000/QALY		0%			100%	

For patients with a pre-treatment VA between 6/12 and 6/24 (makes no assumption with regard to disease-modifying effect). Treatment is continued for 2 years. The cost of drug, administration and monitoring, adverse events and PDT were as reported in Table 4.23 of the TAR.

In this revised analysis, the costs of drug, administration and monitoring, management of adverse events and PDT are identical to those reported for the SHTAC analysis (Table 4.23, page 137 of the TAR). The costs associated with blindness differ because prediction of outcomes in the Pfizer submission model differs from that in the SHTAC model. Incremental costs associated with blindness over 10 years were estimated to be £4,863 less in the pegaptanib arm than the usual care arm by the revised Pfizer model, compared to £3,123 less estimated by the SHTAC model (£15,789 - £12,666, table 4.23, page 137). Incremental QALYs were estimated as 0.42 over 10 years. The ICER was estimated as £115,035/QALY (95% confidence intervals £92,519 to £157,706) over 2 years and £15,068/QALY (£11,328 to £21,423) over 10 years. The probability of cost-effectiveness over 10 years was 94% at a threshold of £20,000/QALY and 100% at a threshold of £30,000/QALY.

The deterministic sensitivity analyses performed by SHTAC (reported in Table 4.24, page 138) were repeated using the revised Pfizer submission model. The results are presented in Table A-2 (Appendix 3). The ICER estimate remained below £20,000/QALY in all analyses with the exception of: 1) time-frames of 5 years or less; 2) populations with poorer pre-treatment VA; 3) assuming a day case procedure for all administrations; and 4) all costs of blindness set to their lower limits.

Based on these analyses which address all SHTAC major concerns and accept all additional costs suggested by SHTAC, we request the 10 year IC/QALY of £15,068 from the revised Pfizer model for patients with pre-treatment VA between 6/12 and 6/24 is presented in the Executive Summary as an alternative lower estimate for the cost-effectiveness of pegaptanib.

4) Results from the ranibizumab models by SHTAC and Novartis are subject to additional uncertainty and provide contradictory conclusions that are not fully addressed

a) Significant methodological uncertainty is inherent within the ranibizumab model and this is not adequately addressed, particularly in the Executive Summary

For predominantly classic lesions, indirect comparisons between ranibizumab and Best Supportive Care (BSC) were made using data from the TAP and ANCHOR studies, which are prone to uncertainty.

The indirect comparison performed in the Novartis model appears to have been based on risk differences rather than risk ratios (TAR page 117). This methodology resulted in probabilities of less than zero or greater than 1 in some cases, which were simply truncated to a range of 0 to 1. Absolute risk differences are widely accepted to be inappropriate as a measure of treatment effect for indirect comparisons, since differences in underlying risk between the trials (arising for example from differing patient populations or definition of end-points) are not accounted for. Given the difference between the TAP and ANCHOR trial populations (for example with respect to lesion type), this methodology is clearly inappropriate.

The indirect comparison performed by SHTAC applied data reported for the subgroup of patients in the TAP trial with predominantly classic lesions in TAP Report 3.[2] No further detail of the methodology was reported; therefore Pfizer is unable to comment on the appropriateness of the methods. Since current NICE guidance recommends PDT for patients with classic no occult lesions, we presume that this comparison utilised data for patients with predominantly classic but not 100% classic lesions (i.e. 50-99% classic lesions). While SHTAC may have applied best methodological practice to the best available data, it should be noted that a great deal of uncertainty is necessarily inherent in this analysis given the available data.

- Firstly, indirect comparisons are by definition more prone to uncertainty than direct comparisons.

- Secondly, in the TAP trial patients were not stratified by lesion type,[3] the analysis of the population with 50-99% classic lesions reported in TAP Report 3 was post-hoc and specified after the main analysis, and only 39 patients with this lesion type were assigned placebo.[2] As the authors clearly state, these results should be treated with caution.[2]

- Thirdly, only 18 patients (13%) in the ANCHOR trial had classic with occult CNV present; the remainder being classic with no occult (Table 3.6 of TAR).

Therefore, there is a great deal of uncertainty in the incremental cost-effectiveness estimates for ranibizumab versus BSC in patients with predominantly classic lesions as defined by previous NICE guidance (50-99% classic).

Another potential source of uncertainty for ranibizumab is the choice of utility estimates. A sensitivity analysis was performed for the Pfizer model which demonstrated the IC/QALY results were not significantly influenced when the Novartis utility estimates were used. Although the SHTAC model employed the same utility estimates as used by the Pfizer model, there was no sensitivity analysis applied to the Novartis model to show the IC/QALY results using these selected utility estimates. However, there is an indication within the TAR that the Novartis results were sensitive to the utility estimates (TAR page 159).

The Executive Summary does not currently highlight any of these uncertainties and therefore provides a misleading level of confidence in the IC/QALY results for ranibizumab. We request it is made clear that these uncertainties exist and the impact could be to increase the IC/QALY estimates of the deterministic base case (to those shown in the Novartis model) and hence lower the probabilities of cost-effectiveness compared to those currently shown in the Executive Summary.

b) Significant differences between the Novartis and SHTAC model results are not explained

The results reported from the TAR for ranibizumab from the Novartis analysis and the SHTAC analysis are summarised in Table 4.

Table 4. Incremental cost-effectiveness estimates for pegaptanib and ranibizumab over 10 years

	Deterministic Estimate	Probabilistic Sensitivity Analysis (probability of cost-effectiveness)		Deterministic Estimate Corrected by SHTAC[1]
		£20,000/QALY	£30,000/QALY	
Minimally classic / occult (2 years of treatment)				
Novartis model, Min classic	£25,796[2]	Not reported	59%[3]	£55,906[4]
Novartis model, Occult	£26,454[5]	Not reported	57%[3]	£56,234[4]
SHTAC model	£25,098[6]	15%[7]	81%[7]	-
Classic no occult versus PDT (1 year of treatment)				
Novartis model	£4,489[8]	Not reported	100%[3]	£28,176[4]
SHTAC model	£15,638[9]	72%[10]	97%[10]	-
Predominantly classic versus BSC (1 year of treatment)				
Novartis model*	£14,781[11]	Not reported	96%[3]	£30,203[4]
SHTAC model	£11,412[12]	95%[13]	99%[13]	-

1. Drug and administration costs assumed reduced injections; efficacy data taken from trials in which 12 or 24 doses were administered with no adjustment for the impact of reduced dosing on outcomes (TAR p111-112; 114). Adjustment made for double counting of concomitant cost and inclusion of triamcinolone (classic no occult), and costs associated with sham injection (all).
2. Table 4.9 of TAR
3. TAR page 114
4. Sensitivity analysis performed by SHTAC using manufacturer's model; Table 4.11
5. Table 4.8 of TAR
6. Table 4.31 of TAR
7. TAR page 156
8. Table 4.5 of TAR
9. Table 4.29 of TAR
10. TAR page 154
11. Table 4.6 of TAR
12. Table 4.30 of TAR
13. TAR page 155

For minimally classic and occult lesion types, estimates from the Novartis analysis were in the region of £26,000/QALY and from the SHTAC analysis were approximately £25,000/QALY. However, it should be noted that the Novartis analysis made some unsubstantiated assumptions, including a reduction of the number of administrations from 24 to 14 with no adjustment to outcomes (TAR page 114), and continuation of treatment effect beyond trial end (TAR page 112). Adjustment of the Novartis analysis to include 24 injections as scheduled in the MARINA trial resulted in estimates in excess of £55,000/QALY (TAR table 4.11, page 121).

For predominantly classic lesions with PDT as a comparator (i.e. of relevance to classic with no occult lesions), the Novartis estimate was corrected from £4,489/QALY to £28,176/QALY to account for errors in the costs included and the unsubstantiated assumption for reduced injections from 12 to 8. The SHTAC analysis estimate was £15,638/QALY.

For predominantly classic lesions with BSC as a comparator (i.e. of relevance to 50-99% classic lesions as defined by previous NICE guidance), the Novartis estimate was corrected from £14,781/QALY to £30,203/QALY. The SHTAC analysis estimate was £11,412/QALY.

There are no explanations provided as to why there is such uncertainty between the estimates from the SHTAC model and the corrected Novartis model. The noted methodological uncertainty around the indirect analysis and the choice of utility could prove to be important contributory factors. We conclude that the higher IC/QALY estimates from the corrected Novartis model submission should be reported in the Executive Summary to reflect the level of methodological uncertainty in the deterministic base case estimates for ranibizumab.

5) Recent data on non-selective VEGF safety from ranibizumab randomised trials should be included to inform the risk:benefit ratio.

Correspondence to the authors for the MARINA and ANCHOR trials was recently published in the New England Journal of Medicine.[4,5] This correspondence highlighted two key issues:

1) When combined across the two trials, there is an increased rate of non-ocular haemorrhage that is statistically significantly for ranibizumab versus control.
2) The stroke incidence observed within the ranibizumab trials may be lower than expected in real-life practice due to the trial selection bias whereby subjects with existing cardiovascular disease are under-recruited.

The second point is particularly important considering the preliminary safety data released from the SAILOR trial (http://www.ashp.org/s_ashp/article_news.asp?CID=167&DID=2024&id=18443). This data shows a statistically significant higher frequency of stroke in patients who received the ranibizumab 0.5mg dose versus 0.3mg dose. This data also showed that those patients who had had a stroke at some time before receiving ranibizumab appeared to be at higher risk for another stroke.

These recent safety data should inform the risk:benefit ratio for ranibizumab as they are from randomised trials.

APPENDIX 1

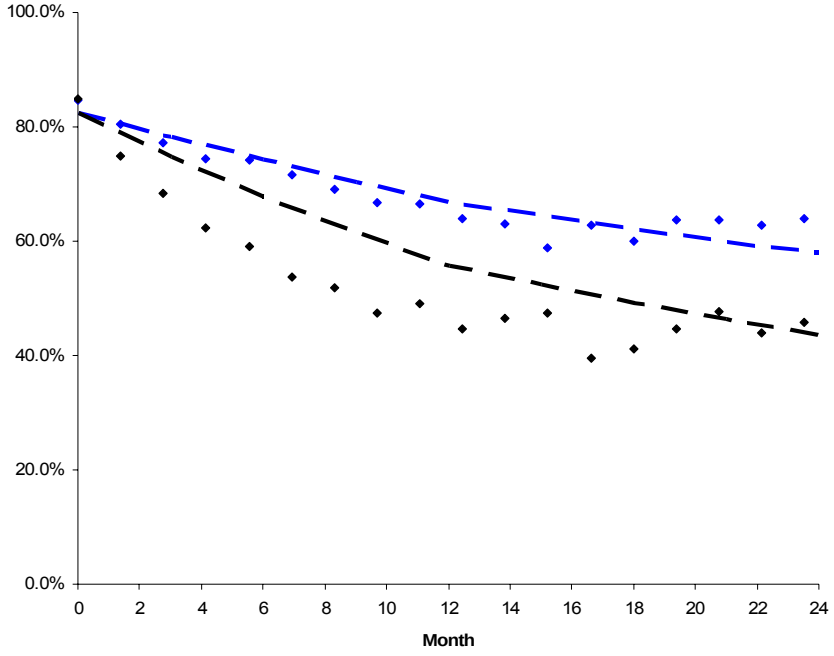
A1. Validation of early Pfizer models with respect to VISION trial data

The structure of the early Pfizer model consisted of five visual acuity states defined in the same way as the SHTAC model (Figure 4.1 of the TAR) and the dead state. The cycle length was the same as the SHTAC model (3 months). The starting VA distribution of the population was set to equal that of the VISION trial population. The allowed transitions were as described in Figure 4.1 of the TAR for the SHTAC model. In each model cycle, a patient could remain in their current state, move up by one state, or move down by one or two states, governed by transition probabilities for the gain of at least 3 lines, loss of 3 to 6 lines, and loss of at least 6 lines respectively. Patients could move to the dead state from any state in the model. Different transition probabilities were applied in year 1 and year 2 of the model.

The percentage of patients with a VA of >6/60 was calculated from the model and compared with data extracted from the VISION trial dataset. We observed that this approach resulted in very poor prediction of the trial data for the sham cohort.

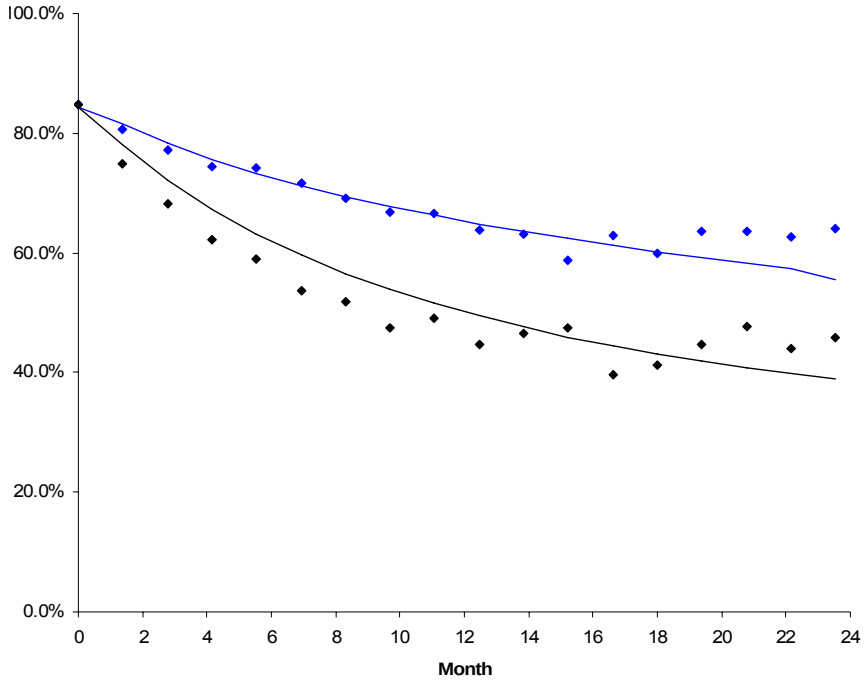
The prediction of this early model, using the probabilities applied in the SHTAC model (reported in Table 4.12 of the TAR), is compared with the VISION trial data in Figure A-1.

Figure A-1. Percentage of pateints with VA >6/60: symbols represent VISION trial data, dashed lines represent model prediction using SHTAC probabilities



This approach was abandoned in favour of an approach analogous to that adopted by Smith et al[1] in order to incorporate the time-dependence of VA change, as well as the dependence on pre-treatment VA observed by Smith et al[1]. Time-dependent transition probabilities for the loss and gain of individual Snellen lines were derived from parametric survival models fitted to patient-level data from the VISION trial. Survival models were fitted with treatment group and baseline Snellen score as covariates, and other models were fitted with the addition of age, gender, and lesion type, or lesion size. The prediction of the Pfizer submission model is compared with the VISION trial data in Figure A-2.

Figure A-2. Percentage of patients with VA >6/60: symbols represent VISION trial data, solid lines represent Pfizer submission model prediction



APPENDIX 2

A2. Calculation of QALYs over 2 years from VISION trial data

The number of patients in the VISION dataset in each of the 5 utility states defined in the SHTAC and Pfizer models over the 2-year trial period is shown in Table A-1 for patients with a pre-treatment VA of 6/12 to 6/24.

Table A-1. VISION trial data: Number of patients by Utility state; pre-treatment VA 6/12 to 6/24.

	Pegaptanib						Sham					
Week	>6/12	≤6/12 to >6/24	≤6/24 to >6/60	≤6/60 to >3/60	≤ 3/60	Total	>6/12	≤6/12 to >6/24	≤6/24 to >6/60	≤6/60 to >3/60	≤ 3/60	Total
0	0	121	41	0	0	162	0	119	39	0	0	158
6	11	87	55	3	1	157	7	71	73	3	1	155
12	14	73	59	12	1	159	7	64	67	16	3	157
18	13	73	52	10	3	151	7	48	75	22	4	156
24	13	63	62	12	5	155	7	45	64	23	10	149
30	14	63	54	15	5	151	11	44	53	29	15	152
36	10	60	57	12	10	149	3	38	59	35	15	150
42	14	50	63	18	8	153	6	38	46	36	22	148
48	9	61	53	17	9	149	7	36	50	29	26	148
54	12	54	53	22	9	150	7	35	44	33	29	148
60	10	19	26	8	3	66	2	14	19	7	11	53
66	8	21	25	9	4	67	3	10	19	8	10	50
72	8	21	21	8	3	61	4	8	18	6	15	51
78	5	21	23	12	1	62	5	9	15	9	16	54
84	7	19	19	9	3	57	5	9	14	6	12	46
90	6	19	20	14	0	59	4	10	15	9	8	46
96	11	16	20	11	1	59	5	12	12	7	14	50
102	6	20	23	11	1	61	4	11	15	10	11	51
Utility Weight	0.89	0.81	0.57	0.52	0.40		0.89	0.81	0.57	0.52	0.40	

Pegaptanib data represents patients randomised to 0.3mg in both years of the trial
Sham data represents patients randomised to sham in year 1 and sham or discontinue in year 2.

The percentage of patients in each utility state was calculated at each assessment. Patients were assumed to transition into the utility state recorded at the next assessment at the beginning of each 6-week period. The mean utility weights used in the SHTAC model (Table 4.19 of the TAR) were applied to calculate QALYs for each cohort over the 2-year period. QALYs attributable to patients in each utility state in each 6-week period were calculated as:

$$\text{QALY} = (\%\ \text{patients} / 100) \times (\text{utility weight}) \times (\text{time})$$

Where time was 6 weeks = 6/52 years.

Total QALYs in each 6-week period were calculated by summing QALYs for each utility state, and total QALYs over 2 years were calculated as the sum of these estimates for all 6-week periods.

APPENDIX 3

A3. Pfizer revised model deterministic sensitivity analysis

Table A-2. Pfizer revised deterministic sensitivity analysis (pre-treatment VA of 6/12 to 6/24)

		Incremental cost	Incremental QALYs	ICER
Reference case		£6,324	0.42	£15,068
Structural assumptions				
Time horizon (10 years)	3 years	£9,276	0.14	£64,727
	5 years	£8,023	0.24	£33,309
	8 years	£6,764	0.36	£18,697
Disease modifying effect	Year 3 only	Not Applicable, no assumption regarding disease-modifying effect is made in the reference case		
	Year 3 onwards			
Stop treatment on entering 6/60 state		£5,627	0.38	£14,816
Methodological uncertainty				
Discount rates (3.5% for costs and outcomes)	0% for cost & outcome	£5,655	0.48	£11,661
	6% for cost & outcome	£6,720	0.38	£17,615
Baseline cohort characteristics				
Age of cohort at start of simulation (75 years)	<75 years	£4,736	0.49	£9,669
	≥75 years	£7,097	0.38	£18,723
Proportion of cohort that is male (50%)	All male	£6,267	0.43	£14,639
	All Female	£6,345	0.41	£15,311
Visual acuity at baseline (6/12 to 6/24)	As VISION trial (6/12 to 6/95)	£7,640	0.33	£23,034
	6/24 to 6/60	£8,343	0.26	£31,518
Parameter uncertainty				
Number of injections	9 in Year 1 (8.4)	£6,784	0.42	£16,164
	8 in Year 2 (6.9)	£7,085	0.42	£16,882
	9 in Year 1 (8.4) and 8 in Year 2 (6.9)	£7,544	0.42	£17,975
Cost of out-patient attendance	25 percentile	£6,028	0.42	£14,363
	75 percentile	£6,624	0.42	£15,783
Cost of injection procedure	Costed as day case procedure	£10,711	0.42	£25,522
Health state utilities	Standard gamble values	£6,324	0.38	£16,427
	TTO values (Lower CI)	£6,324	0.42	£14,957
	TTO values (Upper CI)	£6,324	0.43	£14,773
Costs of blindness	High uptake/ high costs	-£1,689	0.42	Pegaptanib dominates
	Low uptake/ low costs	£10,328	0.42	£24,610
	High costs/ medium uptake	£5,364	0.42	£12,782
	Low costs/ medium uptake	£9,317	0.42	£22,201
	High uptake/ medium costs	£94	0.42	£224
	Low uptake/ medium costs	£6,880	0.42	£16,394

Deterministic sensitivity analyses performed by SHTAC (reported in Table 4.24, page 138) were repeated using the revised Pfizer submission model.

APPENDIX 4

A4.1 Pfizer response to SHTAC general concerns (p107-108)

Bullet 1

The following statement is made with regard to the Pfizer submission model "*The analysis assumes that the post-treatment effect, estimated in the first year following discontinuation of treatment can be applied for all subsequent years of model. This may overestimate the benefit associated with pegaptanib treatment*".

This statement is misleading in that it may lead readers to believe that the Pfizer submission model makes assumptions about continuation of some assumed treatment effect or post-treatment effect in the extrapolation of outcomes. No assumptions were made with regard to continuation of treatment effect. Rather, outcomes after treatment discontinuation were modelled using data describing VA change after treatment discontinuation collected within the VISION trial.

Furthermore the statement that the "*post-treatment effect, estimated in the first year following discontinuation of treatment*" is "*applied for all subsequent years of model*" implies that some "fixed effect" is propagated for the remainder of the model time-frame. This misrepresents the use of time-dependent probabilities estimated by extending the survival curves fitted to the patient-level data. In the Pfizer model, outcomes in the usual care cohort were modelled after 2 years using time-dependent probabilities estimated by extending the survival curves fitted to the patient-level data collected in the 2-year trial period. Outcomes in the pegaptanib cohort after treatment discontinuation were modelled in a similar way using survival curves fitted to 1-year follow-up data for patients in the VISION trial that discontinued treatment after 1 year. The degree of uncertainty in the extrapolation of outcomes was explored by fitting three alternative sets of survival functions to these data (exponential, Weibull and loglogistic). Thus, no assumptions were made with regard to a "disease-modifying" effect, or continuation of treatment effect after 2 years. Rather, the outcomes after treatment discontinuation observed in the VISION trial were applied, and uncertainty in the extrapolation was explored as fully as possible given the available data.

Clearly the extrapolation of outcomes beyond trial follow-up is the most important source of uncertainty in all of the analyses. However, the statement "*post-treatment effect, estimated in the first year following discontinuation of treatment*" is "*applied for all subsequent years of model*" should be revised to accurately describe the methods for extrapolation applied in the Pfizer submission model, and the analysis of uncertainty in the extrapolation.

Bullet 2

Since mortality is accounted for in the model, the fact that the model time-frame was not altered for the sub-group analysis by age would not be expected to impact on the IC/QALY estimates for the older age-group. For the younger age group, the incremental benefit and cost-offsets would be expected to be larger if the time-frame were increased. Thus, had the time-frame been altered for this sub-group analysis, a lower IC/QALY estimate would be expected for the younger age group.

The TAR should include a statement that failure to alter the analysis time-frame would be expected to result in conservative estimates of the cost-effectiveness of pegaptanib in the younger age group.

Bullet 3

The interpolation procedure used in the survival analysis is analogous to that employed by Smith et al.[1] and was appropriate in performing survival analysis using repeated measurements at specified time intervals. It is difficult to predict the impact that it may have on estimation of individual probabilities, or on the modelled outcomes resulting from the interaction of numerous sets of time-dependent transition probabilities. However, the model predictions within the first two years were carefully validated with respect to the VISION trial data and the IC/QALY estimate within the first

two years reported by the model is conservative with respect to estimates calculated directly from the trial data (Table 1 of this response).

The TAR should recognise that this validation was performed in this bullet point.

Bullet 4

The TAR should note that optical coherence tomography and fluorescein angiography are not prerequisites for pegaptanib treatment (in contrast to photodynamic therapy) since the results of these tests are not required to inform treatment decisions once therapy has been initiated. The TAR should also note that in the Pfizer submission model, the cost of vision assessments was assumed to be included within a standard ophthalmology ward attendance, since National Reference Costs represent the average cost for such attendances, and vision assessment is expected to be performed in the majority of ophthalmology attendances.

A4.2 Pfizer response to other SHTAC concerns highlighted in the TAR

P103 paragraph 1. This paragraph reports that the mean number of treatments over 2 years is lower than the number reported in the VISION trial with no explanation of why this is the case. This gives the impression that the Pfizer submission model underestimates the cost of treatment while applying the outcomes observed in the VISION trial. In fact, the number of treatments is lower in scenario A and B because these analyses apply rules for treatment discontinuation in order to reflect real-life practice with pegaptanib, and also because of deaths during the treatment period.

The reasons that the model predicts a lower number of administrations than observed in the trial should be explained in the TAR.

P104 paragraph 2. The cycle length adopted in the Pfizer submission model is criticised on the basis that it is not driven by considerations of appropriateness to the rate of disease progression. On page 115, paragraph 2 of the TAR, SHTAC make the following statement: "*the cycle length of three months is believed to be the minimum interval over which visual acuity levels are likely to alter for patients receiving these interventions*". This statement is not substantiated by a reference, and is counterintuitive for a continuous biological process. Furthermore, AMD trials making assessments at more regular intervals (for example the VISION trial [6 weekly] and the MARINA trial [4 weekly]) have reported changes in visual acuity (VA) between assessments made at shorter time-intervals than 3 months. Since data for pegaptanib were available every 6 weeks, a 6-week cycle length is appropriate in order to make best use of the data, and also enabled evaluation of alternative scenarios for treatment discontinuation within a 6-weekly dosing schedule.

Statements in the TAR regarding appropriateness of cycle length (page 104, paragraph 2; page 115, paragraph 2) should be amended to reflect the fact that VA has been observed to change over periods of 4 weeks (for example in the MARINA trial), and that longer cycle lengths are expected to model outcomes less accurately than shorter ones, particularly over shorter analysis time-frames (such as the 2-year analysis) and where no half-cycle correction is applied.

P104 paragraph 3 line 6-9. Although there is no discussion in the submission about the impact that the mapping of odds ratios for depression and fracture to VA states may have had on cost-effectiveness estimates, it is clear that since the incremental costs associated with depression and fracture are so small (less than £10) any impact of the mapping is unlikely to affect cost-effectiveness estimates. The reader is unable to draw this conclusion as the incremental costs associated with depression and fractures are not reported in the TAR.

This paragraph should include a statement to the effect that, since the incremental costs associated with depression and fractures are small, any impact of this mapping is unlikely to have an important effect on the cost-effectiveness estimates.

References

[1] Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. Br J Ophthalmol 2004 Sep;88(9):1107-12.

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[3] Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. Treatment of age-related macular degeneration with hotodynamic therapy (TAP) Study Group. Arch Ophthalmol. 1999 Oct;117(10):1329-45.

[4] Gillies MC and Wong TY. Ranibizumab for neovascular Agre-related macular degeneration. NEJM 2007; 356(7): 748.

[5] Liew G and Mitchell P. Ranibizumab for neovascular Agre-related macular degeneration. NEJM 2007; 356(7): 747-8.