Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley
Camberley
Surrey GU16 7SR

Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
London
WC1V 6NA

26th October 2012

Dear Sirs,

Re: Ranibizumab for the treatment of visual impairment due to diabetic macular oedema – Appraisal Consultation Document (Rapid Review of TA237)

Thank you for your email dated 28th September inviting comments on the Appraisal Consultation Document (ACD) and Evaluation Report for the above appraisal.

Whilst Novartis welcomes NICE's preliminary recommendation for patients with a central retinal thickness of 400 micrometres or more, we remain committed to ensuring all patients with visual impairment due to diabetic macular oedema (referred to hereafter simply as DMO) who could benefit from ranibizumab treatment receive access. We firmly believe that, taking into account the revised Patient Access Scheme (PAS), ranibizumab is a cost effective treatment option for all patients with DMO and that NICE should therefore issue positive guidance for the use of ranibizumab to treat all patients with DMO. When the further benefits to the NHS of issuing positive guidance are considered, in particular the NHS savings that would be applied to ranibizumab purchased for the treatment of wet age related macular degeneration (w-AMD) patients, the cost-effectiveness argument for the full population is overwhelming. In this response we provide our arguments to support this revision of the ACD.

NICE has requested comments on the below three questions which we have addressed in summary followed by detailed comments in Sections A-F.

1. Has all of the relevant evidence been taken into account?

Novartis do not feel all the relevant evidence has been taken into account, on three grounds:

a) Relevant data on the proportion of patients receiving treatment in the better-seeing, worse-seeing and same seeing eye have not been taken into account. In Section A, we set out alternative scenarios for the cost effectiveness of ranibizumab which take into account the impact of patients requiring bilateral treatment. We believe

this evidence would have been helpful to the Appraisal Committee's (the Committee's) deliberations in preparation of this ACD and should be considered by the Committee. These scenario analyses clearly demonstrate that the ICERs for the full DMO population discussed in the ACD are likely to be overestimated.

This evidence was not submitted as part of its initial submission for rapid review as Novartis had been advised by NICE that the rapid review process is designed to consider the implications of incorporating a PAS within the parameters of existing analyses and that Novartis was not in a position to present new analyses that relied on substantial alterations to the executable model. During a meeting with NICE on 25 January 2012, Novartis was advised against providing new evidence or analyses and, according to NICE, failure by Novartis to comply with such advice could result in rejection of its submission for rapid review. Accordingly, and in line with advice from NICE, Novartis relied on the description of the Committee's considerations in the TAG for direction as to what changes to the economic model would be acceptable within the rapid review process.

As noted by the TA237 Committee at its meeting on 4th September 2012, the analysis of the Evidence Review Group (ERG) had gone further than the rapid review process appears to allow, specifically with respect to the modeling of bilateral treatment. Had Novartis been allowed, we would also have welcomed the opportunity to provide additional analysis as detailed as that submitted by the ERG. In order to address this, Novartis have had only one opportunity (during this consultation phase as agreed with the NICE project team) to submit a revised analysis for consideration.

b) Available evidence suggests there are poorer longer-term outcomes associated with laser photocoagulation (laser) than is inferred in the ACD (ACD, Section 4.18 & 4.21). As clinical experts suggested laser may be more beneficial over time, the ACD concludes that the ICER could be higher than that estimated by the ERG (eg, £27,999+ for scenario 3) and likely to be over the £30,000/QALY threshold. However, evidence presented in section B refutes the grounds for suggesting the ICER may be higher.

c) The impact that the PAS has on use of NHS resources wider than the specific indication of DMO has not been taken into account (ACD, Section 3.45). The Committee's consideration of the significant cost savings arising from the PAS when applied across all existing ranibizumab indications does not appear to have been taken into account in the ACD. We note at paragraph 6.2.13 of the Guide to the Methods of Technology Appraisal June 2008 (the Guide) that:

'*The Institute is asked to take account of the overall resources available to the NHS when determining cost effectiveness*.'

Further, paragraph 6.2.14 of the Guide provides that:

'... The Committee does take account of how its advice may enable the more efficient use of available healthcare resources..."

We therefore urge the Committee to reconsider the evidence for ranibizumab for the treatment of DMO in light of the significant, positive impact on NHS resources associated with all current and future indications including w-AMD. This is an important feature of the technology in this appraisal that is not captured directly in the cost-effectiveness

assessment for DMO alone, and we therefore urge the Committee to reconsider its conclusions at paragraph 4.25 of the ACD in light of this.

2. <u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u>

Novartis do not feel the summary of clinical and cost-effectiveness for the whole DMO patient population considered in the ACD is a reasonable interpretation of the evidence. The main reasons are as follows:

a) **Non-reference case utility values have been used to influence interpretation of the evidence.** Utility values which were derived outside of the NICE Reference Case have greatly influenced the Committee's conclusions regarding the cost effectiveness of ranibizumab (Brown 1999). We expand upon our concerns regarding analyses that do not meet the NICE Reference Case in Section C.

b) **The glycaemic characteristics of patients in the RESTORE study are generalisable to clinical practice.** We remain concerned with the Committee's conclusion about the implications of the generalisability of the RESTORE study population to patients likely to be seen in routine NHS practice, with respect to glycaemic control. The basis of our concerns are set out in Section D.

c) **There is an invalid assessment of the innovation potential of ranibizumab.** We also remain concerned about the Committee's interpretation of the evidence with regards to the innovative nature of ranibizumab for the treatment of DMO (further details can be found in Section E).

3. <u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>

Novartis do not believe this to be the case.

The provisional guidance fails to recommend ranibizumab for all patients with DMO which does not fully take into account the evidence base. Furthermore, feedback from clinical experts suggests that the preliminary recommendation may be misinterpreted. We expand on our concern in section F.

Once again, we are grateful for the opportunity to comment on the ACD and look forward to continued dialogue with NICE regarding the issues raised in this response.

Yours sincerely,

[redacted]

Novartis believes that there are a number of points that should be given further consideration by the Appraisal Committee when interpreting the evidence:

A. Proportion of patients receiving treatment in the better-seeing eye (BSE)

We request the Committee reconsiders the cost effectiveness of ranibizumab for the treatment of the whole population with DMO. We believe the proportion of patients treated in the BSE has been misinterpreted, inflating the ICER estimates. The ERG's adaptation to the model, as accepted by the Committee in paragraph 4.15 of the ACD, calculates a weighted ICER for ranibizumab based on the proportion of patients treated in only the BSE, only the worse-seeing eye (WSE) and treated in both eyes. Also in paragraph 4.15 of the ACD, the Committee suggested that scenario 3, where 30% of the benefit of the BSE is attributable to the WSE, was '*the most reasonable reflection of the clinical situation for people with [DMO]*'.

We have taken the ERG's approach but set alternative scenarios for the cost effectiveness of ranibizumab for the full DMO population by varying the proportion of BSEs based on evidence from RESTORE. Novartis believes that the ICERs set out in this section are a more accurate reflection of the evidence and demonstrate the cost effectiveness of ranibizumab for the treatment of the full DMO population.

Further to the point raised by the Novartis representative at the Appraisal Committee meeting of 4th September, we would like to expand upon the data previously supplied to the ERG regarding the proportion of treated eyes that were better-seeing in the RESTORE study (20%). As presented in Table 1, approximately 20% of patients were treated in the BSE. However, given the definition of a clinically relevant difference in vision between eyes, a large proportion of patients in RESTORE were treated in an eye with the *same* vision as the fellow eye ('same-seeing eye'; SSE). Thus, it does not follow that if 20% of patients were treated in the BSE, the remainder were treated in the WSE. In RESTORE, 43.9% of patients were treated in either the BSE or the SSE. With regards to improvements in utility, it would seem reasonable to assume that the value attributed to improving vision in the SSE would be equivalent to that of the BSE.

Thus we wish to draw the Committee's attention to the fact that its assessment of the most plausible ICER for ranibizumab of at least £27,999 in the full DMO population is likely to be an overestimate. Following the ERG's approach of calculating a weighted ICER, but using the proportions of patients treated in the BSE described above, the ICER is substantially reduced (Table 2)[1]. Taking scenario 3, the ICER is **£21,746** assuming 44% of patients are treated in only the BSEs, 35% of patients are treated bilaterally and the remainder in only the WSE (Table 2).

If the concept of clinically relevant SSEs is ignored, the proportion of BSEs in RESTORE is greater than the 20% assumed in the ACD (32.5% treated in the BSE and 67.2% in the WSE; BSE defined as ≥ 1 letter than the fellow eye (RESTORE data on file). Taking this proportion of BSEs (32.5%) the ICER is **£24,552** under scenario 3 (Table 3).

[1] In these tables, only the WSE utility scenarios 2 to 5 have been presented for simplicity as the Committee appears to have excluded 1 and 6 as implausible; only the Czoski-Murray utilities have been used for reasons described in section B.

It is plausible that the patients with SSEs (22%) would fall into the group of patients requiring treatment bilaterally. This would bring the estimate of bilateral disease based on observational evidence (35%) closer to the RESTORE study estimate (62%; 22+35=57%). Under such assumptions, in scenario 3, the ICER is **£21,566** (Table 4).

Table 1: Definitions of BSE, WSE and SSE and the proportion of patients for whom that eye was the study eye at baseline in the RESTORE study (Bressler 2010; RESTORE data on file 2012)

Term for subject's study eye	Definition	Patients for whom that eye was the study eye, n (%)
BSE	• Both eyes have baseline visual acuity of 50 letters or more and this eye's visual acuity is greater than the other eye's by ≥5 letters. • Either eye has baseline visual acuity of less than 50 letters and this eye's visual acuity is greater than the other eye's by ≥10 letters.	72 (21.8%)
WSE	• Both eyes have baseline visual acuity of 50 letters or more and this eye's visual acuity is less than the other eye's by ≥5 letters. • Either eye has baseline visual acuity of less than 50 letters and this eye's visual acuity is less than the other eye's by ≥10 letters.	185 (56.1%)
SSE	• Both eyes have baseline visual acuity of 50 letters or more and the visual acuity of the eyes differs by <5 letters. • Either eye has baseline visual acuity of less than 50 letters, and the visual acuity of the eyes differs by <10 letters.	73 (22.1%)

Note: 50 letters is approximately equivalent to 20/100 or 6/30

Table 2: ICERs under WSE utility scenarios 2 to 5 - 44% unilateral BSE, 21% unilateral WSE, 35% bilateral treatment (Czoski-Murray utilities)

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	WSE	Bilateral	Mean	BSE	WSE	Bilateral	Mean	Net	ICER
	44%	21%	35%		44%	21%	35%			
Cost	£11,291	£10,362	£17,020	£13,110	£5,663	£2,822	£5,663	£5,064	£8,037	
QALYs										
SA2	5.088	6.263	4.911	5.274	4.700	6.207	4.466	4.936	0.338	**£23,735**
SA3	5.088	6.085	4.733	5.174	4.700	5.973	4.232	4.805	0.370	**£21,746**
SA4	5.088	5.848	4.496	5.041	4.700	5.661	3.921	4.630	0.411	**£19,535**
SA5	5.088	5.551	4.199	4.875	4.700	5.272	3.531	4.411	0.464	**£17,332**

Table 3: ICERs under WSE utility scenarios 2 to 5 - 32% unilateral BSE, 33% unilateral WSE, 35% bilateral treatment (Czoski-Murray utilities)

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	**WSE**	**Bilateral**	**Mean**	**BSE**	**WSE**	**Bilateral**	**Mean**	**Net**	**ICER**
	32%	33%	35%		32%	33%	35%			
Cost	£11,291	£10,362	£17,020	£12,990	£5,663	£2,822	£5,663	£4,725	£8,264	
QALYs										
SA2	5.088	6.263	4.911	5.414	4.700	6.207	4.466	5.115	0.299	**£27,679**
SA3	5.088	6.085	4.733	5.293	4.700	5.973	4.232	4.956	0.337	**£24,552**
SA4	5.088	5.848	4.496	5.132	4.700	5.661	3.921	4.744	0.387	**£21,338**
SA5	5.088	5.551	4.199	4.930	4.700	5.272	3.531	4.479	0.451	**£18,337**

Table 4: ICERs under WSE utility scenarios 2 to 5 - 32% unilateral BSE, 11% unilateral WSE, 57% bilateral treatment (Czoski-Murray utilities)

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	**WSE**	**Bilateral**	**Mean**	**BSE**	**WSE**	**Bilateral**	**Mean**	**Net**	**ICER**
	32%	11%	57%		32%	11%	57%			
Cost	£11,291	£10,362	£17,020	£14,454	£5,663	£2,822	£5,663	£5,351	£9,104	
QALYs										
SA2	5.088	6.263	4.911	5.116	4.700	6.207	4.466	4.732	0.384	**£23,701**
SA3	5.088	6.085	4.733	4.995	4.700	5.973	4.232	4.573	0.422	**£21,566**
SA4	5.088	5.848	4.496	4.834	4.700	5.661	3.921	4.361	0.473	**£19,253**
SA5	5.088	5.551	4.199	4.633	4.700	5.272	3.531	4.096	0.536	**£16,978**

Additional analyses of the RESTORE study were undertaken to identify the proportion of patients whose study eye was the WSE at baseline, but became the BSE at month 12 (Table 5). This was done in response to the ERG's comment in its report for this rapid review,

> '*... for the subgroups of patients in which a former WSE becomes the BSE after treatment, or in which the former BSE deteriorates to become the WSE, SA6 [100% of BSE utility gain] may be the most reasonable to assume within the current modeling framework, though this may tend to slightly overstate the overall QALY gain'* .

Table 5 presents BSE, WSE and same-seeing eyes (SSE) from the RESTORE trial at baseline and at month 12 by treatment arm. The combination therapy arm is excluded, as this is no longer relevant to the decision problem[2]. At baseline, 59.6% of patients were receiving treatment in the WSE. By month 12, this had reduced to 38.6% of ranibizumab-treated patients. Thus, as noted by the ERG, these data suggest that perhaps WSE utility scenario 4 or 5 may be more appropriate for the basecase analysis to account for the subgroup of patients in whom the WSE becomes the BSE. Referring back to Table 2, the ICER then reduces to at least **£19,535** (scenario analysis 4)**.**

Table 5: Shift table for status of the treated eye at baseline to 12 months (RESTORE safety set)

	At baseline, n (%)	At month 12, n (%)

[2] This accounts for the difference in n(%) between tables 1 and 5.

			BSE	WSE	SSE
Ranibizumab 0.5mg	BSE	29 (25.4)	24 (21.1)	1 (0.9)	4 (3.5)
	WSE	**68 (59.6)**	9 (7.9)	41 (36.0)	18 (15.8)
	SSE	17 (14.9)	8 (7.0)	2 (1.8)	7 (6.1)
	Total	114 (100.0)	41 (36.0)	**44 (38.6)**	29 (25.4)
Laser	BSE	21 (19.3)	10 (9.2)	5 (4.6)	6 (5.5)
	WSE	**65 (59.6)**	7 (6.4)	47 (43.1)	11 (10.1)
	SSE	23 (21.1)	6 (5.5)	6 (5.5)	11 (10.1)
	Total	109 (100.0)	23 (21.1)	**58 (53.2)**	28 (25.7)

Furthermore, clinical opinion supports that whilst ranibizumab-treated WSEs may become BSEs, laser-treated WSEs do not; the objective of laser is to maintain and stabilize vision, rather than to improve it. This is observed in RESTORE where 56.1% of patients in the laser group are treated in the WSE at baseline reducing to only 53.2% at month 12 (Table 5). Thus, a scenario where the ranibizumab and laser treatment arms are assumed to have different proportions of patients experiencing change from WSE to BSE over time would further reduce the ICER[3].

In summary there are 3 areas, relating to the proportion of BSEs assumed in the analysis, where Novartis considers the ICERs set out in the ACD for the full population have been overestimated. We have therefore provided alternative scenarios which the committee should consider:

1. The proportion of patients with the same BCVA in each eye are not accounted for (results in a revised ICER of **£21,746)**
2. The proportion of patients whose WSE at baseline becomes their BSE through treatment are not accounted for (results in a revised ICER of **£19,535)**
3. The difference between treatment arms in the proportion of WSEs that become BSEs are not accounted for (suggesting that these ICERs would reduce further).

In conclusion, Novartis urge the Committee to reconsider the cost effectiveness of ranibizumab for the treatment of full DMO population. The above evidence strongly supports that a plausible ICER for the full population is likely to be in the region of £21,000 rather than £27,999 as previously concluded by the Committee.

B. Long-term treatment outcomes with laser treatment

Based on clinical opinion at the time of the first Appraisal Committee meeting in February 2011, the Committee agreed that the benefits to vision from laser are believed to be maintained longer than ranibizumab (ACD, Page 54, Section 4.18). The Committee concluded that the ICER would likely increase "…*if people who had laser photocoagulation maintained any improvements in vision after treatment longer than people treated with ranibizumab*" (ACD, Page 56, Section 4.21). Two independent sources of evidence suggest that this perception is not supported:

[3] A limitation of the ERG's improvements to the cost effectiveness model to generate a weighted ICER is that the total QALY gain for treatment of the WSE is greater than the total QALY gain for treatment of the BSE. Thus, different rates of BSEs and WSEs between arms generate unintuitive results and a weighted ICER cannot be estimated.

i) In a UK RCT, the prospective BOLT study (Michaelides et al, 2010) enrolled patients with clinically significant macular oedema (CSME) diagnosed 36 months previously (median) having received a median of 3.5 laser treatments prior to study entry. This study was noted in response to the first ACD for this TA237 appraisal. BCVA in laser-treated patient decreased from a mean of 54.6 to 50.0 letters over the 12 months of the study despite having received a further 3 macular laser treatments during the study). This means an average of 6.5 lasers were given over an average of 4 years, and in the fourth year 4.6 letters were lost.

This again highlights how laser outcomes may have been overestimated in the model, and at least the longer term effectiveness assumed in the basecase is likely to be conservative[4].

ii) The DRCRnet protocol I study (2010) comparing ranibizumab plus prompt laser (laser given within 7 to 10 days of study start) with ranibizumab plus deferred laser (as required laser allowed from 24 weeks) has recently published 3 year outcomes for these 2 arms. It was observed that at 3 years the deferred laser arm, in which 54% of patients did not receive any laser (median laser treatments, 0), had a significantly greater visual acuity gain at three years compared to the prompt laser arm in which all patients received a mandatory laser treatment at baseline, and patients received a median of 3 laser treatments (BCVA gain 9.7 vs 6.8; p=0.02).

Furthermore, beyond week 16, in the prompt laser group mean BCVA decreased by 0.4 letters per year, while the deferred laser group mean visual acuity change increased by 0.7 letters per year.

This supports the hypothesis that laser has no benefit in addition to ranibizumab, and in fact may be worse in that, the longer term outcomes from laser may result in visual acuity dropping faster than that seen with ranibizumab therapy. Thus, laser and ranibizumab treatments are less likely to converge in the long term.

As a result of the DRCRnet protocol I (2010) study findings, the investigators conclude:

"The finding that the beneficial effect on visual acuity apparent within the first 6 months of treatment continued over at least 3 years of follow-up despite a steadily decreasing number of injections of ranibizumab suggests that this treatment protocol is not just transiently blocking the effects of VEGF on macular edema. Rather, the treatment may be having a more fundamental effect on the basic mechanism(s) of the disease, that is, the mechanism(s) by which VEGF is formed, secreted, or degraded or its efficiency in stimulating a response. Another possibility is that DME resulting from VEGF has a limited life span of activity and can resolve after 1 to 2 years in many cases. The anti-VEGF therapy theoretically can prevent damage during this period and then no longer is required as frequently as the production of VEGF diminishes."

[4] Drop outs between year 1 and 2 of the BOLT study mean the year 2 data are less robust.

In conclusion, as agreed with the NICE project team, we have provided evidence available since the Committee's deliberation. This indicates that the Committee's previous concerns - that the persistence of ranibizumab effect in the long term was implausible - may be unfounded.

We consider that the DRCRnet protocol I (2010) three year data confirms that the basecase assumptions in the cost effectiveness model, rather than underestimating the effectiveness of laser, may actually overestimate its effectiveness in the longer term. Novartis therefore requests that the Committee reconsider its conclusions stated in section 4.21 of the ACD that the basecase ICER would increase beyond £30,000 per QALY, in part, because the benefits of laser would be maintained for longer than ranibizumab. In light of the evidence summarised above, an ICER of £21,566 for the full DMO population (Table 4) is likely to remain below £30,000 per QALY.

C. Applying relevant utility estimates

Novartis challenges the Committee's conclusion that the most appropriate utility values fall between the two sources of Brown 1999 and Czoski-Murray 2009. This gives equal weight to both studies, whereas we believe more weight should be given to the Czoski-Murray utilities which NICE have previously used, are robustly regarded, and are aligned with the NICE Reference Case. Novartis suggests that the Brown 1999 utility estimates are not a plausible alternative base case and therefore should only be considered as a scenario analysis.

NICE's Reference Case clearly stipulates that the valuing of changes in patients' health related quality of life (HRQoL) (ie, utilities) should be based upon societal preferences of the UK general public (NICE 2008). However, the Committee has considered the ERG analyses which present utilities reported directly by visually impaired patients in the US (Brown 1999). The Committee does not clearly distinguish these from the Reference Case in the ACD, nor is the appropriateness of these non-Reference Case analyses explained (a procedural step recommended by the Guide).

As the Committee is already aware, the utilities used in the Novartis basecase for the rapid review submission, derived from the algorithm published by Czoski-Murray and colleagues, were elicited from members of the public fitted with contact lenses that simulate vision loss due to age-related macular degeneration. Utility values from this contact lens study were preferred by the Appraisal Committee in TA155 and also by the Committee in its preliminary recommendation for ranibizumab in the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (ID328) (where they were referred to as 'the Brazier utilities'). In the latter appraisal (ID328), the Czoski-Murray utility values were considered to have the added advantage of being adjusted for age; a concern previously raised by the present Committee during TA237.

The shortcomings of the contact lens study are acknowledged. However, given the well recognised limitations of the generic-preference measures in capturing the impact of visual impairment on utility, and the obvious advantage of simulation using contact lenses over descriptive vignettes, the utilities reported by Czoski-Murray would appear to be the most appropriate utilities that reflect the NICE Reference Case.

We note the Committee's specific concern that Czoski-Murray's study subjects may not have had time to fully adjust to visual impairment and therefore may have overstated the impact

on their health related quality of life. Published literature reviews of the relevant evidence have confirmed that there is an influence of the respondent group on valuations. For example, Peeters et al (2010) reported that patients give statistically significantly higher valuations than members of the general public using the time trade-off method (TTO); as also reflected in the Brown utilities being higher than those elicited by Czoski-Murray and colleagues. Whether or not the concept of adaptation should be captured in utility values is a normative question relevant across diseases and appraisals; it is not specific to this appraisal. We do not consider the shortcomings of the Czoski-Murray data to be important enough to warrant consideration of non-Reference Case analyses.

Thus, we believe that it is unhelpful to compare patient values with societal values within the ERG's Scenario Analyses 3 as the source of values will contribute additional variance in the utilities. This does not compare 'like with like' and, therefore, ignores the objective of the NICE Reference Case. Whilst we fully understand the need to consider the impact of alternative utility values in this analysis given the uncertainty, Novartis strongly requests that the Committee align with NICE methodology and recognise the appropriateness of applying utility values derived from Czoski-Murray et al 2009 to the basecase (and consider the Brown 1999 utilities as a scenario analysis only). Accordingly, we consider that the Committee's conclusion that "*the true range of utility values would probably lie in between those estimated from these 2 studies*" is not relevant as it is not evidence-based.

D. RESTORE baseline HbA1c values reflective of clinical practice

Novartis challenges the Committee's conclusions regarding glycaemic control in UK clinical practice for the following reasons:

- Based on interim baseline data from a Novartis-sponsored UK study, "Ranibizumab Treatment of Diabetic Macular Oedema with Bimonthly Monitoring After a Phase of Initial Treatment" (RELIGHT)[5], the glycaemic control levels reported in RESTORE are generalisable to the UK trial population, and were not influenced by inclusion/exclusion criteria based on HbA_{1c}. RELIGHT did not have any HbA_{1c} inclusion or exclusion criteria and reported an HbA_{1c} mean (SD) of 7.96 (1.713).

- Contrary to the Committee's conclusions, real world data from a retrospective observational study, "Prevalence of Diabetic Macular Edema (DME) in Europe: The Pan European Prevalence Assessment of DME with Visual Impairment" (PREVAIL), supports the suggestion that the UK DMO patient population with visual impairment has glycaemic control comparable to that reported in RESTORE; the mean HbA_{1c} within PREVAIL for UK patients with visual impairment due to DMO was reported as 7.8 (1.0).

Thus, the body of evidence suggests that the data from RESTORE is generalisable to UK clinical practice with respect to glycaemic control, and that the ICER for the exploratory HbA_{1c} subgroup of <8% is more relevant to the Committee's deliberations (the ERG's probabilistic estimate of £12,895/QALY). On this basis, the Committee's most plausible

[5] The RELIGHT trial is undergoing data collection for an analysis of the primary endpoint, and this is trial data from 92 patients of the 115 recruited. The remaining 23 patients have not had their data returned from the clinical trial sites at present.

basecase ICER is likely to be overestimated; a more accurate ICER for the full DMO population is well below £30,000/QALY.

E. Accounting for innovation

The Committee concluded that ranibizumab could "*not properly be considered to provide distinctive pharmacological innovation because in terms of both pharmacological progress and potential benefits for people with diabetic macular oedema, the development of the anti-angiogenic agents pegaptanib sodium and bevacizumab preceded that of ranibizumab*" (ACD, Page 59-60, Section 4.25).

As also noted the Novartis response to the TA237 ACD and in its appeal to NICE for that appraisal, Novartis does not agree that bevacizumab or pegaptanib preceded ranibizumab in terms of pharmacological progress or potential benefits:

- To our knowledge, the investigation of ranibizumab preceded bevacizumab for the treatment of DMO.
- Pegaptinib failed to demonstrate a favourable risk/benefit profile for DMO, and its license application to the EMA was withdrawn; it is unreasonable that NICE acknowledge pegaptanib as a medical innovation in this indication.
- The potential benefits to patients of bevacizumab are uncertain; the data supporting the use of unlicensed intravitreal bevacizumab in DMO are limited both in size and duration. A key uncertainty is the ocular and systemic safety profile of bevacizumab when used to treat patients with DMO, which is even more poignant given the recent SmPC amendment in Europe, health authority warnings (in France, Sweden, Finland) and communication from the Data Safety and Monitoring Committee of the IVAN study following a safety meta-analysis of the CATT and IVAN studies.
- Unlike bevacizumab, ranibizumab was specifically designed for intraocular use with low systemic exposure. This is particularly relevant for patients with DMO, already at risk of systemic adverse events.

Furthermore, the conclusions of this Committee conflict with the previous assessment of ranibizumab by NICE in wAMD where ranibizumab was regarded as a significant innovation, regardless of the development timings and potential benefits of bevacizumab and pegaptanib (TA155; Rawlins et al 2009). The rationale for these differing conclusions is not clear. We are therefore concerned that the Committee's conclusion on innovation in this appraisal unfairly prejudices ranibizumab and is unfounded.

In its response to the Kennedy Report, NICE concluded that to be considered innovative a product needs to represent a 'step change', make a significant and substantial impact on health-related benefits and improve the way a current need is met. However, we are concerned that the Committee has failed to assess fully whether ranibizumab represents a 'step change' and its important impact on health-related benefits for patients with DMO. Ranibizumab is the first and only licensed intervention for the treatment of visual impairment due to DMO. Through a full regulatory standard clinical trial programme, the health benefits to patients have been demonstrated; ranibizumab can deliver a clinically meaningful improvement in vision whereas laser generally maintains vision without improvement and is destructive to the retina.

On this basis ranibizumab clearly represents an innovative treatment. We urge the Committee to consider the cost effectiveness of ranibizumab for the full DMO population in light of this.

F. Preliminary recommendation

Based on the evidence presented in section A-E, Novartis have demonstrated that ranibizumab is cost-effective within the full DMO population. This evidence supports the argument that the ICER's stated in the ACD are in fact all overestimated. We therefore conclude that ranibizumab should be recommended as a treatment option for all patients with DMO.

In the event that the current preliminary guidance is not expanded to the full DMO population, as strongly supported by the above arguments, Novartis suggests rewording the standing text. Feedback from clinical experts suggests that the preliminary recommendation may be open to misinterpretation. To be reflective of the patient population discussed in TA237, the rapid review and the Committee's intent, Novartis suggests the following amended wording to bullet point 1.1 (in bold):

" Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- *the person has a* ***baseline*** *central retinal thickness of 400 micrometres or more*
  and

- *the manufacturer provides ranibizumab with the discount agreed as part of the patient access scheme (as revised in 2012)".*

References

Beck RW et al (2009). Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmology. 127(3):245–251.

Bressler et al (2010). Vision-related function after Ranibizumab treatment by better- or worse-seeing eye. Am Acad Ophtha. 117:747-756.

Brown GC (1999). Vision and Quality-of-Life. Tr Am Ophth Soc. 97:473-511.

Czoski-Murray C et al (2009). Valuing condition-specific heealth states using simulation contact lenses. Value in Health. 12(5):793-9.

Diabetic Retinopathy Clinical Research Network (DRCRnet). Intravitreal ranibizumab or triamcinolone acetonide in combination with laser photocoagulation for diabetic macular edema (2010). Version 6.

Diabetes UK. HbA1c Standardisation: Information for Clinical Healthcare Professionals. 2009. Accessed 18 Oct 2012. Available from: <http://www.diabetes.org.uk/Guide-to-diabetes/Monitoring/Blood_glucose/Glycated_haemoglobin_HbA1c_and_fructosamine/HbA1c_Standardisation_Information_for_Clinical_Healthcare_Professionals/?print=1>

Dirven et al (manuscript under preparation). Prevalence of Diabetic Macular Edema (DME) in Europe: The Pan European Prevalence Assessment of DME with Visual Impairment (PREVAIL) Study.

Kennedy I (2009). Appraising the value of innovation and other benefits: A short study for NICE.

McTaggart-Cowan H (2011). Elicitation of informed general population health state utility values: A review of the literature. Value in Health. 14:1153-7.

Michaelides M et al (2010). A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology. 117(6):1078-86.

NICE (National Institute for Health and Clinical Excellence) (2008). Guide to the methods of technology appraisal. June 2008.

Novartis Pharma UK (2012). Data on file. Ranibizumab Treatment of Diabetic Macular Oedema with Bimonthly Monitoring After a Phase of Initial Treatment (RELIGHT). (NCT01258205).

(Novartis Pharma UK (2009). Data on file. RESOLVE (Study D2201) Clinical Study Report. Report No.: RFB002(Ranibizumab); CRFB002D2201.

Peeters et al (2010). Health state valuations of patients and the general public analytically compared: a meta-analytical comparison of patient and population health state utilities. Value in Health. 13(2):306-9.

Rawlins et al (2009). Pharmacoeconomics: NICE's approach to decision-making. Brit J Clin Pharmacology. 70(3):346-9.