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9th March, 2015

Dear Meindert,

NICE Single Technology Appraisal (STA). Aflibercept for treating diabetic macular oedema (DMO) [ID717] - Appraisal consultation document (ACD).

Thank you for the opportunity to provide comments on the above appraisal where Novartis are a registered commentator.

Novartis welcomes the decision by NICE to approve an alternative treatment option for those patients with diabetic macular oedema and a central retinal thickness of 400 micrometres or more at the start of treatment.

The following document answers the following questions as requested by NICE – the responses for question two are provided in the order in which they are written within the ACD:

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

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

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

Yours sincerely,

[redacted]

[redacted]

[redacted] [redacted]

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

Systematic Review & Network Meta-analysis

Novartis conducted a systematic review and network meta-analysis in DMO relevant to the NICE decision problem in Q1 2014. The outputs of this work were published on July 16th in PLOSone journal[1].

The manufacturer appears not to have considered all the appropriate and relevant evidence within their network meta-analysis. Of significance and impacting the effect size of aflibercept was not including the phase II Da Vinci[2] study despite there being an appropriate aflibercept licensed 2q8 arm that informs the relative effectiveness estimates in the network. Furthermore, Novartis were not sure why other key evidence that informed the ranibizumab node (central to the decision problem) was omitted. Table 1 below highlights the evidence that was omitted from the manufacturer's network meta-analysis.

Table 1. Key evidence omitted from the manufacturer's network meta-analysis and relevant to the decision problem.

Treatment Node	Omitted Evidence
Aflibercept	Da Vinci[2]
Ranibizumab	READ-2 [3] DRCR.net (Protocol I)[4] RESOLVE[5]

In addition to the ommissions as described above, the manufacturer has chosen to include the REVEAL study[6] as part of the network to inform the relative effectiveness estimate of ranibizumab. This study evaluated ranibizumab in an *exclusively* Asian population and is thus not representative of the UK wider population. Moreover, it should not be included in this evidence network for reasons of heterogeneity of inclusion criteria compared to the other studies.

The other critical flaw in the approach adopted by the manufacturer with respect to the network meta-analysis is that of not accounting for important covariates that impact the relative effectiveness estimates. More specifically, within randomised controlled trials in the retina field, it is imperative to match the study and control arms for baseline best corrected visual acuity (BCVA). This is essential as BCVA as a measurement scale is subject to a ceiling effect – simply put the higher your baseline vision, the lower the delta from baseline would be attainable[7]. There are significant differences with respect to the aflibercept pivotal VIVID[8] & VISTA[8] studies baseline BCVA and the ranibizumab studies – specifically that the VIVID (58.8 letters) & VISTA (59.4 letters) studies have a lower baseline BCVA compared to the pivotal ranibizumab RESTORE[13] (64.8 letters) study and therefore would be more likely to have a larger mean change from baseline BCVA.

Novartis explained this critical issue in detail at the NICE scoping meeting for this appraisal and the chair agreed that this should be accounted for within the network meta-analysis. Indeed, adjustment for important disease modifiers is specifically part of the NICE reference case[15] (Section 5.2.7). The effect of this discrepancy in baseline vision was empirically adjusted for via covariate adjustment within the Novartis published network meta-analysis[1].

Of particular importance to the manufacturer's economic model was the important dichotomous outcome - the proportion of patients obtaining a gain of ≥ 10 letters. This dichotomous outcome was of specific significance threefold; firstly the manufacturer's model adopted a Markov structure with 10 letter states (page 243, Table 66 of manufacturer's submission); secondly the differences between aflibercept and ranibizumab were small and therefore most patients would be affected by transitioning to the *adjacent* Markov state rather than gaining *multiple* states; thirdly that very few patients lost vision and thus the proportion of patient *losing* ≥ 10 letters is of minor relevance. The results of the Novartis network meta-analysis, when adjusting for baseline vision for this pivotal outcome, demonstrate that ranibizumab is in fact numerically favoured, which is in fact in the opposite direction of the evidence presented within the ACD. This would therefore impact the ICER such that aflibercept would in fact be dominated[9] (less effective and costing more).

Table 2. Pair-wise odds ratios (95% credible intervals) from the random treatment effects model with baseline BVCA included as a covariate.

	Laser	Ranibizumab 0.5 mg PRN	Aflibercept 2.0 mg bi-monthly
Laser	–		
Ranibizumab 0.5 mg PRN	5.50 (2.73–13.16)*	–	**1.59 (0.61–5.37)**
Aflibercept 2.0 mg bi-monthly	3.45 (1.62–6.84)*	0.63 (0.19–1.63)	–
Ranibizumab + laser	4.05 (2.16–8.65)*	0.74 (0.35–1.46)	1.18 (0.45–3.66)
Sham	0.85 (0.19–4.56)	0.15 (0.04–0.60)*	0.25 (0.05–1.65)

*p<0.05
Pair-wise odds ratios indicate the relative treatment effect for the treatments compared in the network meta-analysis. A statistically significant odds ratio greater than 1 indicates that the treatment in the corresponding row is superior to the treatment in the corresponding column. BCVA, best-corrected visual acuity; PRN; pro re nata (as needed).

Evidence post committee meeting

Subsequent to the appraisal committee meeting (21st January 2015), an article from The Diabetic Retinopathy Clinical Research Network was published in the New England Journal of Medicine that compared the relative efficacy and safety of an unlicensed, pro re nata (PRN) posology of aflibercept (EU label is loading with 5 consecutive injections and then fixed bimonthly for the first year), unlicensed intravitreal bevacizumab, and an unlicensed dose/posology of ranibizumab. This study is known more commonly in the medical retina field as the Protocol T study[17].

This evidence for the comparison versus ranibizumab is not relevant to the decision problem and appraisal committee since the comparator arm of ranibizumab was dosed at 0.3mg PRN, which is an unapproved dose of ranibizumab in the UK – the license is for 0.5mg[10]. Indeed 0.3mg PRN is not an approved and tested posology in any other country in the world[18]. Lucentis 0.3 mg is approved in the US only for *monthly* treatment in DME[19]. Furthermore, the Protocol T study was only a partially blinded study and thus the results should be interpreted with due caution as with any non-double blinded source of evidence, and in alignment with the methodology checklist detailed in Appendix C of the NICE Guidelines Manual[14].

These critical issues notwithstanding, Protocol T demonstrates a non-clinically relevant gain of +2.1 letters with an unlicensed posology of aflibercept compared to an untested and unlicensed dose and posology of ranibizumab on the primary endpoint and therefore Novartis agrees with the already established page 19 committee conclusion on relative effectiveness and that Protocol T does not change this:

> "The Committee concluded that aflibercept is likely to have similar clinical effectiveness to ranibizumab, based on the results of the network meta-analysis and clinical expert opinion."

The provisional recommendation for aflibercept in DMO is specifically bound by the following conditions:

> *The eye has a central retinal thickness of 400 micrometres or more at the start of treatment and*
>
> *The company provides aflibercept with the discount agreed in the patient access scheme.*

In terms of the above restriction on central retinal thickness of 400 micrometres, the Protocol T study provides some very limited evidence for the comparative effectiveness of aflibercept versus unlicensed intravitreal bevacizumab, and an unlicensed dose/posology of ranibizumab in those patients for whom it is not currently provisionally recommended, i.e. those with thinner retinas of < 400 micrometres (see Table S8 Appendix, page 27 of 52); 112 patients with < 400 micrometre retinas were compared – the mean change from baseline BCVA was *similar* with all three treatments (+10.9 letters with aflibercept, +10.1 letters with an untested and unlicensed dose of ranibizumab, and +9.5 letters with unlicensed intavitreal bevacizumab). Therefore, this would have no impact on the provisional recommendation.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Page 5, Section 3.3.

The ACD states:

> "…the results showed a statistically significant improvement for **all outcomes** in both trials in people having aflibercept compared with laser."

This statement is incongruous and false as confirmed by the next sentence that follows:

> "No statistically significant differences were observed in either trial for the NEI-VFQ-25 Distance Activities subscale."

Page 7, Section 3.9.

As has been described in the preceding section of this document, the inclusion of the REVEAL[6] trial is not appropriate in the context of the NICE decision problem. This study evaluates ranibizumab in an *exclusively* Asian population and is thus not representative of the UK wider population. Moreover, it should not be included in a network for reasons of heterogeneity between the other studies inclusion criteria.

Page 7, Section 3.9.

The ACD states:

> "Results of the network meta-analysis showed a statistically significant improvement in visual acuity as measured by BCVA mean change from baseline and loss of 10 or more ETDRS letters for aflibercept 2Q8 compared with ranibizumab"

The results from the manufacturer's network meta-analysis are misleading as there has been no attempt to empirically account for the significant discrepancies with respect to baseline BCVA (important disease modifier) between the aflibercept and ranibizumab studies as stipulated in the NICE reference case[15] and agreed at the NICE scoping meeting for this appraisal. This specific issue is discussed at length in the previous section (page 2) of this document.

Page 8, Section 3.10.

Novartis notes that the assumption for fellow eye involvement at baseline of 46.5% was not derived from the aflibercept trial data and not as per TA274[12] but rather by expert opinion. The value used in a scenario analysis in TA274 was 35%. This is important since the model is very sensitive to this parameter as confirmed by the tornado plot (Figure 70) on page 316 of the manufacturer's submission.

More specifically, if one *increases* the proportion of fellow eye involvement as has been done within the present submission (by 11.5%), the incremental QALYs also *increase* and the resultant ICER being *lower*. Moreover, the manufacturer has not accounted for the value of 35% even within the lowest bound of the sensitivity analysis, which ranged from 37.2% to 55.8% (Table 76, page 263, manufacturer's submission).

Succinctly put, the net result will be a less favourable ICER than has been determined thus far verses all comparators. The ICER (page 22, Section 4.13) of significance in the key decision context is:

> "…for people with a CRT of greater than 400 micrometres was £21,958 per QALY gained"

Adjusting the level of fellow eye involvement to 35% will *increase* the ICER further into the normal willingness-to-pay threshold of £20k per QALY.

Page 10, Section 3.13.

The manufacturer underestimates the number of injections required in the first year with their technology (aflibercept) and over-inflates the number of injections requires with ranibizumab:

Underestimation:

The ACD reports that the manufacturer modelled 8 treatments with aflibercept in the first year. This assumption is misleading and incongruous with the evidence. The protocol for the VIVID/VISTA studies stipulates that this should be 9 and the actual data was 8.4 and 8.7 respectively. Novartis agrees with the ERG revision of this estimate in Section 3.2, page 14 of the ACD.

Over-inflation:

The manufacturer models ranibizumab with 7.93 injections in the 1st year together with 12 monitoring visits. Novartis concur with the comments from the ERG that the empirical methods of arriving at 7.93 are not appropriate (page 13, section 3.19).

The ACD states:

> "The company acknowledged that the summary of product characteristics for ranibizumab had recently changed to reduce the number of monitoring visits needed in the first year."

This statement is inaccurate as the summary of product characteristics for ranibizumab has indeed been revised. However, not to reduce the number of monitoring visits needed merely in the *first year* but throughout treatment[10].

> "This change was not included in the model because it was not considered by the company to be established practice in England."

The only large scale, multicenter, real-world, published evidence that Novartis are aware of that cites the monitoring frequency associated with ranibizumab based on the *original* monitoring label comes from Tufail et al. (2014)[16]. This provides data from 11,135 patients across 14 UK centres over a maximum period of 5 years. This reports a monitoring frequency in year 1 of 9.2. Novartis considers that this provides the most appropriate evidence to substantiate "established" use on this parameter and therefore the assumption of 12 is incorrect. Whilst this source of evidence is in wAMD, there is no evidence to suggest that it would differ in DMO.

Page 11, Section 3.16.

> "The company performed a scenario analysis for a subgroup of patients with CRT of greater than 400 micrometres, using the probabilities of gaining and losing ETDRS letters for the subgroup of patients in the VIVID and VISTA trials. The results showed that aflibercept dominated both laser and ranibizumab"

This analysis is invalid and misleading since the manufacturer has derived transition probabilities for aflibercept based on the > 400 micrometres data, which has a larger effect size, and compares it to transition probabilities for ranibizumab for the *full* population, which therefore results in an underestimation of the ranibizumab treatment effect in the > 400 micrometre population (this is because the < 400 micrometres population have a lower effect size).

This is therefore not relevant to the decision problem and misleading for decision makers and adopters of this guidance.

Page 13, Section 3.19.

> "The number of ranibizumab injections in the first year (7.93) may have been overestimated by the company"

Novartis agree with the ERG as previously described on the previous page of this document.

> "…company combined the mean number of injections reported in the RESTORE and REVEAL trials with the median number from the DCRC.net trial."

The abbreviation "DCRC.net" should read "DRCR.net."

It is inappropriate to over-inflate the ranibizumab injection frequency by using data from a study (DRCR.net Protocol I) that is not then part of the relative effectiveness estimate within the network meta-analysis. The manufacturer's network meta-analysis does not incorporate evidence from the pivotal DRCR.net study – please see Table 1, page 2 of this document.

> "The number of monitoring visits for ranibizumab (12) in the first year may have been overestimated because the recently revised summary of product characteristics for ranibizumab removes the need for additional hospital monitoring visits in the first year of treatment."

As previously described, this statement is inaccurate as the summary of product characteristics for ranibizumab has indeed been revised. However, not to reduce the number of monitoring visits needed merely in the *first year* but throughout treatment[10].

Page 14, Section 3.20.

> "…revising the number of ranibizumab injections to 7.43, 4.00 and 3.00 in years 1, 2 and 3"

The injection frequencies for years 2 and 3 should be 3.9 and 2.9 respectively as per the evidence published from the RESTORE extension[11].

> "…applying a discount of 3.5% to the costs of blindness"

The ACD also needs to state that the ERG amended the error whereby annual costs of blindness had been applied on a monthly basis (page 13 of ACD and page 123 of ERG report).

Page 14, Section 3.22. <u>Important.</u>

> "The results of the ERG's base-case analysis comparing aflibercept with ranibizumab showed that aflibercept dominated ranibizumab.

This statement is misleading unless the words "ranibizumab at <u>list price</u>" are inserted. The ERG analysis does not demonstrate that aflibercept dominates ranibizumab at the ranibizumab patient access scheme price – the ICER is in the North East quadrant of the cost-effectiveness plane (see ERG report & addendum).

Page 23, Section 4.16. <u>Important.</u>

> "The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It agreed that aflibercept could be considered a slight advance compared with ranibizumab because of the less frequent administration of treatment and the reduced need for monitoring."

This conclusion is incorrect. There is not "less frequent administration" as determined by the number of treatments within the evidence, as concluded by the ERG, and modelled over the three year period in the revised analysis. Please see page 14, Section 3.20 in the ACD:

Table 3. Summary of Injection Frequencies as corrected for errors identified by ERG

	Year 1	Year 2	Year 3
Ranibizumab	7.43	4	3
Aflibercept	8.5	5.45	3

There are also not any advantages for less monitoring with aflibercept – the ranibizumab label does not stipulate any specific numbers that would mean that one would monitor more frequently with ranibizumab than with aflibercept – please see precise wording from Section 4.2 of the ranibizumab SmPC[10]:

> "…monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.
>
> Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography)."

Novartis therefore requests that this statement is removed from the ACD as it is not substantiated by the facts and evidence that were presented, discussed, and critiqued by the Committee.

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

Novartis agrees that the provisional recommendations are sound and a suitable basis for guidance to the NHS.

References:

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