Aberdeen HTA Group

Aflibercept for treating diabetic macular oedema

ERG Addendum 2

Response to the Bayer proposed revised base case in response to the ACD

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This document contains the ERG response to the main revisions proposed by the company (Bayer) to the modelling of the cost effectiveness of aflibercept compared with laser for DMO in the light of the issues raised by Bayer in its comments on the ACD and its associated data appendix.

Bayer maintains that the difference between aflibercept and ranibizumab in terms of mean change in BCVA from baseline has recently been confirmed by the publication of the results of the DRCR.net Protocol T study: Bayer response under Q1 of the Bayer Data Appendix.

The DRCR.net Protocol T study compares the relative efficacy and safety of aflibercept, bevacizumab, and ranibizumab. The ranibizumab dose (0.3mg) used in the Protocol T study, however, is not that recommended in the SmPC and that used in the trials included in the indirect and mixed treatment comparisons of the company submission (0.5mg). Note that only studies assessing 2mg aflibercept and 0.5mg ranibizumab were considered suitable for inclusion in the company's NMA.

Bayer proposes that the monitoring visits for laser in year 1 should be revised from 4 to 12: Bayer response to ACD Issue 1.

The original values were based upon professional guidelines for laser and the SmPC for aflibercept. The revised value of 12 for laser is apparently based upon the frequency of monitoring visits in VIVID/VISTA with these being monthly. Within the electronic model Bayer has suggested revising the monitoring visits for aflibercept in the first year from 8 to 9, though the reasons for this revision are not given. Table 4 of the original Bayer submission suggests that VIVID/VISTA involved monthly follow-up in all arms. But it seems that few patients would, in practice, receive monthly monitoring for laser treatment. This is presumably the reason for the original Bayer submission estimating that monitoring for laser administration would be quarterly rather than monthly. There is an argument that less frequent monitoring than in the trial could lead to poorer outcomes.

REJECTED by the ERG for the base case.

Bayer proposes that the frequency of aflibercept injections in year 2 be based upon equivalence with ranibizumab and an estimate of 4.0 injections as drawn from the RESTORE trial: Bayer response to ACD Issue 2 and Bayer data appendix Issue 1 and 2.

This encompasses two changes: i) equivalence of treatment numbers with ranibizumab, and ii) applying the ranibizumab RESTORE number of 4 injections rather than the less favourable aflibercept VIVID/VISTA number of 5.45 injections. There is an argument that the number of injections within VIVID/VISTA was protocol driven and the SmPC for

aflibercept does permit the period between injections to be increased to beyond 2Q8 from the start of the second year. Dosing within RESTORE was also PRN. But the clinical effectiveness evidence relates to the dosing frequency of the trial and the ERG preference is to retain these estimates for the base case due to their alignment.

Bayer also suggests some inconsistencies in the ERG use of dosing data from the trials. The economic model requires estimates of the mean number of doses in year two among those remaining on treatment at the start of year two. This is because the model does not apply treatment administrations to those modelled as having discontinued treatment or who died. The model continues to simulate patients discontinuing throughout the second year as well, which tends to reduce the average number of injections to below the inputted value.

For patients remaining in the aflibercept 2Q8 arm at week 52, the data in the ERG report are drawn from those supplied by Bayer at clarification. Bayer did not identify this as being incorrect at error check and, therefore, the ERG still considers these as the most relevant data for estimating the number of aflibercept injections among those remaining on treatment at the state of the second year. The [redacted] injections and [redacted] injections referenced by Bayer appear to relate to the mean number during the first two years of aflibercept treatment, and so are not specific to those remaining on treatment at week 52.

The ERG report (page 101) is explicit about the ranibizumab dosing data drawn from Schmidt-Erfurth et al, which reported the results of the RESTORE extension study. The figures reported by Schmidt-Erfurth et al were different from those reported by Mitchell et al probably due to the fact that Schmidt-Erfurth et al only reported data for the 83 patients who entered the extension trial rather than those initially randomised. As a consequence, this appears to treat aflibercept and ranibizumab dosing in year 2 on a consistent basis.

Please note that Bayer have indicated that the dosing estimate for ranibizumab in the second year is based upon data to month 23. Hence, the estimate from the RESTORE extension may also be too low for the second year.

The model simulates around 10% as having ceased treatment by the end of the first year and around a further 10% having ceased treatment by the end of the second year. If Bayer wishes to apply the proposed mean estimates, these may need to be adjusted within the modelling

framework in order for the model to correctly simulate the cited mean values for year 1 and for years 1 and 2.

The Bayer data appendix appears to state that 8.55 injections in the first year is not in line with the aflibercept SmPC and also presents the results of an online survey of 10 UK ophthalmologists which suggests a mean of 6.5 aflibercept injections in the first year and 4.1 aflibercept injections in the second year[z]. The SmPC for aflibercept states:[aa]

> *Diabetic Macular Oedema*
> *The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres. Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.*
> *After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and/or anatomic outcomes. The schedule for monitoring should be determined by the treating physician.*
> *If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.*

To the ERG, on the basis of monthly dosing being 4 weekly rather than per calendar month as advised by ERG expert opinion, this suggests a fixed dosing schedule for those remaining on treatment of weeks 0, 4, 8, 12, 16, 24, 32, 40 and 48, or 9 administrations in the first year with the final injection straddling the year end. Calendar month dosing would imply 8 administrations in the first year. The 4 weekly dosing is in line with the 8.55 mean number of administrations during VIVID/VISTA where administration was 2Q8. The mean estimate of 6.5 aflibercept injections during the first year of the Bayer survey of 10 UK ophthalmologists suggests either that; the ERG has misinterpreted the SmPC; or, the 10 UK ophthalmologists anticipate a much higher discontinuation rate than was observed in VIVID/VISTA; or, a lack of familiarity with aflibercept among the 10 UK ophthalmologists that were surveyed. One of the 10 UK ophthalmologists estimated that only 3 aflibercept injections would be required during the first year. This may in turn raise a question about the reliability of the mean estimate of 4.0 aflibercept injections during the second year of the Bayer survey of 10 UK ophthalmologists.

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[z] Table 1 on page 1 of the Bayer Data Appendix
[aa] http://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/

Note that setting the monitoring visits to what Bayer took to be implied by professional guidelines and the SmPCs but applying the trial dosing for the base case does imply some inconsistency in the handling of protocol driven monitoring visits and protocol driven treatment administrations. As noted previously, there is the argument that less frequent monitoring visits may lead to a change in outcomes due to a change in treatment frequency. This seems less likely to be the case or to seriously affect outcomes compared to a change in treatment frequency.

The original ERG report did question to what degree dosing might be protocol driven, and applied 4.0 aflibercept injections in year 2 within sensitivity analyses.

REJECTED by the ERG for the base case, but included as a sensitivity analysis as per the original ERG report.

Bayer proposes using the same administration cost for laser administration and intravitreal injection: Bayer response to ACD Issue 3 and Bayer data appendix Issue 3.

The main ERG revision was to reduce the cost per laser administration from the £256 of Bayer submission to £139. Bayer is correct in stating that laser administrations are costed at the same price as intravitreal injections in the ongoing STA of dexamethasone for DMO. The submissions for fluocinolone and ranibizumab also applied the SB23Z reference cost for both intravitreal injections and laser administrations. It is plausible to assume the same administration cost for laser as for intravitreal injections: SB23Z at £194, even though the ERG's clinical advisor remains of the opinion that a laser administration is less demanding than an intravitreal administration. Note that the Bayer revised electronic model submitted in response to the ACD appears to fall back to the £256 per laser administration of the original submission rather than equating these costs.

ACCEPTED for the base case by the ERG, on the basis of the same £194 cost being used.

Bayer proposes not using the VIVID/VISTA 85% DMO baseline fellow eye involvement rate and instead using the 46% rate drawn from the Bayer survey of experts: Bayer response to ACD Issue 4and Bayer data appendix Issue 4.

The key here is that rate of fellow eye involvement is conditioned by the 50% proportion eligible for treatment. Applying this to the 85% involvement at baseline results in only 42%

of patients having a fellow eye treated at baseline. This is broadly in line with the 46% estimate presented by Bayer and the 35% estimate of TA274. This approach may have underestimated the importance of fellow eye involvement for two reasons:

- It increases the likelihood of the study eye being modelled as being the BSE, since an untreated fellow eye with DMO will deteriorate at a faster rate than a fellow eye without DMO.
- It reduces the pool for subsequent development of fellow eye DMO involvement to only 15%.

It is unclear how the Bayer estimate of 46% should be combined with the percentage of these patients who would have their eye treated. It may have been most appropriate to apply the 46% FEI and to assume that 100% would be treated.

REJECTED by the ERG for the base case, but with a sensitivity analysis of 46% at baseline and 50% treated and 46% at baseline and 100% treated.

Bayer proposes moving away from the modelling the cost effectiveness through the use of relative risks that was used for the submission, and using instead the shift tables approach: Bayer response to ACD Issue 6 and Bayer data appendix Issue 6.

The ERG report addresses a number of modelling issues and considers the possibility of using the shift tables for the comparison of aflibercept with laser:

> *The model has the facility to base the analysis upon the four weekly TPMs of the VIVID/VISTA trial. This modelling may be a sounder basis for the comparison of aflibercept with laser, and at a minimum it would seem sensible to present this as structural sensitivity analysis. The ERG has not examined this aspect of the model.*

Bayer decided to base its submission upon the relative risk modelling framework, which has been critically evaluated by the ERG, rather than the shift tables approach.

Any claim about whether the relative risk modelling framework of the submission is a better or a worse modelling framework than a shift tables modelling framework would depend upon:

- The structure of the shift tables modelling framework being rebuilt and properly cross checked by the ERG. The relative risk modelling framework used for the submission had a number of errors within it, the correction of which Bayer appears to have accepted. The shift tables approach is not guaranteed to be free from error.
- The outputs of the shift tables modelling framework being cross checked with the relevant inputs and trial data (e.g. the number of aflibercept administrations modelled, the mean numbers of letters gained modelled).
- A comparison of the outputs of the two modelling frameworks and an analysis of the reasons for any differences observed between them.
- The shift tables modelling framework may also be less reliable than the relative risks modelling framework if the patient numbers used to populate the 64 cell (8 health states by 8 health states) transition probability matrices are relatively small. While this may not apply to the all patients modelling, it may apply to subgroup modelling such as the CRT < 400μm subgroup. The shift tables of any subgroup would require an examination of the spread of patient counts across the cells of the transition probability matrices.
- A reliable implementation of probabilistic modelling. The shift tables modelling approach does not appear to be in line with NICE guidelines as there is no option of implementing the shift tables probabilistically.

REJECTED by the ERG because the shift tables approach was not the modelling framework on which the original company's submission was based upon. Therefore, the validity of the modelling using this approach and its alignment with the NICE methods guide have not been formally evaluated by the ERG.

Bayer proposes using the mortality rate from Preis et al rather than from Mulnier et al: Bayer data appendix page 3 PROPOSED AMENDED ERG BASE CASE FOR AFLIBERCPT VERSUS LASER.

As explained on page 17 of the ERG report Mulnier et al suggest a mortality multiplier of 1.93 for male diabetics and 1.77 for female diabetics compared to the general population. These are less than the 1.95 mortality multiplier for diabetics compared to the general population that Bayer proposes, as drawn from Preis et al. The starting age of the model of 63

years might suggest using the estimates from Mulnier et al of 1.84 for men and 2.44 for women.

Within the STA of ranibizumab for DMO the Mulnier et al mortality multiplier for diabetics compared to the general population was coupled with a mortality multiplier for diabetics with DMO compared to diabetics without DMO of 1.27 as drawn from Hirai et al. This resulted in an overall mortality multiplier estimate of 2.45 for diabetics with DMO compared to the general population.

The Bayer preferred mortality multiplier for diabetics compared to the general population of 1.95 of Preis et al when coupled with the 1.27 of Hirai et al would seem to suggest a slightly higher overall mortality multiplier for diabetics with DMO compared to the general population of 2.50. This would slightly worsen the cost effectiveness estimates for aflibercept, but not markedly so.

In brief, the Preis et al mortality multiplier for those with DMO compared to the general population is in line with that used to derive the overall 2.45 mortality multiplier for those with DMO compared to the general population.

REJECTED by the ERG as the proposed estimate is in line with that already used.

ERG replication of £21,718 per QALY estimate: Bayer data appendix page 3 PROPOSED AMENDED ERG BASE CASE FOR AFLIBERCPT VERSUS LASER.

The model underlying the estimates of section 5.4 of the original ERG report was supplied to Bayer. Bayer made a number of changes to this to arrive at the cost effectiveness estimate of £21,718 per QALY for aflibercept compared to laser. The changes made by Bayer have not all been documented in the Bayer data appendix. The ERG has made the following changes to the model underlying the estimates of section 5.4 of the original ERG report as supplied to Bayer, the changes to the ERG dropdowns being as per the electronic model submitted by Bayer after the ACD.

- Revised the number of monitoring visits for laser from 4 to 12 in the first year[bb] as per Bayer response to ACD Issue 1.

[bb] Implemented in the *Tx_Input* worksheet by setting cell F167=12.

- Revised the number of monitoring visits for aflibercept from 8 to 9 in the first year[cc].
- Revised the number of aflibercept injections from 8.5 to 8.55 in the first year[dd].
- Reverted to the original Bayer DMO mortality multiplier of 1.95[ee] as per Bayer data appendix page 3 PROPOSED AMENDED ERG BASE CASE FOR AFLIBERCPT VERSUS LASER.
- Reverted to the original Bayer DMO baseline percentage of 46%[ff] as per Bayer response to ACD Issue 4 and Bayer data appendix Issue 4.
- Reverted to the original Bayer £256 cost per laser administration[gg] as raised in Bayer response to ACD Issue 3 and Bayer data appendix Issue 3, though this is not entirely in line with the Bayer proposed amendment of revising this to be in line with the £194 cost per intravitreal injection.
- Revised the number of aflibercept injections from 5.45 to 4.0 in year 2 and from 3.0 to 2.3 in year 3[hh] as per Bayer response to ACD Issue 2 and Bayer data appendix Issue 1 and 2.
- Reverted to it being assumed that those blind in maintenance would still be treated[ii].
- Applied the shift tables[jj] as per Bayer response to ACD Issue 6 and Bayer data appendix Issue 6.

These changes result in a cost effectiveness estimate of £21,718 per QALY as per the revised model submitted by Bayer.

Revised ERG modelling: cost effectiveness of aflibercept versus laser

The ERG has revised the modelling to accept Bayer proposed revision to the cost of laser administration[kk]. In the following this is referred to as the second ERG revised model to distinguish it from the first ERG revised model that was used to provide the estimates of section 5.4 of the original ERG report. This revises the model to apply the same cost of

[cc] Implemented in the *Tx_Input* worksheet by setting cell C157=9.
[dd] Implemented in the *Tx_Input* worksheet by setting cell C78=8.55.
[ee] Implemented in the *ERG* worksheet by setting the drop down of cell C10 to "No".
[ff] Implemented in the *ERG* worksheet by setting the drop down of cell C15 to "No".
[gg] Implemented in the *ERG* worksheet by setting the drop down of cell C17 to "No".
[hh] Implemented in the *ERG* worksheet by setting the drop down of cells C18 andC19 to "No".
[ii] Implemented in the *Executive_Summary* worksheet by setting the Blindness treated during maintenance dropdown to "Yes".
[jj] Implemented in the *Executive_Summary* worksheet by setting the Shift Table drop down to "Yes".
[kk] Implemented in the ERG worksheet by setting the drop down of cell C39 to "Yes".

administration for laser as for intravitreal injections. Sensitivity analyses are presented which explore the impacts of addressing some of the issues raised by Bayer:

- Assume a laser administration cost of £139 as per the model of section 5.4 of the original ERG report[ll]; i.e. reversing the Bayer proposed revision to the cost per laser administration as per Issue 3 of the Bayer response to the ACD and Issue 3 of the Bayer data appendix.
- Assume only 4.0 aflibercept administrations in year 2[mm], as per the proposed revision of Issue 2 of the Bayer response to the ACD and Issues 1 and 2 of the Bayer data appendix.
- Assume 46% DMO FEI at baseline with 100% treatment of this[nn], as a half-way house to the the proposed revision of Issue 4 of the Bayer response to the ACD and Issue 4 of the Bayer data appendix.
- Assume 46% DMO FEI at baseline with 50% treatment of this[oo], as per the proposed revision of Issue 4 of the Bayer response to the ACD and Issue 4 of the Bayer data appendix.
- Assume 2.3 treatment visits for aflibercept in year 3[pp], as raised in Issues 1 and 2 of the Bayer data appendix.

Table 1: 2nd ERG revised model: NMA relative risks: All patients

	Net Cost	Net QALY	ICER
ERG revised base case	£12,626	0.381	£33,123
Laser cost £139	£12,931	0.381	£33,921
Aflibercept injections yr 2 = 4.0	£11,738	0.381	£30,793
46% FEI of which 100% treated	£14,167	0.418	£33,928
46% FEI of which 50% treated	£11,385	0.346	£32,864
Anti-VEGF injections yr 3 = 2.3	£12,256	0.381	£32,152

Revising the costs of laser improves the base case cost effectiveness estimate from £33,921 per QALY to £33,123 per QALY. The other changes examined, including the changes to aflibercept dosing as proposed by Bayer, have some impacts but they are not major.

[ll] Implemented in the Cost_Input worksheet by setting C24=£139.
[mm] Implemented in the Tx_Input worksheet by setting C78=4.0.
[nn] Implemented in the PH worksheet by setting I13=0.465 and I15=1.00.
[oo] Implemented in the PH worksheet by setting I13=0.465 and I15=0.50.
[pp] Implemented in the *Tx_Inputs* worksheet by setting cell C79=C99=2.3.

Revised ERG modelling: cost effectiveness of aflibercept versus laser: sensitivity analyses

Further sensitivity analyses are presented for the revised base case to parallel the most significant sensitivity analyses of section 5.4 of the original ERG report:

- Apply the VIVID/VISTA EQ-5D random effects bilateral quality of life function[qq].
- Apply the VIVID/VISTA EQ-5D GEE bilateral quality of life function[rr].

Table 2: 2nd ERG revised model sensitivity analyses: NMA relative risks: All patients

	Net Cost	Net QALY	ICER
ERG revised base case	£12,626	0.381	£33,123
VIVID/VISTA EQ-5D random effects QoL	£12,626	0.111	£114,050
VIVID/VISTA EQ-5D GEE QoL	£12,626	0.110	£114,463

As in the original ERG report, applying the VIVID/VISTA EQ-5D bilateral quality of life functions which significantly worsen the cost effectiveness estimates.

The ERG has also explored the impact of applying the VIVID/VISTA CRT subgroup specific relative risks and discontinuation rates to the ERG revised model in the light of Bayer ACD comments, rather than the relative risks of the NMA; i.e. applied the VIVID/VISTA relative risks for all patients, the CRT ≥ 400µm subgroup and the CRT < 400µm subgroup as per data supplied by Bayer at clarification. This modelling is as per the ERG *Critique of dexamethasone and fluocinolone economic data and additional exploratory subgroup analyses based on CRT level*[ss] document tabled at the first assessment committee meeting.

Table 3: Relative risks within the modelling

	NMA	VIVID/VISTA trial data		
	All patients	All patients	CRT ≥400µm	CRT <400µm
Gain 15 letters	3.09	3.83	[redacted]	[redacted]
Gain 10 letters	2.07	2.48	[redacted]	[redacted]
Lose 10 letters	[redacted]	[redacted]	[redacted]	[redacted]
Lose 15 letters	0.03	0.06	[redacted]	[redacted]

[qq] Implemented in the Utility_regression_models worksheet by copying the relevant values into cells D53:D57.
[rr] Implemented in the Utility_regression_models worksheet by copying the relevant values into cells D53:D57.
[ss] http://www.nice.org.uk/guidance/gid-tag472/documents/macular-oedema-diabetic-aflibercept-id717-committee-papers2

Across all patients, the VIVID/VISTA relative risks tend to suggest more patients gain letters with aflibercept than those of the NMA. Within the VIVID/VISTA data the relative risks of gaining letters within the CRT ≥ 400µm subgroup are superior to the all patients group, while for the CRT < 400µm subgroup they are inferior to the all patients group. Similarly, within the VIVID/VISTA data the relative risks of losing letters within the CRT ≥ 400µm subgroup are superior to the all patients group, while for the CRT < 400µm subgroup they are inferior to the all patients group.

Within the modelling that applies the relative risks of VIVID/VISTA, the probabilities of gaining and losing letters within the laser arm that these relative risks are applied to have also been made subgroup specific as per data supplied by Bayer at clarification.

Table 4: Monthly probabilities of gaining/losing letters for laser arm in VIVID/VISTA

	All patients	CRT ≥400µm	CRT <400µm
Gain 15 letters	0.00674	[redacted]	[redacted]
Gain 10 letters	0.01697	[redacted]	[redacted]
Lose 10 letters	[redacted]	[redacted]	[redacted]
Lose 15 letters	0.00781	[redacted]	[redacted]

It is worth noting that a number of the remaining elements of the model are not subgroup specific. For instance, the all patient relative risk of discontinuation of the company NMA has been retained for all the following analyses. Dosing as well as the number of laser administrations have also not been made subgroup specific.

Table 5: 2nd ERG revised model: VIVID/VISTA relative risks: All patients

	Net Cost	Net QALY	ICER
ERG revised base case	£12,633	0.454	£27,832
Laser cost £139	£12,938	0.454	£28,503
Aflibercept injections yr 2 = 4.0	£11,743	0.454	£25,871
46% FEI of which 100% treated	£14,176	0.495	£28,615
46% FEI of which 50% treated	£11,391	0.414	£27,514
VIVID/VISTA EQ-5D random effects QoL	£12,633	0.128	£98,670
VIVID/VISTA EQ-5D GEE QoL	£12,633	0.127	£99,119
Anti-VEGF injections yr 3 = 2.3	£12,263	0.454	£27,015

As would be anticipated, applying the relative risks of VIVID/VISTA for all patients rather than those of the NMA improves the cost effectiveness of aflibercept from £33,123 per QALY to £27,832 per QALY. As for the NMA analysis, applying the VIVID/VISTA EQ-5D bilateral quality of life functions significantly worsen the cost effectiveness estimates.

Table 6: 2nd ERG revised model: VIVID/VISTA relative risks: CRT ≥ 400µm subgroup

	Net Cost	Net QALY	ICER
ERG revised base case	£12,639	0.589	£21,442
Laser cost £139	£12,943	0.589	£21,958
Aflibercept injections yr 2 = 4.0	£11,744	0.589	£19,925
46% FEI of which 100% treated	£14,186	0.640	£22,181
46% FEI of which 50% treated	£11,396	0.541	£21,070
VIVID/VISTA EQ-5D random effects QoL	£12,639	0.162	£77,886
VIVID/VISTA EQ-5D GEE QoL	£12,639	0.161	£78,268
Anti-VEGF injections yr 3 = 2.3	£12,266	0.589	£20,809

Due to the VIVID/VISTA relative risks being somewhat better for the CRT ≥ 400µm subgroup than for all patients, the cost effectiveness within this group is also estimated to be somewhat better at £21,442 per QALY. The sensitivities are much as for the other analyses, and applying the VIVID/VISTA EQ-5D bilateral quality of life functions significantly worsen the cost effectiveness estimates.

Table 7: 2nd ERG revised model: VIVID/VISTA relative risks: CRT < 400µm subgroup

	Net Cost	Net QALY	ICER
ERG revised base case	£12,706	0.263	£48,255
Laser cost £139	£13,013	0.263	£49,421
Aflibercept injections yr 2 = 4.0	£11,818	0.263	£44,883
46% FEI of which 100% treated	£14,252	0.287	£49,585
46% FEI of which 50% treated	£11,452	0.240	£47,722
VIVID/VISTA EQ-5D random effects QoL	£12,706	0.069	£184,567
VIVID/VISTA EQ-5D GEE QoL	£12,706	0.068	£185,829
Anti-VEGF injections yr 3 = 2.3	£12,336	0.263	£46,851

Due to the VIVID/VISTA relative risks being somewhat worse for the CRT < 400µm subgroup than for all patients, the cost effectiveness within this group is also estimated to be somewhat worse at £48,255 per QALY. Once again, the sensitivities are much as for the

other analyses and applying the VIVID/VISTA EQ-5D bilateral quality of life functions significantly worsen the cost effectiveness estimates.

Summary of the revised base case of the second ERG revised model

The ERG rejects most of the changes proposed by Bayer for the base case.

The ERG accepts the revision of the cost of a laser administration to be the same as the cost of an intravitreal injection, despite ERG expert opinion still being of the opinion that a laser administration is less demanding than an intravitreal injection.

The ERG views the Bayer suggestion that the number of aflibercept injections in the second year could be the same as those observed in the RESTORE trial for ranibizumab as reasonable to consider. The SmPC for aflibercept permits extending the dosing interval to be longer than 2Q8 from the start of the second year, and dosing within the RESTORE trial was PRN. However, the VIVID/VISTA dosing is what was administered and is in line with the clinical effects observed. Therefore, the ERG maintains that the VIVID/VISTA dosing should be used for the base case. There is also the consideration, as per the ERG report, that discontinuations within the modelling have tended to artificially reduce the mean number of aflibercept doses modelled to below the inputted values.

The revision of the cost of laser has only a small effect. For the all patients NMA based analysis the cost effectiveness of aflibercept compared to laser improves from £33,921 per QALY to £33,123 per QALY. If aflibercept dosing in the second year is as per the ranibizumab RESTORE trial with only four administrations, the cost effectiveness estimate improves to £30,793 per QALY.

Summary of the additional sensitivity analyses of the second ERG revised model

A full range of sensitivity analyses has not been conducted, but of the other sensitivity analyses that have been conducted only the VIVID/VISTA EQ-5D quality of life estimates have much of an impact. These significantly worsen the cost effectiveness estimate of the NMA based analysis across all patients to around £114k per QALY.

If the relative risks and baseline risks are drawn from VIVID/VISTA rather than from the NMA, for the all patients analysis the cost effectiveness estimate improves to £27,832 per

QALY. If only four aflibercept administrations are required in the second year, the cost effectiveness estimate improves further to £25,871 per QALY. The VIVID/VISTA EQ-5D quality of life estimates worsen the cost effectiveness estimate to around £99k per QALY.

Using the VIVID/VISTA relative risks and baseline risks specific to the CRT ≥ 400µm subgroup suggests a cost effectiveness estimate of £21,442 per QALY. This improves to £19,925 if only four aflibercept administrations are required in the second year. Applying the VIVID/VISTA EQ-5D quality of life estimates worsens the cost effectiveness estimate to around £78k per QALY.

Using the VIVID/VISTA relative risks and baseline risks specific to the CRT < 400µm subgroup suggests a cost effectiveness estimate of £48,255 per QALY. This only improves to £44,883 if four aflibercept administrations are required in the second year. Applying the VIVID/VISTA EQ-5D quality of life estimates worsens the cost effectiveness estimate to around £185k per QALY