# Input from manufacturer on the 2nd draft assessment "BROLUCIZUMAB FOR THE TREATMENT OF ADULTS WITH NEOVASCULAR (WET) AGE-RELATED MACULAR DEGENERATION (AMD)"

Project ID: PTJA09

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Comments on the 2nd draft rapid assessment on Brolucizumab for the treatment of adults with neovascular (wet) age-related macular degeneration (AMD)

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment of Brolucizumab for the treatment of adults with neovascular (wet) age-related macular degeneration (AMD) was open to review by the manufacturer [Novartis] between **24/02/2020 and 28/02/2020**.

Comments received from:

| Market Authorisation Holder |
| --- |
| **Novartis** |

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from Market Authorisation Holder [Novartis]

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| 15 | Line 4 | **Text from EUnetHTA assessment:**<br>"Two systematic reviews (27, 28) that included bevacizumab as a comparator in the treatment of nAMD were identified in the literature search. Result of meta-analysis made by Solomon et al. was that bevacizumab and ranibizumab were similar in terms of vision related outcomes and numbers of adverse events among participants followed for at least one year (28). Similarly, SR written by Pham et al. (27) found no difference in vision related outcomes between bevacizumab and ranibizumab nor ranibizumab and aflibercept. Writers estimated, that mean difference between bevacizumab and aflibercept in terms of change in BCVA suggest no difference between these regimens either."<br><br>**Novartis comment:**<br>The evidence quality of ULB literature is not critically evaluated in the executive summary, thus overlooks the limitations. The authors acknowledge that the SR by Solomon et al. is a low quality review (per page 79, line 12) and the SR by Pham et al. to be of a critically low quality (per page 79, lines 18-19).<br><br>**Proposed amendment:**<br>"Two systematic reviews (27, 28) that included bevacizumab as a comparator in the treatment of nAMD were identified in the literature search. Result of meta-analysis made by Solomon et al. was that bevacizumab and ranibizumab were similar in terms of vision related outcomes and numbers of adverse events among participants followed for at least one year (28). Similarly, SR written by Pham et al. (27) found no difference in vision related outcomes between bevacizumab and ranibizumab nor ranibizumab and aflibercept. Writers estimated, that mean difference between bevacizumab and aflibercept in terms of change in BCVA suggest no difference between these regimens either. *However, the evidence quality for each of these systematic reviews was determined to be of low and critically low quality, thus the findings must be interpreted with caution*." | 1 | This comment is outside the scope of the factual accuracy check.<br><br>However, the authoring team modified this during the medical editing step that was conducted in parallel to the fact check.<br>The paragraph was updated after 2nd draft was sent to MAH and quality assessments were included in the summary. More detailed information can be found in the results section and in the appendices. |
| 43<br>60 | Line 15<br>Line 23 | **Text from EUnetHTA assessment:**<br>"The number of patients and vision-related QoL results were asked to be presented separately for patients who received treatment for the first affected eye and second-affected eye, but they were not provided separately."<br><br>"Therefore, the authoring team asked MAH to provide information about this subgroup in the scoping document request. The MAH did not provide the requested information."<br><br>**Novartis comment:**<br>Please see Page 70 of the submission file, where a response was originally included. This response | 1 | This comment is outside the scope of the factual accuracy check |

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| | | has been repeated below.<br><br>The results for vision-related QoL have not been provided separately for patients who received treatment for their first-affected eye and those who received treatment for their second-affected eye. Both worst eye VA and best eye VA have been shown to contribute independently to vision-related QOL when assessed via the NEI VFQ-25, the instrument used within the HAWK and HARRIER studies. Therefore, the effect of treating the first-affected or second-affected eye on vision-related QoL, when assessed using the NEI VFQ-25, should be considered as equally relevant.<br><br>Studies investigating vision-related QoL in nAMD have provided evidence of a strong correlation between VA in the best eye and QoL. However, both worst eye VA and best eye VA will contribute to overall QoL, with loss of binocular vision reducing QOL, due to impacts on key aspects of vision such as depth perception. It is therefore unethical to consider separate treatment approaches for each eye, or to consider withholding treatment from the first-affected eye. The withholding of treatment from an eye could also result in considerable anxiety and depression for a patient, due to the knowledge that the sight in this eye may deteriorate as a result of absence of treatment.<br><br>Initiating treatment in the first eye to present clinically is supported by high-quality European and international clinical guidelines for the treatment of nAMD, which refer to the treatment of the disease in general, and do not differentiate treatment recommendations for the first or second eye to be affected. Indeed, in the NICE appraisal of ranibizumab (TA155),[1] the NICE Committee evaluated whether "it would be appropriate to consider recommending treatment in the better-seeing eye only: that is, not to treat where patients present with only one eye affected" and the Committee noted that "it would be unacceptable, and clinically inappropriate, not to treat the first eye that comes to clinical attention".<br><br>Consequently, the number of patients and vision-related QoL results have not been presented separately for patients who received treatment for the first-affected eye and second-affected eye.<br><br>**Proposed amendment:**<br>"The number of patients and vision-related QoL results were asked to be presented separately for patients who received treatment for the first affected eye and second-affected eye, but they were not provided separately *as, aligned with the NICE Committee's appraisal of ranibizumab (TA155),[1] it would be unacceptable, and clinically inappropriate, not to treat the first eye that comes to clinical attention*"<br><br>"Therefore, the authoring team asked MAH to provide information about this subgroup in the scoping document request. The MAH did not provide the requested information *as, aligned with the* | | |

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| | | *NICE Committee's appraisal of ranibizumab (TA155),[1] it would be unacceptable, and clinically inappropriate, not to treat the first eye that comes to clinical attention."* | | |
| 46 | Line 13 | **Text from EUnetHTA assessment:**<br>"It would be essential to recognize the factors predicting dosing failure (Q8W treatment need)"<br><br>**Novartis comment:**<br>The European Medicines Agency (EMA)-approved posology wording for brolucizumab provides physicians with the flexibility to extend patients on a q8w regimen back to a q12w regimen,[2] which was not permitted in the HAWK and HARRIER trials. Therefore, this statement suggesting that q8w treatment represents dosing failure is inaccurate.<br><br>**Proposed amendment:**<br>*"It would be essential to recognize the factors predicting q12w/q8w treatment need."* | 1 | Has been re-phrased: "There is a need to recognise baseline patient characteristics predicting Q8W treatment need." |
| 46<br>68<br>91 | Line 13<br>Line 11<br>Line 33 | **Text from EUnetHTA assessment:**<br>"It would be essential to recognize the factors predicting dosing failure (Q8W treatment need)"<br><br>"Baseline characteristics were not predictive for patients maintaining on a Q12W dosing interval until week 48."<br><br>"It would be beneficial for both patient and hospital if brolucizumab treatment could be targeted to patients who are able to remain in Q12W dosing"<br><br>**Novartis comment:**<br>The above statements are contradicting, given the statement that predictive factors of dosing failure are essential, followed by the statement relating to the data that show that baseline characteristics are not predictive of patients able to be maintained on a q12w dosing interval. Data outlining that baseline factors are not predictive of q12w/q8w treatment need were provided in the submission file. In the draft REA report, the authoring team acknowledge these data (Page 68, Line 11), thus this statement appears inconsistent with the data available.<br><br>Whilst baseline characteristics are not predictive of patients able to be maintained on a q12w dosing interval and instead, in many cases patients with a higher anti-VEGF need can be identified through the signs of disease activity, as per the HAWK and HARRIER.<br>In HAWK and HARRIER, the third brolucizumab loading injection (at Week 8) was followed by a 12-week interval, to identify patients' individual anti-VEGF therapy need. During this interval, disease activity assessments (DAAs) were performed after 8 and 12 weeks. If disease activity was identified by the Investigator at either of these DAAs, the dosing interval was adjusted to q8w. Once patients were adjusted to a q8w interval, they remained on that interval until the end of the study (Week | 1 | This comment is outside the scope of the factual accuracy check.<br><br>For clarification, the first sentence has been updated as "There is a need to recognise baseline patient characteristics predicting Q8W treatment need." |

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| | | 96/Exit) and could not return to a q12w interval. The DAA criteria included: Decrease in BCVA of ≥ 5 letters compared with baseline; Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75 µm compared with Week 12; Decrease in BCVA of ≥ 5 letters due to wAMD disease activity compared with Week 12 and New or worse IRF/intraretinal cysts compared with Week 12.<br><br>Results of the HAWK and HARRIER trials demonstrated a high predictive value associated with the initial q12w cycle for patients treated with brolucizumab, with over 80% of brolucizumab 6 mg patients who successfully completed the first q12w interval remaining on q12w interval until Week 48, allowing ophthalmology clinics to plan ahead with regards to clinic capacity.<br>Among patients with no q8w need during the initial q12w cycle, the estimate of the probability for a patient to be maintained on q12w regimen up to Week 48 was 80.9% (HAWK) in the brolucizumab 3 mg arm, and 85.4% (HAWK) and 81.7% (HARRIER) in the brolucizumab 6 mg arms<br><br>**Proposed amendment:**<br>*"Factors at baseline are not predictive of q12w/q8w treatment need"* | | |
| 89 | Line 9 | **Text from EUnetHTA assessment:**<br>"Brolucizumab is a follow-up drug in anti-VEGF treatment section of nAMD.<br><br>**Novartis comment:** This statement is misleading.<br><br>**Proposed amendment:**<br>*"Brolucizumab is the latest drug licensed for the treatment of nAMD."* | 1 | This sentence has been removed |
| 89 | Line 9 | **Text from EUnetHTA assessment:**<br>"It (brolucizumab) might be considered a modified version of ranibizumab taken into account, that is part of the same antibody molecule than ranibizumab, only the single-chain component of antibody".<br><br>**Novartis comment:**<br>This statement is incorrect. Brolucizumab is not a modified version of ranibizumab.<br><br>**Proposed amendment:**<br>*"Brolucizumab is a humanised scFv inhibitor of VEGF-A for the treatment of wAMD. An scFv is an autonomous binding agent that is no longer dependent on a heavy molecular support structure and still retains full binding capacity to its target. It comprises only the variable domains of the monoclonal antibody (joined by a short flexible linker peptide) that are responsible for binding to its receptor."* | 1 | This sentence has been removed |
| 89 | Line | **Text from EUnetHTA assessment:** | 1 | These comments are outside the |

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| | 40 | "Change of retinal thickness is an intermediate outcome measure. It is only modestly correlated with changes in vision and cannot be intepreted serperately from visual acuity change or used as a substitute for visual acuity or other patient reported outcomes (63). The change in retinal thickness and correlation to visual acuity is 1 one-way: the gain in visual acuity is releted to decrese in retinal thickness but reduction in retinal thickness is not always related to gain in visual acuity, especially in late stage of nAMD disese. In HAWK and HARRIER studies, statistically significant difference was observed in the change of total CSFT between brolucizumab and aflibercept arms. CSFTtot is an intermediate outcome and therefore clinical relevance for this statistically shown difference cannot and should not be evaluated seperatly from changes in visual acuity. Clinical relevance of possible differences observed in other anatomical outcomes such as IRF, SRF, sub-RPE fluid and CNV can not be evaluated either."<br><br>**Novartis comment:**<br>This text is inaccurate and does not reflect the available literature that demonstrates the clinical relevance and importance of change in retinal thickness and its association with visual acuity. Changes in retinal thickness are a feature related to disease manifestation and are an indicator for disease activity that can be observed via OCT up to 20 days ahead of visual decline. Further evidence continues to emerge on the importance of disease control, particularly anatomical outcomes such as fluid accumulation and associated retinal thickness, and guidelines from EURETINA, NICE and AAO stipulate that retreatment should be driven by SRF/IRF on OCT scans. The importance of fluid management was demonstrated in the UK by Chakravarthy *et al.* (2020), identifying that patient eyes with at least two visits with absence of IRF or SRF demonstrated significantly higher VA gains compared with eyes with fewer clinic visits with absence of fluid.[3] These findings are supported by post-hoc analyses of the CATT and IVAN randomised controlled trials, which demonstrated that higher variation in foveal centre point retinal thickness was associated with significant reduction in measures of visual function.[4]<br><br>**Proposed amendment:**<br>"*Change of retinal thickness is correlated with changes in vision.* The change in retinal thickness and correlation to visual acuity is 1 one-way: the gain in visual acuity is *related* to *decrease* in retinal thickness but reduction in retinal thickness is not always related to gain in visual acuity, especially in late stage of nAMD *disease. A post-hoc analyses of the CATT and IVAN randomised controlled trials demonstrated that higher variation in foveal centre point retinal thickness was associated with significant reduction in measures of visual function*.[4] In HAWK and HARRIER studies, statistically significant difference was observed in the change of total CSFT between brolucizumab and aflibercept arms. *The importance of fluid management was demonstrated in the UK by Chakravarthy et al. (2020), identifying that patient eyes with at least two visits with absence of IRF* | | scope of the factual accuracy check.<br><br>However, "only" has been removed from the second sentence. |

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| | | *or SRF demonstrated significantly higher VA gains compared with eyes with fewer clinic visits with absence of fluid*.[3] | | |
| 90 | Line 23 | **Text from EUnetHTA assessment:**<br>"The presented mean changes of NEI-VFQ-25 scores from baseline at week 96 − 3.8 in brolucizumab 6mg vs 2.8 aflibercept 2mg arms in HAWK and 3.8 vs 2.6 respectively in HARRIER − suggest that the change in vision related quality of life is not clinically meaningful."<br><br>**Novartis comment:**<br>The minimal clinically important difference (MCID) of a patient-reported outcome measure (PROM) may vary depending on the patients and clinical context in which the PROM is given. Interpretation or application of MCID requires consideration of all caveats underlying the MCID, including the patients in whom it was derived and the time points used for deriving the MCID.[5, 6] Furthermore, the MCID can also vary depending on the variability of the health of the population ahead of time.[7]<br>The clinical anchor with subgroup categorized by BCVA change (≥15 letters gained, <15 letters lost or gained, or ≥15 letters lost) showed substantial difference in mean change in NEI VFQ-25 composite scores and three pre-specified subscale scores (near activities, distance activities, and vision-specific dependency) over 12 months in ANCHOR and MARINA trial.[8] Therefore, we strongly believe that the mean change in NEI VFQ-25 scores in HAWK and HARRIER from baseline at Week 48 is important for consideration (as within 12 months) for clinically meaningful change in vision-related QoL.<br><br>**Proposed amendment:**<br>"*The presented mean changes of NEI-VFQ- 25 scores from baseline at Week 48 4.1 in brolucizumab 6mg vs 4.5 aflibercept 2mg arms in HAWK and 4.8 vs 3.6 respectively in HARRIER − suggest that the change in vision related quality of life is clinically meaningful*." | | This comment is outside the scope of the factual accuracy check. |
| 90 | Line 28 | **Text from EUnetHTA assessment:**<br>"It is to emphasize that the benefit-risk balance is positive for brolucizumab 3mg also ((67)EPAR). In EPAR it is stated, that no strong evidence has been provided by the MAH to clearly support the choice of the 6mg dose instead of 3mg dose."<br><br>**Novartis comment:**<br>This statement is inaccurate. The EPAR does not detail what the authors state.<br><br>**Proposed amendment:**<br>1) remove the above statement or<br>2) replace the above statement with the factual information as it is described in the EPAR:<br>*"Uncertainties have been initially raised on the choice of the dose of 6 mg. Among the two phase III* | | In EPAR p. 115 it is stated:<br>"It is to emphasize that the benefit-risk balance is positive for both 3 mg and 6 mg doses. No strong evidence has been provided by the Applicant to clearly support the choice of the higher dose."<br>Consequently, we feel that the text in the assessment is in line with EPAR. |

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| | | *clinical studies, brolucizumab 3mg was tested in only one study (HAWK study, not tested in HARRIER). Indeed, efficacy data revealed a comparable profile for brolucizumab 3 mg and 6 mg. According to the safety data, ocular safety profile seemed to be comparable for doses 3 mg and 6 mg. Regarding, systemic safety profile, as mentioned above, there is a theoretical risk of systemic event due to pharmacological plausibility but considering confounding factors in the treated population and the low systemic exposure in case of intravitreal administration, this risk is not confirmed. Pharmacokinetic and pharmacodynamics data are reassuring at 6mg but this safety profile is also to be considered in the context of bilateral treatment which would necessitate total dose of 12 mg for which no pharmacokinetic data are available. The choice of the lower dose would be a precautionary measure but considering that the Applicant want to maintain the dose of 6mg, a close monitoring is needed in post-marketing to confirm absence of systemic AE in case of bilateral treatment."* | | |
| 91 | Line 10 | **Text from EUnetHTA assessment:**<br>"Writers estimated, that mean difference between bevacizumab and aflibercept in terms of change in BCVA suggest no difference between these regimens either, but planned NMA performed by the same authors is not published."<br><br>**Novartis comment:**<br>The discussion of this literature fails to mention the low quality of the two included reviews and makes conclusions about the difference between bevacizumab and aflibercept without performing an NMA. These conclusions seem to be based off of supposition and not founded in robust methodology, thus the findings should be interpreted with caution.<br><br>**Proposed amendment:**<br>"Writers estimated, that mean difference between bevacizumab and aflibercept in terms of change in BCVA suggest no difference between these treatments either, but planned NMA performed by the same authors is not published *thus the findings should be interpreted with caution."* | 1 | This comment is outside the scope of the factual accuracy check.<br><br>However, the authoring team has added some sentences regarding the quality of the evidence used in the JA report. |
| 46<br>93 | Line 28<br>Line 5 | **Text from EUnetHTA assessment:**<br>"According to MAH, brolucizumab is expected to have long lasting efficacy and reduced frequency of injections compared to other currently available anti-VEGF treatments. However, the trial design does not allow any conclusions to be made about treatment burden (injection frequency) between brolucizumab and aflibercept."<br><br>"Because dosing schemes were different for brolucizumab and aflibercept in HAWK and HARRIER trials, the trial design doesn't allow any conclusions to be made about treatment burden (injection frequency) between these two drugs."<br><br>**Novartis comment:** | 1 | This comment is outside the scope of the factual accuracy check. |

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| | | The HAWK and HARRIER trials demonstrated brolucizumab to be non-inferior to aflibercept in terms of BCVA from Baseline to Week 48, with a lower number of doses of brolucizumab compared with aflibercept. As highlighted in the report, the mean number of injections received from Baseline to Week 96 were 10.2 and 10.9 for brolucizumab in HAWK and HARRIER, compared with 11.3 and 12.1 for aflibercept in HAWK and HARRIER respectively.<br><br>**Proposed amendment:**<br>1) Remove the above statements, or 2) replace with: **"***Over 96 weeks, the mean number of active injections administered in the brolucizumab treatment arms of HAWK and HARRIER was between 1 and 1.5 fewer than the number administered in the aflibercept arms."* | | |
| 12<br>28 | Line 14<br>Line 23 | **Text from EUnetHTA assessment:**<br>"Both fixed-effects and random-effects models were developed and the one associated with the lowest deviance information criterion (DIC) was selected."<br><br>**Novartis comment:**<br>A random-effects model had to be at least 3 points lower than the fixed-effects model to be chosen. This extra detail should be added here for clarity.<br><br>**Proposed amendment:**<br>"Both fixed-effects and random-effects models were developed and the one associated with the lowest deviance information criterion (DIC) was selected, *unless the absolute difference between the DIC values of the two models was less than three points, them the fixed-effect model was chosen."* | 2 | Amended as proposed |
| 14 | Line 6<br>Line 11 | **Text from EUnetHTA assessment:**<br>"For the following outcomes there were some differences favouring brolucizumab: … Mean change in central retinal thickness, baseline to one year: difference in 3 of the 4 assessed dosing schemes of ranibizumab and 2 of the 2 assessed dosing schemes of aflibercept"<br><br>**Novartis comment:**<br>The results of the NMA show that there was a difference in 4 out of 4 assessed dosing schemes of ranibizumab, not 3 out of 4.<br><br>**Proposed amendment:**<br>"Mean change in central retinal thickness, baseline to one year: difference in 4 of the 4 assessed dosing schemes of ranibizumab and 2 of the 2 assessed dosing schemes of aflibercept" | 2 | Has been corrected as suggested |
| 16<br>93 | Line 32<br>Line | **Text from EUnetHTA assessment:**<br>"Indirect comparisons, based on NMA, between brolucizumab and ranibizumab showed no differences in the main outcome (mean change in BCVA) and neither in most of the other efficacy | 2 | No changes made to the report. In addition to the main outcome (mean change in BCVA), there were several |

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| | 15 | outcomes."<br><br>**Novartis comment:**<br>Favourable outcomes for brolucizumab in the change in central retinal thickness were observed.<br><br>**Proposed amendment:**<br>*"Indirect comparisons, based on NMA, between brolucizumab and ranibizumab showed no differences in the main outcome (mean change in BCVA) and neither in most of the other visual acuity outcomes. There were differences favouring brolucizumab compared to nearly all dosing regimens of aflibercept and ranibizumab in the change in central retinal thickness at one and two years."* | | other outcomes such as losing ≥15 letters (year 1 and 2), gaining ≥ 15 letters (year 1 and 2), mean change in CRT (year 1 and 2), and treatment discontinuation. CRT was the only outcome where differences were shown in most of the dosing schemes of both ranibizumab and aflibercept. This is in line with our statement "…and neither in most of the other efficacy outcomes". |
| 23 | Line 30 | **Text from EUnetHTA assessment:**<br>"The PICO selected for the SLR differed from the PICO proposed in the project plan."<br><br>**Novartis comment:**<br>PDT with verteporfin, laser photoagulation therapy, pegaptanib, and macular surgeries were included as comparators in the SLR in case they helped connect the networks with ranibizumab, aflibercept, and brolucizumab. Otherwise these studies were excluded from the indirect comparisons.<br><br>**Proposed amendment:**<br>*"The PICO selected for the SLR differed from the PICO proposed in the project plan to help identify any additional studies that may assist in connecting the networks."* | 2 | No changes made. The main difference was that PICO for SLR conducted by MAH did not include bevacizumab as a comparator. In EUnetHTA project plan the comparators were aflibercept, ranibizumab and bevacizumab. |
| 31 | Line 13 | **Text from EUnetHTA assessment:**<br>"Outcomes related to anatomical parameters of disease activity (Table 3) (except central retinal thickness) are not listed on inclusion/exclusion criteria on MAH (Table 4)."<br><br>**Novartis comment:**<br>Other anatomical outcomes were not included as corresponding evidence from other studies were absent. As such, the remaining anatomical results from HAWK and HARRIER are reported in the clinical evidence section but not assessed through an NMA.<br><br>**Proposed amendment:**<br>"Outcomes related to anatomical parameters of disease activity (Table 3) (except central retinal thickness) are not listed on inclusion/exclusion criteria for on MAH *due to absence of corresponding evidence (i.e. IRF/SRF) from other studies*." | 2 | This comment is outside the scope of the factual accuracy check.<br><br>However, the authoring team has rephrased this sentence because it was incorrectly expressed. |

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| 43 | Line 1 | **Text from EUnetHTA assessment:**<br>"Six patients were lost to follow-up in HAWK study and 4 patients in HARRIER study."<br><br>**Novartis comment:**<br>The timepoint of assessment for loss to follow-up should be reported here.<br><br>**Proposed amendment:**<br>"*At Week 48,* six patients were lost to follow-up in HAWK study and 4 patients in HARRIER study". | 2 | Thank you for clarification. These numbers were taken from submission dossier, fig 7 and fig 8 where the time of analysis was not mentioned. For the final version we have updated the numbers of week 96 analysis which are available in CSRs. |
| 46 | Line 8 | **Text from EUnetHTA assessment:**<br>"It means that brolucizumab can be used as second or third line treatment even without clinical evidence."<br><br>**Novartis comment:**<br>Clarification in the text required.<br><br>**Proposed amendment:**<br>"It means that brolucizumab can *also* be used as second or third line treatment even without clinical evidence." | 2 | Has been amended as proposed. |
| 47 | Line 5 | **Text from EUnetHTA assessment:**<br>"The authoring team requested MAH to provide pooled results of HAWK and HARRIER studies. MAH answered that pooled results were not available. However, as part of NMA, MAH provided some pooled results of key outcomes. These included only mean differences for fixed and random effects models, which are presented in Appendix 8."<br><br>**Novartis comment:**<br>Pooled results for all outcomes are not available for HAWK and HARRIER. Each CSR and publication details the results separately. Pooling data across the two trials would not facilitate the cross-validation of results versus the CSR. However, the direct comparisons pooled the treatment effects for HAWK and HARRIER to help identify and heterogeneity between the trials.<br><br>**Proposed amendment:**<br>"The authoring team requested MAH to provide pooled results of HAWK and HARRIER studies. MAH answered that pooled results were not available. However, as part of NMA, *the direct comparisons pooled the treatment effects for HAWK and HARRIER to help identify and heterogeneity between the trials*. These included only mean differences for fixed and random effects models, which are presented in Appendix 8." | 2 | This comment is outside the scope of the factual accuracy check |

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| 59 | Line 7 | **Text from EUnetHTA assessment:**<br>"Additional secondary endpoint, proportion of subjects maintained on the Q12W regimen up to the disease activity assessment at week 44, with 95% CI in the brolucizumab 6mg arm in HAWK and HARRIER studies, were 55.6% (50.1, 60.7) and 51.0% (45.6, 56.1), respectively. So, almost half of the patients only could remain on the Q12W regimen through the first year."<br><br>**Novartis comment:**<br>51.0% and 55.6% equate to over half of patients.<br><br>**Proposed amendment:**<br>"Additional secondary endpoint, proportion of subjects maintained on the Q12W regimen up to the disease activity assessment at week 44, with 95% CI in the brolucizumab 6mg arm in HAWK and HARRIER studies, were 55.6% (50.1, 60.7) and 51.0% (45.6, 56.1), respectively. So, *more than* half of the patients only could remain on the Q12W regimen through the first year." | 2 | For the final version this sentence has been updated as suggested by medical editor:<br>"…only approximately half of the patients could remain on the Q12W regimen through the first year." |
| 60 | Line 21 | **Text from EUnetHTA assessment:**<br>"Data on HRQoL was requested from MAH, but they informed that HRQoL data measured by a generic tool was not available. Only vision related quality of life data was presented using the NEI VFQ-25 instrument"<br><br>**Novartis comment:**<br>HRQoL data measured via a generic tool were not collected in the HAWK/HARRIER studies, given the well documented lack of sensitivity to changes in visual function associated with generic HRQoL instruments.[9] Vision-related QoL were collected via the NEI VFQ-25 instrument, a validated vision-related QoL tool.<br><br>**Proposed amendment:**<br>"Data on HRQoL was requested from MAH, but they informed that HRQoL data measured by a generic tool was not *included in the studies due to the well documented lack of sensitivity to changes in visual function*. Only vision-related quality of life data was presented using the NEI VFQ-25 instrument". | 2 | This comment is outside the scope of the factual accuracy check. |
| 69 | Figure 4.17 | **Text from EUnetHTA assessment:**<br>Figure 4.17. Proportion of patients maintained of Q12W dosing interval until week 48 (FAS)<br><br>**Novartis comment:**<br>This figure is incorrect, and does not refer to the predictability of the initial q12w dosing cycle.<br><br>**Proposed amendment:**<br>Figure 4.17 to be replaced by Figure 24 from the MAH submission file: *Figure 24: Proportion of* | 2 | The figure is correct and no changes are made for the final version. In the text above the figure it is indicated that the table refers to the "Proportion of patients maintained on Q12W dosing interval until week 48 by baseline characteristics". We are not discussing the predicting value of the initial Q12W |

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| | | *patients who successfully completed the first q12w interval remaining on the q12w interval until Week 48, by Baseline characteristics (FAS).* | | cycle. |
| 75<br>77 | Table 4.25a<br>Table 4.25b | **Text from EUnetHTA assessment:**<br>"OR <1 favours brolucizumab, MD >1 favours brolucizumab"<br><br>**Novartis comment:**<br>Incorrect interpretation of NMA results reported.<br><br>**Proposed amendment:**<br>*"OR >1 favours brolucizumab, MD <1 favours brolucizumab"* | 2 | This has been checked and corrected. |
| 75 | Line 8 | **Text from EUnetHTA assessment:**<br>"However, compared to the following treatment options, brolucizumab had greater odds of losing at least 15 letters"<br><br>**Novartis comment:**<br>Incorrect interpretation of the results presented. This statement refers to gaining at least 15 letters.<br><br>**Proposed amendment:**<br>"However, compared to the following treatment options, brolucizumab had greater odds of *gaining* at least 15 letters" | 2 | This has been corrected. |
| 76 | Line 2<br>Line 8 | **Text from EUnetHTA assessment:**<br>"There was a difference observed between brolucizumab 6mg and aflibercept as well as brolucizumab 6mg and ranibizumab for mean change in retinal thickness at one year"<br>"There was a difference observed between brolucizumab 6mg and nearly all comparators for mean change in retinal thickness at two years."<br><br>**Novartis comment:**<br>It is not mentioned that the difference is in favour of brolucizumab.<br><br>**Proposed amendment:**<br>"There was a difference observed *in favour of brolucizumab 6mg when compared to all dosing regimens of aflibercept 2 mg and ranibizumab 0.5 mg for mean change in retinal thickness at one year*"<br><br>"There was a difference observed *in favour of brolucizumab 6mg when compared to* nearly all comparators for mean change in retinal thickness at two years." | 2 | This comment is outside the scope of the factual accuracy check. |
| 76 | Table | **Text from EUnetHTA assessment:** | 2 | This seems to be related to comment |

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| | 4.25b | Mean change in CRT, Baseline to 1 year for for LP→Rani 0.5TREX versus brolucizumab 6 mg q8w/q12w: -57.86 [-89.88, -25.87]"<br><br>**Novartis comment:**<br>Mean change in CRT, Baseline to 1 year for LP→Rani 0.5TREX versus brolucizumab 6 mg q8w/q12w should be in **bold** as the difference is significant (see values above).<br><br>**Proposed amendment:**<br>*"-57.86 [-89.88, -25.87]"* | | on page 14, line 11 and it has been corrected accordingly. |
| 77<br>91 | Line 9<br>Line 23 | **Text from EUnetHTA assessment:**<br>"However, different dosing schemes can't be compared with each other in terms of injection frequency."<br><br>"The same flaw applies to other treatment options included in the NMA: the different dosing schemes can not be compared with each other in terms of injection frequency"<br><br>**Novartis comment:**<br>An NMA for injection numbers using a regimen-based approach was not conducted as the number of injections was directly related to the type of regimen. For this reason, regimen-based pooling approach, similar to that described in the NICE Guidelines for age-related macular degeneration (NICE NG82-Appendix J), was used to estimate the injection frequency. Table 38 in Appendix J and Tables 48 and 49 in the report present similar estimations showing that this method allows an accurate estimation of dosing schemes in terms of injection frequency.<br><br>**Proposed amendment:**<br>*"Despite different treatment regimens, injection frequencies can be compared across studies using regimen-based pooling approach".* | 2 | No changes made. In principle, we agree with what is stated in the comment. The number of injections is directly related to the type of regimen.<br><br>Consequently, we consider that comparing different dosing schemes (e.g. fixed vs. flexible or Q4W vs. Q8W) in terms of injection frequency could be misleading. Even if studies having same dosing regimen can be pooled to estimate the mean number of injections for each regimen, the problem is the comparison of different regimens. |
| 90 | Line 37 | **Text from EUnetHTA assessment:**<br>"No differences were observed for the main outcome (mean change in BCVA), as well as most of the other outcomes."<br><br>**Novartis comment:**<br>Differences were observed between brolucizumab and several comparators for patients gaining and losing at least 15 letters, and between brolucizumab and nearly all comparators for change in retinal thickness. This statement can be made clearer to reflect the results of the NMA. | 2 | No changes made to the report. In addition to the main outcome (mean change in BCVA), there were several other outcomes such as losing ≥15 letters (year 1 and 2), gaining ≥ 15 letters (year 1 and 2), mean change in CRT (year 1 and 2), and treatment discontinuation. CRT was the only |

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| | | **Proposed amendment**:<br>"No differences were observed for the main outcome (mean change in BCVA), as well as most of the other outcomes *except change in retinal thickness*." | | outcome where differences were shown in most of the dosing schemes of both ranibizumab and aflibercept. This is in line with our statement "… as well as most of the other outcomes ". |
| 91 | Line 23 | **Text from EUnetHTA assessment:**<br>"The same flaw applies to other treatment options included in the NMA"<br><br>**Novartis comment:**<br>Wording suggests a mistake or defect, as opposed to a limitation, which is more appropriate. The current wording would suggest the method of regimen-based pooling adopted in NICE Guidance 82,[10] and in the NMA submitted by Novartis, is an error as opposed to being subject to limitations, which would be a more appropriate contextualization.<br><br>**Proposed amendment:**<br>The word flaw to be changed to *limitation.* | 2 | "flaw" has been changed to "limitation" |
| 136 | Appendix 9 | **Text from EUnetHTA assessment:**<br>(B) Detailed questions, 2. Search strategy. "References were not checked and publication bias was not evaluated. Thus, reliability is low."<br><br>**Novartis comment:**<br>Novartis propose that the reliability of the search strategy used in the SLR should be noted as acceptable, given a robust search strategy and multiple databases were used. Reliability was called into question partly for not evaluating publication bias. However, following EUnetHTA guidelines, the quality rating tool developed by the Cochrane Collaboration (version 5.1.0; March 2011) was used to assess the risk of bias. This EUnetHTA approved tool does not account for publication bias. It is important to note that only the additional AMSTAR-2 tool used by the authoring team accounts for publication bias.<br><br>**Proposed amendment:**<br>Quality rating to be reflected as *acceptable*. | 2 | This comment is outside the scope of the factual accuracy check. |
| 136 | Appendix 9 | **Text from EUnetHTA assessment:**<br>(B) Detailed questions, 3. Criteria for selection of studies. "Reliability acceptable"<br><br>**Novartis comment:**<br>Novartis consider the reliability for the selection of studies is high as the reasons for exclusion were stated and applied systematically. The eligibility criteria were based on the PICOs defined in the | 2 | This comment is outside the scope of the factual accuracy check.<br><br>However, the authoring team has clarified the judgement in the table. |

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| | | protocol.<br><br>**Proposed amendment:**<br>Change 'acceptable' to *'high*'. | | |
| 137 | Appendix 9 | **Text from EUnetHTA assessment:**<br>(B) Detailed questions, 10 "Missing patient/data" "Reliability low"<br><br>**Novartis comment:**<br>It would be more appropriate to denote this as reliability uncertain, rather than low, given the impact is unknown.<br><br>**Proposed amendment:**<br>Change 'low' to '*uncertain*'. | 2 | This comment is outside the scope of the factual accuracy check |
| 138 | Appendix 9 | **Text from EUnetHTA assessment:**<br>(B) Detailed questions, 15. Answer this question only if there is a published direct comparison of the treatments being compared: Is there inconsistency? Are results from direct and indirect comparisons different? "Not applicable"<br><br>**Novartis comment:**<br>In the networks, inconsistency was measured between HAWK and HARRIER as direct and indirect evidence was available for brolucizumab 6mg and aflibercept 2mg in HAWK. No inconsistency was identified, and the results from the direct and indirect comparisons were similar.<br><br>**Proposed amendment:**<br>*"No, thus reliability high"* | 2 | This comment is outside the scope of the factual accuracy check |
| 14<br>90 | Line 20<br>Line 41 | **Text from EUnetHTA assessment:**<br>"These include assuming equivalence between some treatments in a specific situation".<br><br>**Novartis comment:**<br>Equivalence between treatments was not assumed within the NMA, but rather between dosing regimens of the same treatment.<br><br>**Proposed amendment:**<br>"These include assuming equivalence between *the dosing regimens at Year one and Year two for the treatments in VIEW 1&2*." | 3 | Has been updated accordingly |
| 31 | 23 | **Text from EUnetHTA assessment:**<br>"Flow chart results do not suit with hits showed in the search history appendix." | 3 | This comment is outside the scope of the factual accuracy check. |

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| | | **Novartis comment:**<br>This is due to the fact that the PRISMA is a combination of both the original search as well as the update.<br><br>**Proposed amendment:**<br>*Remove this sentence from the report.* | | Even though the MAH indicated that PRISMA flowchart is a combination of the original search as well as the updated search, the authoring team cannot verify it with provided data on the submission file. |
| 31 | 25 | **Text from EUnetHTA assessment:**<br>"Misspelling on search strategies and search fields missing in some strategy lines."<br><br>**Novartis comment:**<br>To our knowledge, there appear to be no empty search fields in the reported search strategies.<br><br>**Proposed amendment:**<br>"Misspelling on search strategies." | 3 | The authoring team has not modified the sentence based on MAH comments.<br>In the search strategies from the different databases there are search lines in whose syntax there are no specific fields in which to search. The information specialist understands that this can be the case because the MAH chose to "map" the term in all the fields available in the databases. However, when transferring search strategies from one database to another, the mapping of terms in the same concepts is not used. As a result, we derive that no search fields are used in some of the strategy lines. |
| 42 | Line 23 | **Text from EUnetHTA assessment:**<br>"Withdrawal by subject was also the main reason for study (3.2% brolucizumab, 5.7 aflibercept) or study treatment (2.7% brolucizumab, 5.4% aflibercept) discontinuation."<br><br>**Novartis comment:**<br>Percentage symbol is missing for withdrawal by subject for aflibercept.<br><br>**Proposed amendment:**<br>"*5.7%* aflibercept" | 3 | Percentage symbol has been added for the final version. |
| 48 | Line 1<br>Line 7 | **Text from EUnetHTA assessment:**<br>"In HAWK study, regarding FAS population, the mean change in BCVA from baseline at week 48, for brolucizumab 6mg was 6.6…" | 3 | Has been updated for the final version |

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| | | "In HARRIER study, regarding FAS population, the mean change in BCVA from baseline at week 48, with, for brolucizumab 6mg was 6.9…"<br><br>**Novartis comment:**<br>The results presented here for the mean change in BCVA are the *LS mean change* and should be reported as such.<br><br>**Proposed amendment:**<br>"In HAWK study, regarding FAS population, the *LS* mean change in BCVA..."<br><br>"In HARRIER study, regarding FAS population, the *LS* mean change in BCVA..." | | |
| 48 | Line 8 | **Text from EUnetHTA assessment:**<br>"In HARRIER study, regarding FAS population, the mean change in BCVA from baseline at week 48, with, for brolucizumab 6mg was 6.9 [95% CI 5.7, 8.1] and for aflibercept 2mg and 7.6 [95% CI 5.7, 8.1] letters."<br><br>**Novartis comment:**<br>Incorrect 95% CI values reported.<br><br>**Proposed amendment:**<br>"In HARRIER study, regarding FAS population, the *LS* mean change in BCVA from baseline at week 48, ~~*with,*~~ for brolucizumab 6mg was 6.9 [95% CI 5.7, 8.1] and for aflibercept 2mg and 7.6 [95% CI *6.4, 8.8*] letters." | 3 | CI has been corrected |
| 48 | Line 10 | **Text from EUnetHTA assessment:**<br>"In pairwise ANOVA, the non-inferiority (4 letter margin) of brolucizumab 6mg compared to aflibercept 2mg was demonstrated with a LS mean difference of -0.7 (95% CI -2.4,1.0; P<0.0001)."<br><br>**Novartis comment:**<br>Incorrect p-value reported.<br><br>**Proposed amendment:**<br>(95% CI -2.4,1.0; *P=0.0001)*. | 3 | p-value has been corrected |
| 54 | Table 4.13 | **Text from EUnetHTA assessment:**<br>LS mean change in CSFTtot (µm) from Baseline to Week 48, HAWK, aflibercept 2 mg: -143.6<br>LS mean difference in CSFTtot (µm) from Baseline to Week 48, HAWK, between brolucizumab 6 mg and aflibercept 2 mg: -29.0 (-43.1,-4.6)<br>p-value for treatment difference (2-sided) Week 48, HAWK: 0.0012<br>p-value for treatment difference (2-sided), HARRIER: <0.001.- | 3 | Data has been checked and updated accordingly (based on CSRs) |

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| | | **Novartis comment:**<br>Incorrect values reported.<br><br>**Proposed amendment:**<br>LS mean change in CSFTtot (µm) from Baseline to Week 48, HAWK, aflibercept 2 mg: -143.6<br>LS mean difference in CSFTtot (µm) from Baseline to Week 48, HAWK, between brolucizumab 6 mg and aflibercept 2 mg: -29.0 *(-47.6, -10.4)*<br>p-value for treatment difference (2-sided) Week 48, HAWK: *0.0023*<br>p-value for treatment difference (2-sided) Week 48, HARRIER: *<0.0001* | | |
| 58 | Table 4.15 | **Text from EUnetHTA assessment:**<br>Proportion of subjects with sub-retinal fluid at week 16 and week 48.<br>Proportions with presence of SRF at week 16, HARRIER, aflibercept 2 mg: 34.4<br>Difference (95% CI for difference), HAWK Brolucizumab 6 mg and aflibercept 2 mg: -10.4 (-16.8,-3.7)<br>p-value for treatment difference at Week 16 (2-sided), HAWK, brolucizumab 6 mg and aflibercept 2 mg: 0.0012 .<br><br>**Novartis comment:**<br>Incorrect values reported.<br><br>**Proposed amendment:**<br>Proportions with presence of SRF at week 16, HARRIER, aflibercept 2 mg: *35.5*<br>Difference (95% CI for difference) row, HAWK Brolucizumab 6 mg and aflibercept 2 mg: *-19.7 (-25.8, -13.4)*<br>p-value for treatment difference at Week 16 (2-sided), HAWK, brolucizumab 6 mg and aflibercept 2 mg: *<0.0001* | 3 | Data has been checked and updated accordingly (based on CSRs) |
| 61 | Table 4.17 | **Text from EUnetHTA assessment:**<br>Mean change in VFQ-25 composite scores from baseline, in HAWK and HARRIER studies<br>Week 96, HARRIER, brolucizumab 6 mg: (n=370)<br><br>**Novartis comment:**<br>Incorrect value reported.<br><br>**Proposed amendment:**<br>Mean change in VFQ-25 composite scores from baseline, in HAWK and HARRIER studies<br>Week 96, HARRIER, brolucizumab 6 mg: *(n=338)* | 3 | Data has been checked and corrected accordingly based on CSRs. |

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| 62 | Line 17 | **Text from EUnetHTA assessment:**<br>"Intraocular inflammation (endophthalmitis, uveitis and vitritis) were more frequent in brolucizumab 6mg groups − 6 (0.17%) in HAWK and 4 (0.11%) in HARRIER − than in aflibercept 2mg groups − 0 (0%) and 1(0.3%), respectively."<br><br>**Novartis comment:**<br>Incorrect values reported.<br><br>**Proposed amendment:**<br>"Intraocular inflammation (endophthalmitis, uveitis and vitritis) were more frequent in brolucizumab 6mg groups − 6 *(1.7%)* in HAWK and *5 (1.4%)* in HARRIER − than in aflibercept 2mg groups − 0 (0%) and *3 (0.8%),* respectively" | 3 | Data has been checked and corrected accordingly based on CSRs. |
| 62 | Line 22 | **Text from EUnetHTA assessment:**<br>"Deaths were not suspected to be related to study treatment by the Investigator in HARRIER".<br><br>**Novartis comment:**<br>No deaths were considered to be related to study treatment by the Investigator in both HAWK and HARRIER. This should be made clear.<br><br>**Proposed amendment:**<br>"Deaths were not suspected to be related to study treatment by the Investigator in *HAWK and* HARRIER". | 3 | Text checked and updated. |
| 63 | Table 4.19 | **Text from EUnetHTA assessment:**<br>Serious ocular adverse events up to week 96 by preferred term for the study eye<br>Retinal artery occlusion row, HARRIER, brolucizumab 6 mg: 1 (0.0)<br><br>**Novartis comment:**<br>Incorrect value reported.<br><br>**Proposed amendment**<br>Serious ocular adverse events up to week 96 by preferred term for the study eye<br>Retinal artery occlusion row, HARRIER, brolucizumab 6 mg: 1 *(0.3)*. | 3 | Data has been checked and updated accordingly. |
| 64 | Table 4.20 | **Text from EUnetHTA assessment:**<br>Non-ocular adverse events up to week 96 Pneumonia brolucizumab 6mg: "HAWK"<br><br>**Novartis comment:**<br>Text "HAWK" reported instead of correct value. | 3 | Data has been checked and updated accordingly. |

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| | | **Proposed amendment:**<br>Non-ocular adverse events up to week 96 Pneumonia brolucizumab 6mg: *32 (8.9)*. | | |
| 71 | Table 4.24 | **Text from EUnetHTA assessment:**<br>LSM estimates for change of central subfield thickness (CSFT, µm) from baseline at 12 weeks 12, 40 and 56.<br>Aflibercept 2 mg: -178.77 (15.53)<br>Difference 80% CI: -5.72 (-33.15, 21.70)<br>Week 40 p-value: 0.7881<br><br>**Novartis comment:**<br>Incorrect value reported.<br><br>**Proposed amendment**:<br>Aflibercept 2 mg: *-178.29 (16.70)*<br>Difference 80% CI: *-19.17 (-49.86, 11.52)*<br>Week 40 p-value: 0.7881: *0.4221*. | 3 | Data has been checked and updated accordingly (based on CSRs). |
| 74 | Line 5 Line 13 Line 14 Line 19 | **Text from EUnetHTA assessment:**<br>"mean difference 16.87; 95% CI 13.37-20.41 at one year and 21.21; 95% CI 17.46-24.99 at 5 two years"<br>"odds ratio 0.07; 95% CI 0.03-0.18"<br>"odds ratio 0.29; 95% CI 0.08-0.95"<br>"odds ratio 0.11; 95% CI 0.05-0.23"<br><br>**Novartis comment:**<br>The CI listed should be re-written as *CrI*, as the data correspond to credibility intervals from the NMA using a Bayesian framework.<br><br>**Proposed amendment:**<br>"mean difference 16.87; 95% *CrI* 13.37-20.41 at one year and 21.21; 95% *CrI* 17.46-24.99 at 5 two years"<br>"odds ratio 0.07; 95% *CrI* 0.03-0.18"<br>"odds ratio 0.29; 95% *CrI* 0.08-0.95"<br>"odds ratio 0.11; 95% *CrI* 0.05-0.23" | 3 | All "95% CI" phrasing related to NMA have changed to "95% CrI". |
| 75 | Table 4.25a | **Text from EUnetHTA assessment:**<br>Patient losing at least 15 letters, baseline to 1 year, OR[b] [95% CrI]. LP→Rani 0.5q8: 0.11 [0.0, 2.09]<br><br>**Novartis comment:**<br>Incorrect value reported. | | Has been corrected. |

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| | | **Proposed amendment**:<br>Patient losing at least 15 letters, baseline to 1 year, OR[b] [95% CrI]. LP→Rani 0.5q8: 0.11 [*0.2*, 2.09] | | |
| 75 | Lines 10-13<br>Line 17 | **Text from EUnetHTA assessment:**<br>"- sham IVT (odds ratio 10.99; 95% CI 5.47-23.43)<br>- ranibizumab: dosing scheme LP -> 0,5mg Q12W (odds ratio 7.57: 95 % CI 1.89-30.06)<br>- ranibizumab: dosing scheme 0,5mg PRN (odds ratio 1.74: 95 % CI 1,07-2.84)<br>- brolucizumab LP -> 3mg Q12W/Q8W (odds ratio 1.37: 95 % CI 1.01-1.86)"<br>"odds ratio 16.06; 95% CI 7.47-37.99"<br><br>**Novartis comment:**<br>The CI listed should be re-written as *CrI*, as the data correspond to credibility intervals from the NMA using a Bayesian framework.<br><br>**Proposed amendment:**<br>"- sham IVT (odds ratio 10.99; 95% *CrI* 5.47-23.43)<br>- ranibizumab: dosing scheme LP -> 0,5mg Q12W (odds ratio 7.57: 95 % *CrI* 1.89-30.06)<br>- ranibizumab: dosing scheme 0,5mg PRN (odds ratio 1.74: 95 % *CrI* 1,07-2.84)<br>- brolucizumab LP -> 3mg Q12W/Q8W (odds ratio 1.37: 95 % *CrI* 1.01-1.86)"<br>"odds ratio 16.06; 95% *CrI* 7.47-37.99" | 3 | All "95% CI" phrasing related to NMA have changed to "95% CrI". |

[i] Character of comment
- 'major'=1
- minor'= 2

'linguistic'=3