# Peer Review File

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**Reply to the reviewers' comments**

| | Original comments of the reviewer | Reply by the author(s) | Changes |
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| Reviewer 1 | 1. Remove "the" before "Age-Related Macular Degeneration" in the title | Thanks for this comment. We have modified our text as advised. | Line 1 |
| Reviewer 1 | 2. Line 51: Bevacizumab is already widely used off label, I would not say it is "becoming widely used off label" | Thanks for this comment. We have modified our text as advised. | Lines 48 and 49 |
| Reviewer 1 | 3. Line 57: should say "interlocks" | Thanks for this comment. We have modified our text as advised. | Line 55 |
| Reviewer 1 | 4. Line 73: "Thus, demands the attention of all 74 eye care providers" is not a complete sentence | Thanks for this comment. We have modified as "Thus, it demands the attention of all 74 eye care providers." | Line 71 |
| Reviewer 1 | 5. Line 77-78: Did you mean "preclinical" instead of "paraclinical" and "grading system" instead of "gardening sytem"? | Thanks for this comment. We mean "paraclinical findings" techniques or findings that are not purely clinical but may be related, such as those of OCT or other imaging.<br><br>We have corrected the "grading system" in the text. | Line 76 |
| Reviewer 1 | 6. Line 97: "presence of" or "appearance of" would sound better than "Showing up of" | Thanks for this comment. We have modified our text as advised. | Line 99 |

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| Reviewer 1 | 7. Line 101: “the length of time that AMD is presented” could be rephrased “duration of AMD” | Thanks for this comment. We have modified our text as advised. | Line 103 |
| Reviewer 1 | 8. Line 115: should be “imbalance” | Thanks for this comment. We have modified our text as advised. | Line 117 |
| Reviewer 1 | 9. Line 116: should be “serous” | Thanks for this comment. We have modified our text as advised. | Line 118 |
| Reviewer 1 | 10. Line 153: I would not called bevacizumab a “less expensive anti-VEGF alternative”, but rather a “ less expensive anti-VEGF treatment” | Thanks for this comment. We have modified our text as advised. | Line 160 |
| Reviewer 1 | 11. Line 154: “Several” should be lower case | Thanks for this comment. We have modified our text as advised. | Line 161 |
| Reviewer 1 | 12. You should add that the PANDA trial results from the USA, in the conbercept description | Thank you. We added “PANDA-1 and PANDA-2 are phase 3, randomized, quadruple-masked, multi-centered trials that assess three arms: 0.5 mg conbercept, 1.0 mg conbercept, and 2.0 mg aflibercept. The study's primary objective is the mean change in BCVA after 36 weeks. The results of this study are expected to be available by the end of 2021 (40, 41)” | Lines 172-175 |
| Reviewer 1 | 13. Line 168: why did you include the word “presumably” – what is presumed? | Based on some studies mentioned in reference 43, like the HOBBY study (NCT04047472), the efficacy of brolucizumab 3 x q4w up to Week 8 followed by q12w injections vs. aflibercept 3 x q4w up to Week 8 followed by q8w is under evaluation and the final results have not been published, so we used "presumably" in this sentence. | |
| Reviewer 1 | 14. Earlier you mention faricimab as an anti-VEGF option, even though it is not FDA | Thank you. We added “Faricimab is another anti-VEGF agent. In addition to targeting VEGF-A, faricimab also | Lines 179-184 |

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| | approved yet, but then later on do not mention any of the AMD clinical trial results such as AVENUE, STAIRWAY, LUCERNE, TENAYA, | targets the Ang-Tie/pathway, making it a potentially beneficial bispecific medication. Phase II STAIRWAY and AVENUE trials demonstrated clinical effectiveness in the treatment of w-AMD, while the phase II BOULEVARD trial demonstrated superiority to monthly ranibizumab in the management of DME when administered on a monthly basis (as opposed to every three months). Faricimab is now pending FDA approval to treat nAMD and DME (44)." | |
| Reviewer 1 | 15. Line 191: What is PBS? Define it | Thank you. In the referenced study, phosphate-buffered saline (PBS) was used as a sham treatment. So we have modified it as " In a mouse model of corneal neovascularization, abicipar at a dose range of 8 mg/kg/day for 9 days reduced neovascularization by 84% as compared to the sham treatment." | Lines 204-206 |
| Reviewer 1 | 16. Line 192: What is "intervention mode" | Thank you. In the referenced study, to evaluate abicipar antiangiogenic effect in the corneal model, mice were given 8 mg/kg intraperitoneal abicipar daily for 11 days in the preventive paradigm (day 1 to day 9) or 10 days in the intervention model (day 14 to day 23). The study showed that in both modes, abicipar suppressed neovascularization. We have changed our text as "In addition, mice were given 8 mg/kg intraperitoneal abicipar daily for 11 days in the prevention mode (day 1 to day 9) or 10 days in the intervention model (day 14 to day 23); in both modes, abicipar suppressed vascular growth (47)." | Lines 207-209 |
| Reviewer 1 | 17. Line 203: "Incidence" should be "incident" | Thanks for this comment. We have modified our text as advised. | Line 219 |
| Reviewer 1 | 18. Line 222: "BAMBO" should be "BAMBOO" | Thanks for this comment. We have modified our text as advised. | Line 238 |

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| Reviewer 1 | 19. Line 240: Include the name of the phase 2 trial, "MAPLE". Also include this trial in the table | Thanks for this comment. We have modified our text as advised. | Line 255<br><br>Table 1<br>Line 272<br><br>Table 2<br>Line 280 |
| Reviewer 2 | 1. The term 'neovascular AMD' (abbrev nAMD) is preferred to 'wet AMD'. | Thanks for this comment. We have modified our text as advised. | |
| Reviewer 2 | 2) The written language could be improved in several places in the manuscript. A few examples will be provided below. | Thanks for this comment. We have modified our text as advised. | |
| Reviewer 2 | 1) The Methods section needs to be updated with more detail, which should include the starting (as well well end date) of the included search (e.g. Jan 1998?). Inclusion and exclusion criteria should be clearly stated. | Thank you. We have edited the method section as "The electronic databases PubMed, Medline, and Scopus were searched for relevant papers. In order to guarantee that the scope of the study was as broad as feasible, all scientific articles published in English between January 1970 and June 2020 were chosen. When an English abstract of a non-English work was available, it was used. Registered trials were also checked https://clinicaltrials.gov, https://www.cochranelibrary.com, and https://who.int. The utilized keywords were including "age-related macular degeneration", "dry age-related macular degeneration", "wet age-related macular degeneration", "Abicipar", "Anti-VEGF therapy", "choroidal neovascularization", "vascular endothelial growth factor", and their combinations." | Lines 90-97 |
| Reviewer 2 | 2) Line 106: are these nutrients 'micro' or 'macro'? | Thanks for this comment. We have corrected it to micronutrients | Line 108 |

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| Reviewer 2 | 3) Line 115: replace ‘unbalance’ with ‘imbalance’ | Thanks for this comment. We have corrected our text as advised. | Line 117 |
| Reviewer 2 | 4) Lines 116-7: sentence requires revision | Thank you. We have changed it as “If bleeding and serous exudation into the macula are not controlled, fibrosis and scar formation occur, resulting in diminished central vision” | Lines 118 and 119 |
| Reviewer 2 | Lines 120-1: the sentence requires revision. The role of laser photocoagulation needs to be appropriately contextualised. Similarly, PDT needs to be discussed appropriately. | Thank you. We revised it as “ANCHOR study showed photodynamic therapy (PDT) provided lower clinical benefits than ranibizumab in patients with age-related macular degeneration with new-onset, predominantly classic CNV (16). However, PDT has been employed as a second-line treatment option in nonresponder nAMD patients and an adjuvant treatment to enhance anti-VEGF effects. The results of a case series showed that five of eight nonresponder eyes were treated successfully with a modified PDT protocol following a 36-month follow-up period (17).” | Lines 122-127 |
| Reviewer 2 | 6) Lines 121-4: Significant revision is required. A clear statement is required to indicated that no efficacy has been shown for these treatments up to date, whilst others (photobiomodulation) are new, and under investigation. | Thank you. We edited it as “In nAMD treatment, photobiomodulation, intravitreal corticosteroid injections, and surgical removal of CNV have all been used (16, 18). Some of these modalities are currently being evaluated; however, due to poor visual results or lack of disease control over a long period as compared to vascular epithelial growth factor (VEGF) antagonists, they have a limited role in the treatment of nAMD (16, 18). | Lines 128-131 |
| Reviewer 2 | ) Line 162: revision required, e.g. insert ‘between conbercept and aflibercept is’ the addition of…….. | We added “(39). PANDA-1 and PANDA-2 are phase 3, randomized, quadruple-masked, multi-centered trials that assess three arms: 0.5 mg conbercept, 1.0 mg conbercept, and 2.0 mg aflibercept. The study's primary | Lines 172-175 |

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| | | objective is the mean change in BCVA after 36 weeks. The results of this study are expected to be available by the end of 2021 (40, 41)." | |
| Reviewer 2 | 8) Line 177: requires revision: cannot say fewer required concentration'. Suggested revision: 'lower drug concentration required to achieve appropriate tissue concentration and biological effects'…..; the next part of the sentence on permeation needs to be updated appropriately. | Thank you. We revised our text as advised. "These characteristics lead to lower drug concentration required to achieve appropriate tissue concentration and biological effects of the DARPin family to treat different pathologies like neoplasia (48)." | Lines 192-194 |
| Reviewer 2 | 9) Lines 185-6: revise with corrected VEGF isoform (numbers) for different species e.g. VEG 165 vrs 164? | Thank you. We double-checked isoforms in reference and revied this sentences as "This is also higher than the affinity of aflibercept for $VEGF_{165}$ (200 fM) (47). Abicipar can also bind to human VEGF-$A_{110}$, rabbit, and rat VEGF-$A_{165,}$ and it can cross-react with VEGF-A of other species to aid preclinical medication progression (47)." | Lines 199-202 |
| Reviewer 2 | 10) Line 221: 'stage 3'? Revise | Thanks for this comment. We have revised it as "Only the findings of 64 individuals of a greater phase-III trial (55) with a total of 271 subjects were presented in this article." | Line 237 |
| Reviewer 2 | 11) Line 239: replace 'related' with 'compared' | Thanks for this comment. We have corrected our text as advised. | Line 254 |
| Reviewer 2 | 12) Line 245: omit ':' | Thanks for this comment. We have corrected our text as advised. | Line 259 |