# Comparative Efficacy of Anti-Vascular Endothelial Growth Factor (anti-VEGF) Agents for Treatment of Neovascular Age-Related Macular Degeneration (nAMD): A Systematic Review and Network Meta-Analysis

POSA3

Danyliv, Andrii[1]; Skelly, Adrian[1]; Dennis, Natalie[2]; Quenéchdu, Arthur[2]; Willms, Kyle[3]

[1]Novartis Pharma AG, Basel, Switzerland; [2]Amaris, Health Economics and Market Access, Paris, France; [3]Amaris, Health Economics and Market Access, Toronto, Canada

## INTRODUCTION

- Anti-VEGF monotherapy is currently the preferred treatment for neovascular age-related macular degeneration (nAMD) [1] that requires regular monitoring and retreatment, with some anti-VEGFs posing significant burden to patients and care providers [2].
- Brolucizumab is the most recent anti-VEGF approved for nAMD treatment with a majority of patients on q12w interval immediately after loading phase through Year 1. It demonstrated non-inferiority to aflibercept for best-corrected visual acuity (BCVA) improvement and was superior to aflibercept in outcomes of disease activity, anatomical outcomes such as retinal thickness reduction and retinal fluid markers [3-5].
- We conducted a systematic literature review (SLR) followed by network meta-analysis (NMA) comparing efficacy and treatment discontinuation of brolucizumab relative to other approved and marketed anti-VEGFs in nAMD patients, as well as pooling of injection frequency and safety for these treatments.

## METHODS

- We conducted a SLR to identify published (before May 2020) randomized controlled trials (RCTs) comparing any licensed anti-VEGF treatment regimens, including brolucizumab, aflibercept and ranibizumab, or sham in adult patients with nAMD.
- RCTs reporting outcomes of ≥44 weeks were included. Studies with >10% of patient population having polypoidal choroidal vasculopathy were excluded. Appropriate data imputation methods were utilized for missing SD/SE data.
- A Bayesian NMA was conducted for the outcomes of mean change of BCVA and retinal thickness from baseline as well as discontinuation in first two years of treatment. Mean injection frequency and rates of serious adverse ocular events (SAOEs) were estimated by pooling data for each treatment regimen using random-effect models (to account for the between-trial heterogeneity, $\tau^2$).
- In the NMA, heterogeneity was assessed by Cochran's Q test for each pairwise comparison, and inconsistency $I^2$ statistic for each evidence loop.

### Assumptions

- To accommodate variable reported time points, one year was assumed to be represented by the outcomes reported between 48 and 52 weeks, while year two between 96 and 104 weeks.
- Central retinal thickness, central foveal thickness, central subfield thickness, and central macular thickness were considered as the same measure (retinal thickness), as validated by Novartis's medical expert.
- Treatment-naïve patients were considered comparable to mixed patients/trials not reporting previous anti-VEGF treatment use.
- In order to connect the networks for NMAs, patients of VIEW 1&2 trials were considered to have continuous treatment arms despite PRN regimen at 52 weeks.

## RESULTS

- Of 57 eligible studies from the SLR, 15 RCTs were included in the NMA base case analysis. The rest were excluded due to various methodological reasons, mostly due to comparing non-licensed regimens or doses (**Figure 1**).
- Brolucizumab demonstrated superior BCVA gains compared to sham at year 1 (Y1) (mean difference (MD): 16.9 letters [95%CrI: 13.38, 20.42]) and year 2 (Y2) (MD: 21.23 letters [95%CrI: 17.43, 24.97]) and between year 1 and 2 (Y1-Y2) (MD: 4.31 letters [95%CrI: 0.66, 7.95]), and was comparable to other anti-VEGFs (**Figure 2 & 3**). Similar results were observed for change in BCVA between year 1 and 2.

**Figure 1: PRISMA diagram.**

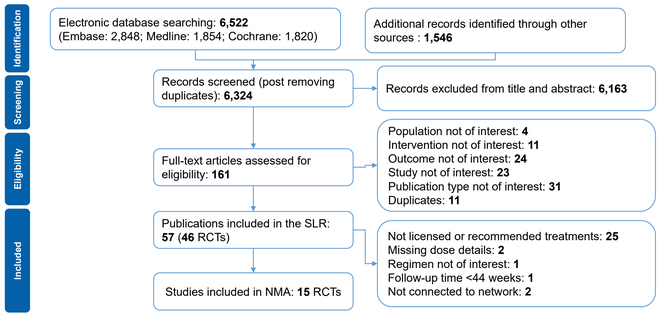



**Figure 2: Network diagrams for change in BCVA from baseline outcome at Year 1 and 2.**

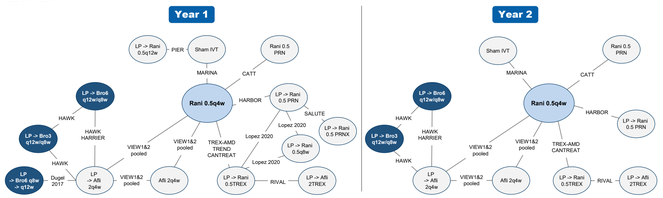
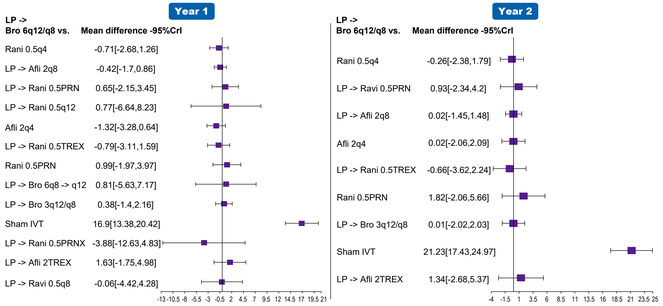



**Figure 3: Mean difference in BCVA change from baseline of brolucizumab vs. other treatments (fixed-effects model).**




Afli: aflibercept; Bro: brolucizumab; LP: loading phase of three initial monthly injections; PRN: pro-re-nata regimen; PRNX: PRN regimen with the potential to extend the assessment interval; Rani: ranibizumab; SE: standard error; TREX: treat and extend regimen; qN: injections that are administered on a fixed schedule every N weeks.

- Brolucizumab showed superior retinal thickness reduction compared to most of comparators including ranibizumab (0.5mg PRN; Year 1 MD: -75.54 µm [95%CrI: -111.36, -39.46]; Year 2 MD: -69.05 µm [95%CrI: -111.21, -26.65]) and Aflibercept (2mg q4w; Year1 MD: -40.26 µm [95%CrI: -60.82, -19.71]; Year 2 MD: -39.62 µm [95%CrI: -61.14, -18.51]) (**Figure 4 & 5**)

**Figure 4: Network diagrams for change in retinal thickness from baseline at Year 1 and 2.**

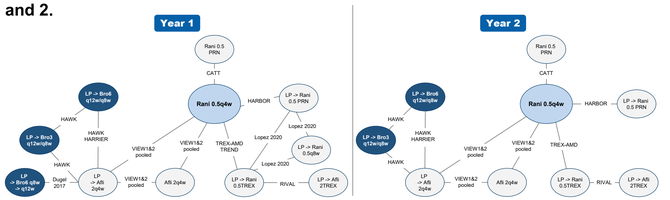
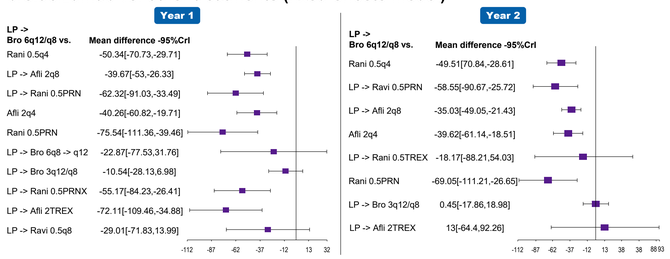



**Figure 5: Mean difference in retinal thickness reduction from baseline of brolucizumab vs. other treatments (fixed-effects model).**




Afli: aflibercept; Bro: brolucizumab; LP: loading phase of three initial monthly injections; PRN: pro-re-nata regimen; PRNX: PRN regimen with the potential to extend the assessment interval; Rani: ranibizumab; SE: standard error; TREX: treat and extend regimen; qN: injections that are administered on a fixed schedule every N weeks.

- Brolucizumab had comparable discontinuation rates (pooled mean ± SE) to other anti-VEGFs for both Year-1 (brolucizumab: 0.081 ± 0.013, aflibercept: 0.094 ± 0.011, and ranibizumab: 0.088 ± 0.007) and Year-2 (brolucizumab: 0.151 ± 0.036, aflibercept: 0.171 ± 0.015, and ranibizumab: 0.166 ± 0.012).
- Annualized injection frequency analyzed at year 2 was lowest for brolucizumab at 5.7 injections (**Table 1**).
- Pooled rates of SOAEs are summarized in **Table 2**. Mean intraocular inflammation (IOI) rates at Year 2 were 0.01, 0.00, 0.00 for brolucizumab, aflibercept and ranibizumab, respectively.

**Table 1: Pooled injection frequencies of treatment regimens (random effects model).**

| Intervention | Year 1 (Annualized) | | Year 2 (Annualized) | |
|---|---|---|---|---|
| | Mean | SE | Mean | SE |
| **AFL 2q4** | 11.90 | 0.13 | - | - |
| **AFL 2q4 -> PRN** | - | - | 8.70 | 0.07 |
| **LP -> AFL 2TREX** | 9.70 | 0.22 | 8.50 | 0.27 |
| **LP -> AFL 2q8** | 7.14 | 0.15 | 6.35 | 0.25 |
| **LP -> AFL 2q8 -> PRN** | - | - | 6.10 | 0.06 |
| **LP -> BRO 3q12/q8** | 6.60 | 0.05 | 5.70 | 0.07 |
| **LP -> BRO 6q12/q8** | 6.66 | 0.05 | 5.70 | 0.20 |
| **LP -> RAN 0.5PRN** | 7.20 | 0.39 | 6.70 | 0.12 |
| **LP -> RAN 0.5PRNX** | 5.50 | 0.31 | - | - |
| **LP -> RAN 0.5TREX** | 9.48 | 0.10 | 8.88 | 0.11 |
| **LP -> RAN 0.5q8** | 7.60 | 0.05 | - | - |
| **RAN 0.5PRN** | 6.90 | 0.18 | 6.30 | 0.20 |
| **RAN 0.5q4** | 11.78 | 0.13 | 11.53 | 0.35 |
| **RAN 0.5q4 -> PRN** | - | - | 8.90 | 0.08 |

AFL: aflibercept; BRO: brolucizumab; LP: loading phase of three initial monthly injection; PRN: pro-re-nata regimen; PRNX: PRN regimen with the potential to extend the assessment interval; RAN: ranibizumab; SE: standard error; TREX: treat and extend regimen; qN: injections that are administered on a fixed schedule every N weeks, i.e. q4, q6, q8, or q12
**Note**: Baseline pooling is conducted for treatments with more than one trial

**Table 2: Pooled SOAEs at Year 2 for treatment molecules (random effects model).**

| | Cataract | Endophthalmitis | IOI | Retinal detachment | RPE tear | Retinal tear | Stroke |
|---|---|---|---|---|---|---|---|
| **Aflibercept** | 0.006 | 0.005 | 0.000 | 0.004 | 0.002 | 0.003 | 0.009 |
| **Brolucizumab** | 0.003 | 0.006 | 0.010 | 0.003 | 0.004 | 0.005 | 0.006 |
| **Ranibizumab** | 0.005 | 0.009 | 0.000 | 0.005 | 0.002 | 0.004 | 0.010 |
| **Sham** | - | 0.000 | - | 0.004 | - | 0.000 | 0.008 |

IOI: intraocular inflammation; RPE: retinal pigment epithelium; SOAEs: serious ocular adverse events.
**Note**: Baseline pooling is conducted for treatments with more than one trial

## STRENGTHS

- The NMA was conducted in a Bayesian framework based on NICE guidelines, and its results were similar to those from NICE [6,7].
- No inconsistency was identified in the closed loop containing the HAWK and HARRIER trials.

## LIMITATIONS

- It was not possible to conduct meta-regressions adjusted on relevant covariates such as baseline BCVA and treatment regimen due to limited information from networks to allow for the convergence of models.
- For SOAEs and injection frequency, baseline pooling was conducted due to limited information available and direct impact of type of treatment regimen, respectively. In pooling SOAE rates, multiple definitions for stroke were considered, but was consistent with the approach used in the NICE NG82 guideline.
- Finally, this NMA summary includes SOAEs as initially reported in the HAWK and HARRIER trials and does not reflect the latest brolucizumab safety information.

## CONCLUSION

- Among all licensed anti-VEGF treatments, brolucizumab showed superior reduction in retinal thickness and comparable BCVA gains and discontinuation rates, despite having the lowest injection frequency.
- The current study provides the robust, most up-to-date comparison of licensed treatments for nAMD. Furthermore, another update of this NMA conducted in 2021 yielded similar conclusions, which shall be published in due course.

### References

1. Age-related macular degeneration. NICE Guideline (NG82). 2018.
2. Eye Health Council of Ontario. Canadian Journal of Optometry. 2015;77(1).
3. NCT02307682 [Available from: https://clinicaltrials.gov/ct2/show/NCT02307682].
4. NCT02434328. [Available from: https://clinicaltrials.gov/ct2/show/NCT02434328].
5. Novartis brolucizumab (RTH258) demonstrates superiority versus aflibercept in key secondary endpoint measures of disease activity in nAMD, a leading cause of blindness [press release]. 2017.
6. Dias S, et al. NICE DSU Technical Support Document 2. 2011.
7. Guide to the methods of technology appraisal. NICE Guideline (PMG9). 2013

### Acknowledgements

The authors acknowledge Inderpreet Singh and Vinod Goshamahal (Novartis, Hyderabad) for writing and designing the poster layout, respectively.

### Financial Disclosure

This study was commissioned by Novartis.

**Poster presented at the Virtual ISPOR Europe 2021, 30 November–03 December 2021.**

Scan this QR code