**Supplementary Material**

# Economic Benefit of Aflibercept 8 mg Versus Faricimab for Neovascular Age-Related Macular Degeneration or Diabetic Macular Edema in the US

**Running Title:** Costs of aflibercept 8 mg vs. faricimab

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## Supplementary Methods

### *Aflibercept 8-mg and Faricimab Trial Designs*

In PULSAR [1, 2] and PHOTON [3, 4], eligible patients were randomized 1:1:1 (PULSAR) and 1:2:1 (PHOTON) to receive aflibercept 2 mg every 8 weeks (2q8) following three (PULSAR) or five (PHOTON) initial monthly doses, or aflibercept 8 mg every 12 or 16 weeks following three initial monthly doses. Patients in the aflibercept 8-mg groups could have had their dosing intervals shortened, beginning at week 16, to a minimum of every 8 weeks, or extended, beginning at week 52, to a maximum of every 24 weeks if protocol-defined criteria for disease activity were met [1-4].

In TENAYA and LUCERNE [5, 6], eligible patients were randomized 1:1 to receive faricimab 6 mg up to every 16 weeks following four initial monthly doses or 2q8 following three initial monthly doses. A treat-and-extend (T&E) regimen was introduced at the start of year 2 to allow dosing interval modifications up to every 16 weeks based on criteria that denoted disease activity.

In YOSEMITE and RHINE [7, 8], eligible patients were randomized 1:1:1 to faricimab 6 mg every 8 weeks following six initial monthly doses, faricimab 6 mg T&E following four initial monthly doses, or 2q8 after five initial monthly doses. The T&E regimen allowed for dosing interval modifications to a maximum of every 16 weeks based on criteria that indicated disease activity.

### *Model Functionality*

Economic modeling was performed using a Markov cohort model that incorporated various inputs to estimate the direct and indirect costs associated with intravitreal anti–vascular endothelial growth factor injections for a modeled patient cohort for each disease indication (neovascular age-related macular degeneration [nAMD] or diabetic macular edema [DME]). Inputs included the mean number of injections reported in clinical trials of aflibercept 8 mg and faricimab (as detailed in the main Methods section), as well as data on efficacy, treatment discontinuation rates, and mortality rates. Model outcomes were reported per average person in the cohort. For the purposes of this analysis, only single eye involvement (treated eye) and the impact of health state membership on mortality was considered, excluding fellow eye involvement and impact of health state membership on utility. The full functionality of this model has been published previously with inclusion of fellow eye involvement and utility assessment based on health state membership [9]. The model was developed in Microsoft Excel 2016 as previously reported [9], and is not publicly available. The model estimated the number of injections each year by accounting for the proportion of the patient cohort that died or discontinued treatment during each model cycle (6 months), thus reducing the accumulated costs.

The model includes five health states differentiated by best-corrected visual acuity (BCVA) (< 35, 35–49, 50–64, 65–79, or > 79 letters). During each model cycle (6 months), the treated eye could remain at the current level of BCVA, improve by an average of 15 letters, or worsen by an average of 15 letters. The treated eye at the lowest BCVA level (< 35 letters, defined as “blind”) could only remain in this health state

or improve to the next BCVA level (35–49). Eyes at the highest BCVA level (> 79 letters) could only remain in that health state or fall to the previous BCVA level. All health states had the potential of transitioning to a death health state, with an increased risk of death for those with BCVA < 35 letters.

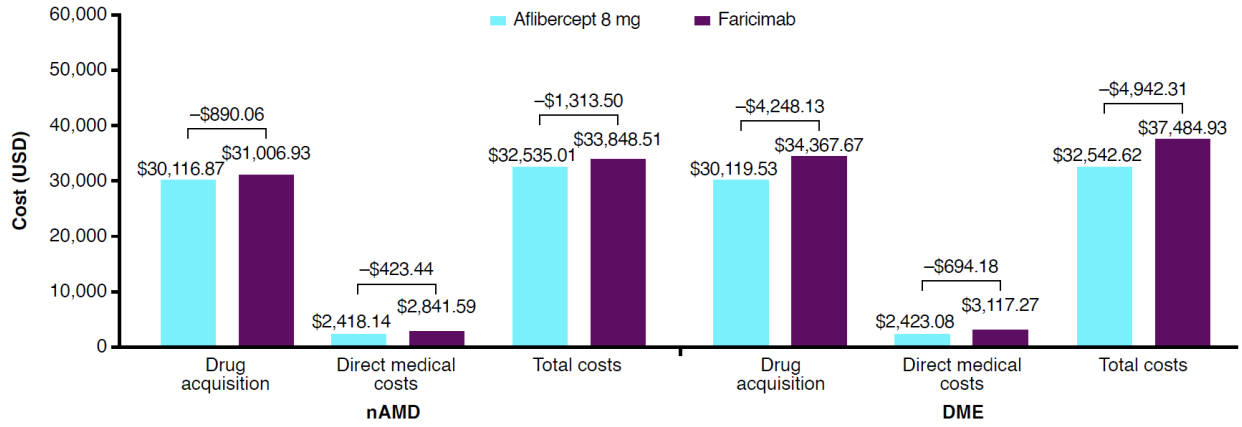
Changes over time in BCVA health state membership were determined using treatment efficacy, applied by increasing the chances of improving the patient's BCVA (by 15 letters) and reducing the chances of worsening the patient's BCVA (by 15 letters). This was converted to a per-cycle probability of transitioning a patient to a higher or lower BCVA-based health state. Although no head-to-head trial data were available, efficacy was assumed to be noninferior between aflibercept 8 mg and faricimab for nAMD and DME based on demonstrations of noninferiority in clinical trials using aflibercept 2 mg as a control [1-8] and the results of a network meta-analysis, which showed comparable efficacy between aflibercept 8 mg and faricimab during 1 year of treatment in patients with nAMD [12].

Health state membership via treatment efficacy impacted mortality by applying an increased risk of death associated with blindness (lowest BCVA level of < 35 letters in the eye with best vision), as detailed below.

The risk of treatment discontinuation was assumed to be the same for all treatments (aflibercept 8 mg and faricimab) for each disease indication. Annual discontinuation risk up to 12 months and after 12 months was assumed to be 3.20% [13] and 3.38% [14], respectively, for patients with nAMD, and 4.09% and 4.49% [15], respectively, for patients with DME.

Survival was adjusted by applying disease-specific (nAMD or DME) hazard ratios to mortality of the general population; these did not vary by treatment. Additionally, a hazard ratio for blindness was applied. Hazard ratios were 1.41 for DME [16], 1.23 for late age-related macular degeneration (i.e., nAMD) [17], and 1.18 for blindness [18]. The baseline age and BCVA distribution in the treated eye at baseline was modeled for each disease indication. The baseline mean age (nAMD: 76 years [13]; DME: 63 years [19]) impacted the general population mortality applied for each modeled patient. Baseline BCVA distribution varied by treatment indication and health states as follows: 11.78% and 4.19% for BCVA of < 35 letters, 19.13% and 12.88% for BCVA of 35–49 letters, 45.12% and 46.56% for BCVA of 50–64 letters, 23.97% and 36.13% for BCVA of 65–79 letters, and 0.00% and 0.24% for BCVA of ≥ 80 letters for nAMD and DME, respectively [20, 21].

**Fig. S1.** Sensitivity analysis of total and incremental cost outcomes over 3 years, including direct costs only.




Excluding indirect costs. Drug acquisition represents 2025 wholesale acquisition costs. Direct medical costs represent direct medical monitoring costs. Brackets over the bars indicate the difference in costs between aflibercept 8 mg and faricimab. *DME* diabetic macular edema, *nAMD* neovascular age-related macular degeneration

**Fig. S2.** Total and incremental cost outcomes over 3 years for scenarios with **a** lower and **b** higher estimates for mean number of injections.


Drug acquisition represents 2025 wholesale acquisition costs. Direct medical costs represent direct medical monitoring costs. Indirect costs represent total cost per injection for carer and patient, including caregiver time, average US hourly wage, and travel costs. The lower estimate for mean number of injections was derived by subtracting 1 SD from the mean number of injections in the base case. The higher estimate for mean of injections was derived by adding 1 SD to the mean number of injections in the base case. Brackets over the bars indicate the difference in costs between aflibercept 8 mg and faricimab. *DME* diabetic macular edema, *nAMD* neovascular age-related macular degeneration, *SD* standard deviation

**Table S1.** Medical monitoring direct costs

| Resources (CPT code) | Description | 2025 unit costs, USD [22, 23] |
|---|---|---|
| Initial Office Visit (99204) | Office or other outpatient visit for the evaluation and management of a new patient, moderate level of medical decision-making, 45–59 minutes | 163.3 |
| Subsequent Office Visit (99214) | Office or other outpatient visit for the evaluation and management of an established patient, moderate level of medical decision-making, 30–39 minutes | 125.18 |
| Fluorescein Angiography (92235) | Fluorescein angiography (includes multiframe imaging) with interpretation and report, unilateral or bilateral | 311.40 |
| Optical Coherence Tomography (92134) | Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; retina | 59.40 |

*CPT* current procedural terminology

## Table S2. Indirect cost parameters and calculated cost per injection

| Parameter | Value |
|---|---|
| Caregiver time taken for an injection appointment [24] | 4 hours |
| Average US wage per working hour [25] | 29.62 USD[a] |
| Reduction on hourly wage for nonworking people's time [26] | 60% |
| Hours of lost patient productivity due to injection and appointment [27] | 11.7 hours (assuming 100% is personal time, i.e., nonworking) |
| Percentage of carers taking time from activities [27] | 22% take time from work (assuming the remaining 78% lose personal time) |
| Percentage of patients who require a caregiver [27] | 72% |
| Average distance traveled to get to an appointment [27, 28] | 17.4 miles[b,c] (total miles traveled for a round trip: 34.8) |
| Cost per mile traveled [29] | 0.67 USD per mile driven by vehicle |
| Total indirect cost per injection for patient | 231.29 USD (207.97 USD [lost time] + 23.32 USD [mileage]) |
| Total indirect cost per injection for carer | 58.70 USD (lost time) |
| **Total indirect cost per injection for carer and patient** | 289.98 USD |

[a] Calculated from median weekly earnings in Q4 2024, assuming a 40-hour working week
[b] Compared with ~31–44 miles (73 miles for rural census tracts) to a neuro-ophthalmologist [30] and 9.9 miles (SD: 11.4 miles) to the nearest cataract surgery provider [31]
[c] Estimated from the average time spent driving to appointment (66 minutes; assuming 33 minutes one-way [27]) and the calculation for distance traveled < 30 miles [28]

# REFERENCES


1. Lanzetta P, Korobelnik J-F, Heier J, et al. Intravitreal aflibercept 8 mg versus 2 mg in neovascular age-related macular degeneration at 48 weeks (PULSAR): a randomised, double-masked, non-inferiority, phase 3 trial. Lancet. 2024;403(10432):1141–52.
2. Korobelnik JF. Aflibercept 8 mg in patients with neovascular age-related macular degeneration: phase 3 PULSAR trial 96-week results. American Academy of Ophthalmology Meeting; November 3–6, 2023; San Francisco, CA, USA.
3. Brown DM, Boyer DS, Do DV, et al. Intravitreal aflibercept 8 mg in diabetic macular oedema (PHOTON): 48-week results from a randomised, double-masked, non-inferiority, phase 2/3 trial. Lancet. 2024;403(10432):1153–63.
4. Do DV. Aflibercept 8 mg for diabetic macular edema: 96-week results from the phase 2/3 PHOTON trial. American Academy of Ophthalmology Meeting; November 3–6, 2023; San Francisco, CA, USA.
5. Khanani AM, Kotecha A, Chang A, et al. TENAYA and LUCERNE: two-year results from the phase 3 neovascular age-related macular degeneration trials of faricimab with treat-and-extend dosing in year 2. Ophthalmology. 2024;131(8):914–26.
6. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022;399(10326):729–40.
7. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet. 2022;399(10326):741–55.
8. Wong TY, Haskova Z, Asik K, et al. Faricimab treat-and-extend for diabetic macular edema: two-year results from the randomized Phase 3 YOSEMITE and RHINE trials. Ophthalmology. 2024;131(6):708–23.
9. Hernandez L, Lanitis T, Cele C, Toro-Diaz H, Gibson A, Kuznik A. Intravitreal aflibercept versus ranibizumab for wet age-related macular degeneration: a cost-effectiveness analysis. J Manag Care Spec Pharm. 2018;24(7):608-16.
10. Korobelnik J. Aflibercept 8 mg in Patients with Neovascular Age-Related Macular Degeneration: Phase 3 PULSAR Trial 96-Week Results. American Academy of Ophthalmology Meeting; November 3–6, 2023, 2023; San Francisco, CA, USA.
11. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022;399(10326):729–40.
12. Wojciechowski P, Wdowiak M, Panek M, et al. Efficacy, safety, and injection frequency with novel aflibercept 8 mg in neovascular age-related macular degeneration: a comparison with existing anti-VEGF regimens using a Bayesian network meta-analysis. Ophthalmol Ther. 2025;14(4):733–53.
13. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537–48.

14. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014;121(1):193-201.

15. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123(6):1351–9.

16. Hirai FE, Knudtson MD, Klein BE, Klein R. Clinically significant macular edema and survival in type 1 and type 2 diabetes. Am J Ophthalmol. 2008;145(4):700-6.

17. Xin X, Sun Y, Li S, Xu H, Zhang D. Age-related macular degeneration and the risk of all-cause and cardiovascular mortality: A meta-analysis of cohort studies. Retina. 2018;38(3):497-507.

18. Christ SL, Zheng DD, Swenor BK, et al. Longitudinal relationships among visual acuity, daily functional status, and mortality: the Salisbury Eye Evaluation Study. JAMA Ophthalmol. 2014;132(12):1400-6.

19. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014;121(11):2247–54.

20. Wolf S, Bandello F, Loewenstein A, et al. Baseline characteristics of the fellow eye in patients with neovascular age-related macular degeneration: post hoc analysis of the VIEW Studies. Ophthalmologica. 2016;236(2):95-9.

21. Fielding S, Cummins E, Cruickshank M, Fraser C, Lois N, Brazzelli M. Aflibercept for the treatment of diabetic macular oedema: a single technology appraisal. Aberdeen HTA Group; 2014.

22. Centers for Medicare & Medicaid Services. Search the Physician Fee Schedule. 2025. https://www.cms.gov/medicare/physician-fee-schedule/search. Accessed May 7, 2025.

23. Centers for Medicare & Medicaid Services. Quarterly addenda updates. 2025. https://www.cms.gov/medicare/payment/prospective-payment-systems/hospital-outpatient/addendum-a-b-updates. Accessed May 7, 2025.

24. Bührer C, Paling T, Gale R, Paulo T, Bagijn M. Cost-effectiveness of faricimab in the treatment of diabetic macular oedema (DMO): a UK analysis. Pharmacoecon Open. 2024;8(3):445–57.

25. U.S. Bureau of Labor Statistics. Table 1. Median usual weekly earnings of full-time wage and salary workers by sex, quarterly averages, seasonally adjusted. 2025. https://www.bls.gov/news.release/wkyeng.t01.htm. Accessed May 7, 2025.

26. Mas A, Pallais A. Labor supply and the value of non-work time: experimental estimates from the field. Am Econ Rev Insights. 2019;1(1):111–26.

27. Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. Am J Ophthalmol. 2015;160(4):725–31.

28. Health Economics Resource Center (HERC). Estimating travel costs. 2022. https://www.herc.research.va.gov/include/page.asp?id=travel-costs. Accessed May 7, 2025.

29. Internal Revenue Service. IRS issues standard mileage rates for 2024; mileage rate increases to 67 cents a mile, up 1.5 cents from 2023. 2023. Last updated December 14. https://www.irs.gov/newsroom/irs-issues-standard-mileage-rates-for-2024-mileage-rate-

increases-to-67-cents-a-mile-up-1-point-5-cents-from-2023. Accessed May 7, 2025.

30. Xue K, Feng Y, Tam V, Lin CC, De Lott LB, Hamedani AG. Sociodemographic and geographic variation in access to neuro ophthalmologists in the United States. J Neuroophthalmol. 2023;43(2):149–52.

31. Lee CS, Su GL, Baughman DM, Wu Y, Lee AY. Disparities in delivery of ophthalmic care; An exploration of public Medicare data. PLoS One. 2017;12(8):e0182598.