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Cost-minimisation analysis of anti-VEGF therapies in neovascular age-related macular degeneration and diabetic macular oedema in Switzerland

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ABSTRACT

Objective: This study compares the direct healthcare costs of anti-VEGF therapies, including treat-and-extend (T&E) and other durable regimens, for unilateral neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DMO) in Switzerland.

Methods: An adapted cost-minimisation model estimated healthcare costs over two years for aflibercept 2 mg, aflibercept 8 mg, faricimab, ranibizumab, and ranibizumab biosimilars using clinical trial injection frequencies. Break-even analyses identified the medication prices and injection frequencies required for higher-cost therapies to achieve cost parity with the least expensive options. A one-way sensitivity analysis (OWSA) assessed key drivers of cost outcomes.

Results: Aflibercept 8 mg was estimated to be associated with the lowest treatment costs for both indications (CHF 11,814 for nAMD; CHF 11,242 for DMO). Faricimab (CHF 13,737) and aflibercept 2 mg (CHF 15,243) followed in nAMD and DMO. Ranibizumab and its biosimilars incurred the highest costs: for nAMD, biosimilars ranged from CHF 16,243 to CHF 17,497 and the reference product reached CHF 18,424; for DMO, biosimilars ranged from CHF 18,187 to CHF 19,596, with the reference product at CHF 20,637. Break-even analyses for nAMD showed that prices would need to drop by −22% (faricimab, CHF 644) to −64% (ranibizumab reference, CHF 218) relative to aflibercept 8 mg. For DMO, reductions ranged from −42% (aflibercept 2 mg, CHF 493) to −81% (ranibizumab reference, CHF 114). The OWSA highlighted medication price and injection frequency as primary cost drivers.

Conclusions: This study estimated that the potentially minimized injection frequency of aflibercept 8 mg in a clinical trial regimen may result in the lowest treatment costs for nAMD and DMO, followed by faricimab and aflibercept 2 mg, respectively.

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Introduction

Age-related macular degeneration (AMD) and diabetic macular oedema (DMO) are significant causes of vision impairment and vision loss in Europe's ageing population[1]. According to 2020 data, approximately 67 million people in the EU are affected by some form of AMD, a figure expected to rise to 77 million by 2050[2]. Neovascular AMD (nAMD), or wet AMD, is an advanced form of AMD and causes most cases of central vision loss, despite being less prevalent than dry AMD[3]. DMO affects one in 15 people with diabetes worldwide and is the main cause of visual impairment connected to diabetic retinopathy, which can potentially lead to the loss of vision and is reported as the main cause of blindness in the working-age population[4–6]. With the estimations suggesting that one in ten Europeans will have diabetes by 2045[7], the prevalence of DMO is also expected to rise[8].

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Anti-vascular endothelial growth factor (VEGF) treatment is currently considered the standard of care or preferred treatment for nAMD and DMO[6,9]. Anti-VEGFs are administered through intravitreal injections and the number of doses required to reach a treatment effect varies by regimen and anti-VEGF agent[10]. In 2014 and 2017, the European Society of Retina Specialists (EURETINA) recommended ranibizumab, bevacizumab, and aflibercept 2 mg for the treatment of nAMD and DMO[6,9]. Off-label bevacizumab is not used in the Swiss clinical setting, according to a statement by the Swiss VitreoRetinal Group, which cites insufficient safety evidence and the drug's off-label status as key reasons[11,12]. The EURETINA publications outline several treatment regimens, with the treat-and-extend (T&E) approach highlighted as a strategy to minimize injection frequency while maintaining treatment efficacy. This regimen adjusts treatment intervals—shortening or extending them—based on the patient's disease activity. Since the publication of these guidelines, several new treatments with more durable regimens have been introduced that reduce injection frequency even further. First, brolucizumab was launched, which, alongside aflibercept 2 mg, became one of the first anti-VEGFs shown to be effective in treatment intervals of a maximum of 16 weeks in nAMD but still required a 4-weekly interval for DMO[13,14]. Subsequently, faricimab was approved by SwisMedic for the treatment of nAMD and DMO[15]. Studies indicate that faricimab provides non-inferior changes in visual acuity with a flexible 16-weekly regimen for both diseases[16,17]. Additionally, aflibercept was recently evaluated in a higher 8 mg dosage for nAMD and DMO, demonstrating non-inferior visual acuity when administered in 16-week (or longer) intervals[18,19].

An optimized treatment interval may improve the patient experience. Frequent treatments can lead to productivity loss. Moreover, patients frequently experience elevated levels of anxiety and stress in anticipation of therapy appointments, and the intravitreal injection procedure may be uncomfortable or even moderately painful for some[20,21]. Furthermore, a subset of patients requires caregiver assistance for support at each appointment[20]. At the same time, the resource demands of anti-VEGF treatments, requiring long-term screening, injections, and consultations can strain hospitals. A recent study has estimated the per-annum economic burden of late-stage AMD to be €7.6 billion in Germany[22]. Therefore, an anti-VEGF therapy requiring fewer intravitreal injection visits could, potentially, both reduce the treatment burden on patients and alleviate the economic burden of these treatments on the healthcare system.

Switzerland ranks among countries with the highest health expenditure per capita, allocating 12.4% of its gross domestic product to healthcare in 2016[23]. This trend is expected to continue as health expenditure rose by 3.8% to CHF 10,684 and is projected to reach CHF 11,594 by 2026[24]. In addition to the overall rise in healthcare spending, the relative share allocated to sensory organ diseases have increased from 3.8% to 4.5%[25]. This highlights the growing importance of cost management in Swiss healthcare, particularly in a disease like nAMD. Supporting this, the study from Reich et al. reported that during the first six months of treatment, the total healthcare expenditure per patient reached CHF 14,856 for ranibizumab and CHF 13,484 for aflibercept[26].

Given that previous cost analyses of nAMD healthcare costs in EU countries were conducted in other settings[27–29], these are not directly transferable to Switzerland due to differences in pricing, reimbursement, and care delivery models. The goal of this study is to evaluate the direct healthcare costs of anti-VEGF therapies for the treatment of unilateral nAMD and DMO in Switzerland, focusing on T&E and other novel, more durable, flexible regimens. Given the significant variation in procedures performed across hospitals and physicians and outcomes in real-world settings, we chose to base this analysis on treatment protocols used in randomised clinical trials.

Methods

This study is an adaptation of a previous cost analysis that compared the direct healthcare costs of anti-VEGFs for unilateral treatment of treatment-naïve nAMD patients in the Netherlands using a cost-minimisation approach[28]. A cost-minimisation analysis models healthcare costs, while assuming equal treatment outcomes. Using costs and healthcare practices specific to Switzerland, the model was adapted to the Swiss healthcare context to measure the costs associated with anti-VEGF treatment for nAMD and DMO in the country. In the analysis, we compare the anti-VEGFs that have been approved in Switzerland: aflibercept 2 mg, aflibercept 8 mg, faricimab, the ranibizumab reference and three ranibizumab biosimilars[30–36]. Although recommended in EURETINA guidelines[6,9], bevacizumab is currently not used in

Switzerland due to limited data and its off-label status and was therefore, excluded from the analysis[11,12]. Brolucizumab was excluded from the analysis as the analysis calculated costs with the assumption of equal treatment effect and safety, and this anti-VEGF induces an increased risk for intraocular inflammation, also limiting its use in Switzerland[37]. While treatment durations often exceed two years[38], a two-year time horizon was chosen to align with the maximum follow-up period of most anti-VEGF clinical trials, minimising uncertainty from extrapolation. Clinical trials and indirect treatment comparisons demonstrated the non-inferiority of anti-VEGF therapies in mean change in visual acuity from baseline or proportion of patients or losing $\geq$15 letters, allowing the model to exclude treatment effects[10,16,17,39–41]. The analysis was conducted from a healthcare payer perspective to provide insights for medical stakeholders on the impact of anti-VEGF treatments and their administration regimens. Following the cost-minimisation approach, clinical outcomes were not modelled, based on the assumption that there are no significant differences between treatments in this regard. The key study characteristics are summarized in Table 1.

Regimens

The study based the injection frequencies on (weighted averages) of the reported number of injections in all available clinical non-inferiority trials with a T&E or similar flexible regimen (Tables 1, 2). When the number of injections was reported at 48 or 96 weeks instead of at 52 or 104 weeks, values were

Table 1. Overview of model characteristics.

	Input
Model type	Cost-minimization analysis
Perspective	Healthcare payer
Time horizon	2 years
Included disease groups	Neovascular age-related macular degeneration (nAMD)
	Diabetic macular oedema (DMO)
Included anti-VEGFs and their regimens	nAMD population:
	Aflibercept 2 mg (T&E regimen)
	Aflibercept 8 mg (Flexible QW16)
	Faricimab (QW8/QW12/QW16)
	Ranibizumab reference (T&E regimen)
	Ranibizumab biosimilars (T&E regimen)
	DMO population:
	Aflibercept 2 mg (T&E regimen)
	Aflibercept 8 mg (Flexible QW16)
	Faricimab (T&E regimen)
	Ranibizumab reference (T&E regimen)
	Ranibizumab biosimilars (T&E regimen)
Cost parameters	Medication
	Administration
	Hospital visit
	Diagnosis
Outcomes	Costs per patient
	OWSA
	Break-even analysis (price)
	Break-even analysis (injection frequency)

Abbreviations: OWSA, one-way sensitivity analysis; T&E, treat-and-extend; QW16, every 16 weeks, QW8/QW12/QW16, every 8/12/16 weeks.

Table 2. Average injection frequency for each anti-VEGF based on selected trials.

	nAMD population – injection frequency				DMO population – injection frequency			
	Year 1	Year 2	Total	Regimen - Source	Year 1	Year 2	Total	Regimen -Source
Aflibercept 2 mg	7.2	4.5	11.6	T&E - ALTAIR, ARIES	7.6	3.7	11.3	T&E - VIBIM, Hirano et al. (2021)
Aflibercept 8 mg	5.4	3.3	8.7	QW16- PULSAR	5.2	3.0	8.3	QW16 -PHOTON
Faricimab	6.2	4.1	10.3	QW8/QW12/QW16 - TENAYA/LUCERNE	8.1	5.1	13.3	T&E -RHINE, YOSEMITE
Ranibizumab reference	9.0	7.8	16.8	T&E- TREX, TREND, CANTREAT, LUCAS	10.7	8.2	18.9	T&E -TREX-DMO
Ranibizumab biosimilars	9.0	7.8	16.8	T&E - TREX, TREND, CANTREAT, LUCAS (Assumed equal to the reference)	10.7	8.2	18.9	T&E TREX-DMO (Assumed equal to the reference)

Sources: ALTAIR[47]; ARIES[48]; PULSAR[10,46]; TENAYA/LUCERNE[17]; TREX[43]; TREND[44]; CANTREAT[49,50]; LUCAS[51,52]; Hirano et al.[45]; PHOTON[18,41]; RHINE & YOSEMITE[53]; TREX-DMO[54]; VIBIM[55,56].

extrapolated to estimate the number of injections over a full 52- or 104-week period. The key characteristics of the included non-inferiority trials are detailed in Supplementary Appendix 1, covering trial design, primary outcomes, and the non-inferiority framework.

A T&E regimen was selected as it is widely used in Switzerland and represents an optimized approach by gradually adapting to the needs of each individual patient[42]. The T&E regimen was incorporated for aflibercept 2 mg, faricimab in DMO, the ranibizumab reference, and the ranibizumab biosimilars. Since no clinical trials were available for the ranibizumab biosimilars, we assumed their injection frequencies in a T&E regimen to be the equal to the reference treatment. Furthermore, T&E data were unavailable for aflibercept 8 mg and faricimab; therefore, similar flexible dosing regimens were incorporated for those treatments (Table 3). The loading phase varied across the clinical trials, ranging from two to five initial monthly doses (Table 3). Subsequently, treatment intervals are adjusted every four weeks, in two-week increments, depending on disease activity. Most trials set a maximum treatment interval of 12 or 16 weeks[43–45].

The flexible 16-weekly (QW16) regimen for aflibercept 8 mg in the treatment of nAMD (in PULSAR) and DMO (in PHOTON) also begins with a three-month loading phase[18,46]. After this, patients follow an 8-week injection interval if disease activity criteria are met at week 16 or 20, and a 12-week interval if criteria are met at week 24. If no criteria are met at weeks 16, 20 or 24, the interval remains at 16 weeks. After 24 weeks, intervals are adjusted every 4 weeks based on disease activity with a minimum interval of 8 weeks and a maximum interval of 16 weeks. In the second year, the maximum dosing interval of nAMD patients extends from 16 to 24 weeks.

The flexible 8/12/16 weekly (QW8/QW12/QW16) regimen of faricimab for nAMD (in TENAYA and LUCERNE) patients starts with a loading phase of four monthly doses[17]. After this, in the first year, the regimen involves an 8-week injection interval if disease activity criteria are met at week 20, and a 12-week interval if criteria are met at week 24. If no criteria are met at weeks 20 or 24, the interval extends to 16 weeks. In the second year, the treatment interval is personalized starting at week 60, with adjustments in 4-week increments for extension and 4 to 8-week increments for reduction, with a minimum interval of 8 weeks and a maximum of 16 weeks. The disease activity of patients was assessed in control visits which took place at the start of the loading phase, at the end of the loading phase, and during every subsequent injection appointment.

Table 3 summarizes the most important characteristics of the studied treatment regimens, Supplementary Appendix 2 the disease activity criteria that were followed in each study, and Supplementary Appendix 3 the number of injections that were in each study and the corresponding the calculation assumptions.

Costs and resource use

The analysis accounts for all resource utilization-related costs related to unilateral anti-VEGF treatment from a healthcare perspective, as validated by two clinical experts, excluding treatment effects and safety considerations (Table 4). Adverse events associated with the intravitreal injection but unrelated to the active

Table 3. Summary of the most important characteristics of the studied treatment regimes.

Anti-VEGF	Population	Study	Regimen	Loading phase	Interval Y1	Interval Y2
Aflibercept 2 mg	nAMD	ALTAIR	T&E (2 W adj.)	Three monthly doses	QW8-QW14	QW8-QW16
Aflibercept 2 mg	nAMD	ARIES	T&E (early)	Three monthly doses	QW8-QW16	QW8-QW16
Aflibercept 8 mg	nAMD	PULSAR	Flexible QW16	Three monthly doses	QW8-QW16	QW8-QW24
Faricimab	nAMD	TENAYA	QW8/QW12/QW16	Four monthly doses	QW8-QW16	QW8-QW16
Faricimab	nAMD	LUCERNE	QW8/QW12/QW16	Four monthly doses	QW8-QW16	QW8-QW16
Ranibizumab	nAMD	TREX	T&E	Three monthly doses	QW4-QW12	QW4-QW12
Ranibizumab	nAMD	TREND	T&E	Two monthly doses	QW4-QW12	N/A
Ranibizumab	nAMD	CANTREAT	T&E	Three monthly doses	QW4-QW12	QW4-QW12
Ranibizumab	nAMD	LUCAS	T&ER	Monthly until inactive disease	QW4-QW12	QW4-QW12
Aflibercept 2 mg	DMO	Hirano et al. (2021)	T&E (4 W adj.)	Five monthly doses	QW8-QW16	QW8-QW16
Aflibercept 2 mg	DMO	VIBIM	T&E	Five monthly doses	QW4-QW12	QW4-QW20
Aflibercept 8 mg	DMO	PHOTON	Flexible QW16	Three monthly doses	QW8-QW16	QW8-QW24
Faricimab	DMO	RHINE	T&E	At least four monthly doses	QW4-QW16	QW4-QW16
Faricimab	DMO	YOSEMITE	T&E	At least four monthly doses	QW4-QW16	QW4-QW16
Ranibizumab	DMO	TREX-DMO	T&E	Four monthly doses	QW4-QW12	QW4-QW16

Abbreviations: DMO, diabetic macular oedema; nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend, QWx, every X weeks.
Sources: ALTAIR[47]; ARIES[48]; PULSAR[10,46]; TENAYA/LUCERNE[17]; TREX[43]; TREND[44]; CANTREAT[49,50]; LUCAS[51,52]; Hirano et al.[45]; PHOTON[18,41]; RHINE & YOSEMITE[53]; TREX-DMO[54]; VIBIM[55,56].

Table 4. Overview of included costs and implementation frequencies.

	Cost per implementation	Implementation frequency	Source
Medication			
Aflibercept 2 mg	846 CHF	Every administration	[57]
Aflibercept 8 mg	846 CHF	Every administration	[57]
Faricimab	831 CHF	Every administration	[58]
Ranibizumab reference	611 CHF	Every administration	[59]
Ranibizumab biosimilar – range 1[1]	556 CHF	Every administration	[59]
Ranibizumab biosimilar – range 2[2]	481 CHF	Every administration	[59]
Diagnosis			
Total diagnosis costs	527 CHF	At the start of treatment	TARMED[3]
Administration			
Intravitreal injection	243 CHF	Every administration	TARMED[4]
Control visit			
Total control visit	210 CHF	Every administration	TARMED[5]

[1]Range 1 was based on the medication price ranges of Byooviz and Ranivisio.
[2]Range 2 was based on the medication price ranges of Ximluci.
[3]Consultation is estimated at 30 min and costs are calculated based on the following TARMED treatment codes: 00.0010, 00.0020, 00.0030. Imaging includes an assessment of BCVA, slit-lamp calculation, SD-OCT, biomicroscopy, FP, and FA. Calculated based on the following TARMED treatment codes: 08.1230, 08.1080, 08.3010, 08.1130, 08.1060.
[4]Cost inputs solely include the technical aspects of the administration. Calculation based on the following TARMED treatment codes: 00.0050, 08.3350, 35.0030.
[5]Consultation is estimated at 15 min and costs are calculated based on the following TARMED treatment codes: 00.0010, 00.0020, 00.0030. Imaging costs include split-lamp examination, SD-OCT, and biomicroscopy and are based on the following TARMED treatment codes: 08.1230, 08.1080, 08.3010.

component were excluded due to limited and inconsistent data. Medication costs were based on public 2024 data from the Swiss Federal Office of Public Health[57–59]. At the time of analysis, three ranibizumab biosimilars were available (i.e. Byooviz, Ranivisio, and Ximluci). The medication ranges for all biosimilars were incorporated, as listed in Table 4. Administration, hospital visit, and diagnosis costs were based on the average 2024 tariffs used for reimbursing medical services in Swiss hospitals, sourced from the database of TARMED. Each patient begins with a diagnosis, which includes a consultation of 30 min together with an assessment of the best-corrected visual acuity (BCVA), a slit-lamp examination, a spectral domain optical coherence tomography (SD-OCT), a biomicroscopy, a fundus photograph (FP), and fluorescein angiography (FA). Subsequently, patients are assumed to attend visits where a routine check-up and an injection are administered during the same appointment. During this check-up and administration, the disease activity of patients is assessed to establish the next treatment interval. We categorize the costs during those visits into two groups: those related to control (including consultation and imaging) and those associated with intravitreal injection administration (including technical aspects of administration). We assume that the control visit consultation covers both screening and administration, so no additional consultation costs are included for administration to avoid double counting. The costs for the control visit in the hospital include a 15-minute consultation including a BCVA assessment, a slit-lamp examination, a SD-OCT scan, and a biomicroscopy. The costs associated with the technical aspects of the injection administration cover a preparatory discussion with the patient, the injection itself, and the expense of operating room usage. Although the model focuses on unilateral treatment, it is possible that patients undergo examination of the fellow eye during their visits. For both diagnostic and follow-up appointments, it is assumed that no additional TARMED codes will be billed if the second eye is also examined. The TARMED code calculations and tax point conversion used in the model are presented in Supplementary Appendix 4.

Sensitivity analyses

A one-way sensitivity analysis (OWSA) was conducted to evaluate the impact of model parameters on the total costs of anti-VEGF treatments. In this analysis, model parameters were varied across their 95% confidence intervals (CIs), derived from their standard errors (SEs). When standard errors or distribution data were unavailable, an SE of 10% of the mean value was assumed.

Furthermore, with some anti-VEGF therapies approaching patent expiration and the introduction of biosimilars, additional treatments are likely to emerge, or the prices of existing medications may decline in the future. The analysis accounted for the biosimilars available at the time but to account for the possibility of further additions in the field, a break-even analysis of medication pricing was performed. This

analysis calculated the medication cost required for an anti-VEGF to equal the total cost of the least expensive alternative. The calculation involved determining the difference in total costs between the cheapest anti-VEGF and the total costs without medication of a second anti-VEGF and then dividing this difference by the number of injections in the clinical regimen of the second anti-VEGF.

Additionally, to account for the differences in the included clinical trial designs and real-world treatment regimen procedures, a break-even analysis was conducted to estimate the cost per injection for each anti-VEGF and the number of administrations required for each to equal the total cost of the least expensive anti-VEGF. This analysis aimed to improve understanding regarding the impact of varying injection frequencies in a real-world setting.

Results

Costs per patient

For nAMD, the costs of aflibercept 8 mg were estimated at CHF 11,814 per patient (i.e. 7,351 CHF medication costs and 4,463 CHF resource costs) over a 2-year horizon, making it the lowest-cost option of all anti-VEGFs assessed in this study. At CHF 13,737 per patient (i.e. 8,549 CHF medication costs and 5,188 CHF resource costs) over a 2-year horizon, faricimab was the second most affordable option, followed by aflibercept 2 mg, with the costs estimated at CHF 15,632 (i.e. 9,838 CHF medication costs 5,749 CHF resource costs). Ranibizumab was the most expensive, with costs for the biosimilars estimated at CHF 17,497 at price range 1 and CHF 16,243 at price range 2, while the ranibizumab reference had total costs of CHF 18,424 over a 2-year time horizon. Its resource costs were 8,145 CHF with medication costs between 8,089 and 10,279 CHF. Medication costs were the main cost driver across all analysed anti-VEGF agents. In all the cases, the costs for the first year were higher than for the second year, with the extent of that difference varying between drugs. Detailed results are presented in Figure 1 and Table 5.

For DMO, aflibercept 8 mg is also associated with the lowest costs per patient, with the total costs estimated at CHF 11,242 per patient (i.e. 6,979 CHF medication costs and 4,264 CHF resource costs) over a 2-year time horizon. Aflibercept in the lower, 2 mg, formulation was the next most economical option, estimated at CHF 15,243 per patient (i.e. 9,584 CHF medication costs and 5,659 CHF resource costs) over two years. Treatment of DMO using faricimab was calculated to amount to CHF 17,537 per patient (i.e. 11,009 CHF medication costs and 6,528 CHF resource costs) over the same time horizon. The model identifies ranibizumab as the most expensive treatment option with the biosimilars generating lower costs compared to the reference product. The costs of the biosimilar ranged from CHF 19,596 to CHF 18,187 at price range 1 and 2. Meanwhile, the ranibizumab reference product led to a total cost of CHF 20,637. The resource costs of ranibizumab were 9,087 CHF with medication costs between 9,100 and 11,550 CHF. Again, medication costs were the main cost driver for all analysed anti-VEGF agents. Detailed results are presented in Figure 2 and Table 6.

Break-even analysis (price)

In addition to per-patient costs, our model calculated the break-even price for each anti-VEGF agent relative to the most cost-saving option at the time of writing, aflibercept 8 mg (Table 7). The estimations

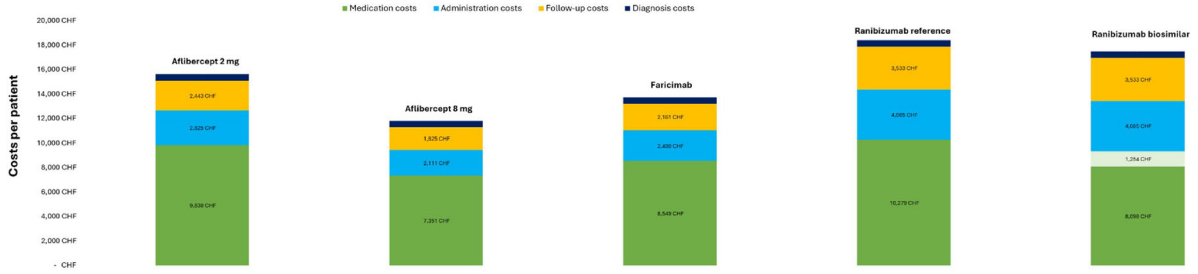

Figure 1. Visual overview of the costs per nAMD patient for all the anti-VEGFs included in the model. Showing the range in medication costs for the ranibizumab biosimilar depending on the price range that is selected (+1,254 at price range 1).

Table 5. Detailed overview of the costs per nAMD patient for all the anti-VEGFs included in the model, with the cheapest ranibizumab biosimilar selected (price range 2).

	Aflibercept 2 mg			Aflibercept 8 mg			Faricimab			Ranibizumab			Ranibizumab (biosimilar)		
	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs
Medication costs	6,048 CHF	3,790 CHF	9,838 CHF	4,602 CHF	2,749 CHF	7,351 CHF	5,143 CHF	3,406 CHF	8,549 CHF	5,524 CHF	4,754 CHF	10,279 CHF	4,352 CHF	3,746 CHF	8,098 CHF
Administration costs	1,737 CHF	1,088 CHF	2,825 CHF	1,321 CHF	789 CHF	2,111 CHF	1,503 CHF	996 CHF	2,499CHF	2,196 CHF	1,890 CHF	4,085 CHF	2,196 CHF	1,890 CHF	4,085 CHF
Control visit costs	1,502CHF	941 CHF	2,443CHF	1,143 CHF	683 CHF	1,825 CHF	1,300CHF	861 CHF	2,161 CHF	1,899 CHF	1,634 CHF	3,533 CHF	1,899 CHF	1,634 CHF	3,533 CHF
Diagnosis costs	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF
Total costs	9,814CHF	5,819CHF	15,632 CHF	7,593 CHF	4,221 CHF	11,814 CHF	8,474CHF	5,263 CHF	13,737 CHF	10,146CHF	8,278 CHF	18,424 CHF	8,974CHF	7,269 CHF	16,243 CHF

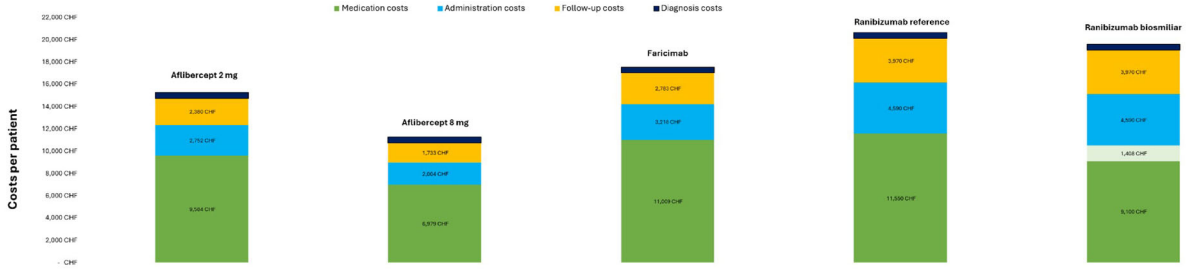

Figure 2. Visual overview of the costs per DMO patient for all the anti-VEGFs included in the model. Showing the range in medication costs for the ranibizumab biosimilar depending on the price range that is selected (+1,408 CHF at price range 1).

performed for nAMD show that to achieve the cost-equivalence of aflibercept 8 mg, the break-even list price of faricimab would need to be CHF 644 (i.e. −22%), while aflibercept 2 mg would have to decrease to CHF 518 (i.e. −39%). In the case of ranibizumab, the break-even price was calculated at CHF 218, which would mean a change in list price of −61% and −55% for the biosimilars (price range 1 and 2, respectively) and −64% for the ranibizumab reference product.

Break-even analysis for DMO showed that the second cheapest option, aflibercept 2 mg would need to have a list price of CHF 493 (i.e. −42%) to match the cost-equivalence of aflibercept 8 mg (Table 7). The break-even price for faricimab was estimated at CHF 356 (−57%). Ranibizumab's break-even price was estimated at CHF 114, requiring reductions of 79% and 76% for the biosimilars (price range 1 and 2, respectively) and 81% for the ranibizumab reference product.

Break-even analysis (injections)

The break-even analysis for the number of injections was performed relative to the agent with the lowest healthcare costs, aflibercept 8 mg in both nAMD and DMO (Table 7). It aimed to determine the mean number of injections at which the other anti-VEGF agents would have the same total costs as the cheapest option. Currently, for the nAMD population, the mean number of injections that was found for faricimab is 10.3, with the analysis break-even number estimated at 8.5 (i.e. −17%). At the same time, if the number of aflibercept 8 mg injections increases by 1.8, its cost becomes equivalent to that of faricimab. For aflibercept 2 mg, the break-even number of injections was 8.1, which is 30% less than the current mean number of 11.6. In the case of ranibizumab, the number of injections would have to drop from 16.8 to 9.7 (i.e. −42%) for the biosimilar at price range 1, to 10.7 (i.e. −36%) for the biosimilar at price range 2 and to 9.1 (i.e. −46%) for the ranibizumab reference.

For aflibercept 2 mg treatment in DMO, the break-even number of injections was calculated at 7.7 instead of the currently administered number, 11.3 (i.e. −32%). At the same time, in case the number of aflibercept 8 mg injections increases by 3.7, its costs become equivalent to that of aflibercept 2 mg. Faricimab, with the current mean number of injections reported at 13.3, would need to decrease it to 7.4 (i.e. −44%). Again, the reduction would need to be the highest in the case of ranibizumab, with the break-even number estimated at 8.4 and 9.3 for the ranibizumab biosimilars (at price range 1 and 2, respectively) and at 7.9 for the ranibizumab reference (i.e. −55%, −51%, and −58% respectively).

One-way sensitivity analysis

We conducted an OWSA to assess the impact that varying a single parameter value has on the model outcomes (Figures 3, 4). To assess this, we applied $a \pm 10\%$ variation to all model inputs. For both patient populations, the medication price was the most impactful parameter for all anti-VEGFs, followed by the injection frequencies of the first year and second year (Figure 3, Figure 4). The upper limit for aflibercept 8 mg in nAMD increased to CHF 12,549 with a higher medication price and to CHF 12,536 with increased injection frequency in year 2. In DME, it rose to CHF 11,940 with a higher medication price and to CHF 11,920 with increased injection frequency in year 1. Despite these increases, the upper values remained

Table 6. Detailed overview of the costs per DMO patient for all the anti-VEGFs included in the model, with the cheapest ranibizumab biosimilar selected (price range 2).

	Aflibercept 2 mg			Aflibercept 8 mg			Faricimab			Ranibizumab			Ranibizumab (biosimilar)		
	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs	Year 1	Year 2	Total costs
Medication costs	6,443 CHF	3,142 CHF	9,584 CHF	4,416 CHF	2,563 CHF	6,979 CHF	6,738 CHF	4,271 CHF	11,009 CHF	6,539 CHF	5,011 CHF	11,550 CHF	5,152 CHF	3,948 CHF	9,100 CHF
Administration costs	1,850 CHF	902 CHF	2,752 CHF	1,268 CHF	736 CHF	2,004 CHF	1,970 CHF	1,248 CHF	3,218 CHF	2,599 CHF	1,992 CHF	4,590 CHF	2,599 CHF	1,992 CHF	4,590 CHF
Control visit costs	1,600 CHF	780 CHF	2,380 CHF	1,096 CHF	636 CHF	1,733 CHF	1,703 CHF	1,080 CHF	2,783 CHF	2,247 CHF	1,722 CHF	3,970 CHF	2,247 CHF	1,722 CHF	3,970 CHF
Diagnosis costs	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF	527 CHF	- CHF	527 CHF
Total costs	10,419 CHF	4,824 CHF	15,243 CHF	7,307 CHF	3,935 CHF	11,242 CHF	10,938 CHF	6,598 CHF	17,537CHF	11,912 CHF	8,725 CHF	20,637 CHF	10,525 CHF	7,662 CHF	18,187 CHF

Table 7. Overview of the results of the break-even analyses.

		Aflibercept 2 mg	Aflibercept 8 mg	Faricimab	Ranibizumab	Ranibizumab biosimilar
nAMD	Break-even price (CHF)	518	N/A	644	218	218
	Current list price (CHF)	846	846	831	611	481
	Difference (%)	−39%	N/A	−22%	−64%	−55%
DMO	Break-even price (CHF)	493	N/A	356	114	114
	Current list price (CHF)	846	846	831	611	481
	Difference (%)	−42%	N/A	−57%	−81%	−76%
nAMD	Break-even nr injections	8.1	N/A	8.5	9.1	10.7
	Current nr injections	11.6	8.7	10.3	16.8	16.8
	Difference (%)	−30%	N/A	−17%	−46%	−36%
DMO	Break-even nr injections	7.7	N/A	7.4	7.9	9.3
	Current nr injections	11.3	8.3	13.3	18.9	18.9
	Difference (%)	−32%	N/A	−44%	−58%	−51%

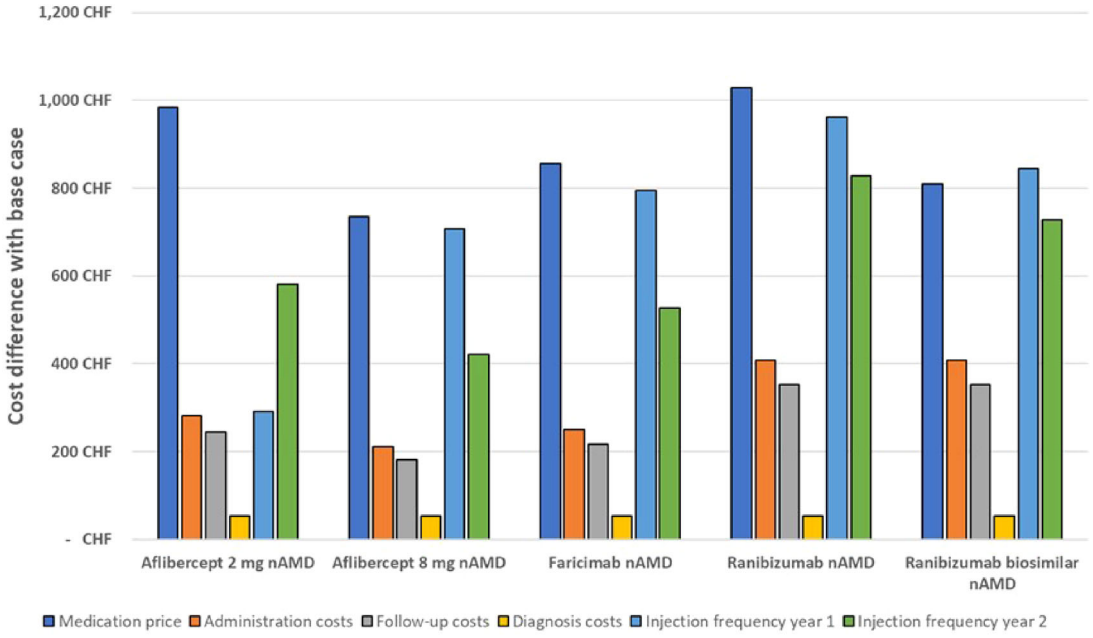

Figure 3. OWSA results for all anti-VEGFs for the nAMD population. Absolute difference compared to the base case outcomes because of the +-10% variation in parameter value inputs.

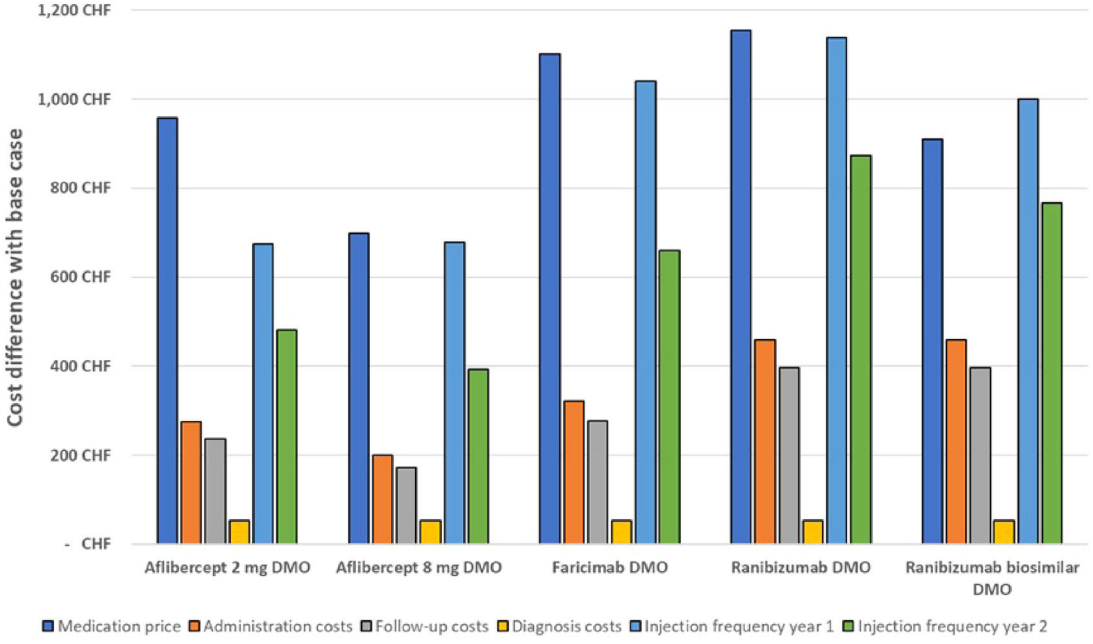

Figure 4. OWSA results for all anti-VEGFs for the DMO population. Absolute difference compared to the base case outcomes because of the +-10% variation in parameter value inputs.

below the deterministic costs of other anti-VEGF therapies. Only for the ranibizumab biosimilars the most sensitive parameter was the injection frequency of the first year, due to its lower medication price.

Discussion

This study highlights the impact of injection frequency on healthcare costs associated with the treatment of both nAMD and DMO. Healthcare costs in Switzerland are relatively high[24], and the use of anti-VEGF therapies with a more durable regimen could contribute to more efficient budget management. Even though a relatively short treatment period was incorporated in this study, the difference in healthcare costs between anti-VEGFs based on their clinical trial regimens was relevant. Aflibercept 8 mg in a flexible QW16 trial regimen was estimated to result in the lowest costs, with CHF 11,814 for nAMD and CHF 11,242 for DMO over two years. Faricimab was calculated to be the second least costly option in nAMD in a QW8/QW12/QW16 trial regimen with costs estimated at CHF 13,737. Aflibercept 2 mg in a T&E trial regimen was estimated the second least expensive option in DMO with the costs estimated at CHF 15,243. Although the ranibizumab biosimilars offer a lower medication price, their expected higher injection frequency in a T&E regimen was estimated to elevate overall healthcare costs, resulting in total costs of up to CHF 16,243 in nAMD and CHF 18,187 in DMO for the cheapest ranibizumab biosimilar. To achieve cost equality in nAMD and DMO with aflibercept 8 mg, ranibizumab biosimilars were calculated to require a medication price of CHF 218 in nAMD and CHF 114 in DMO, respectively.

The OWSA indicated that, besides medication price, the injection frequency had the most impact on results. We based those injection frequencies on clinical trial data. However, trials sometimes differ in their proposed treatment regimens, and this may influence the observed injection frequencies. Therefore, additional break-even analyses were conducted to estimate the relative costs in a real-world setting. Besides the reduced medication price needed to achieve cost equality with the least expensive treatment option, the reduction in injection frequency required for cost equality was calculated. The results indicated that, regarding the nAMD population, injection frequencies for aflibercept 2 mg, faricimab, ranibizumab, and the cheapest ranibizumab biosimilar would need to decrease by 30%, 17%, 46%, and 36%, respectively. While for the DMO population, injection frequencies would need to be reduced by 32%, 44%, 58% and 51%, respectively. Due to their lower medication costs, the cheapest ranibizumab biosimilar could sustain the highest injection frequency while remaining cost-equivalent to aflibercept 8 mg, allowing up to 10.7 and 9.3 injections over two years for the nAMD and DMO populations.

The higher dose of aflibercept 8 mg has been shown to allow for extended treatment intervals compared to aflibercept 2 mg in clinical trials, likely due to its reported 34% longer ocular clearance and possibly longer half-lives through the higher dosage[18,19,60]. While the current study highlights its impact on healthcare costs, it does not fully account for the broader, indirect benefits of a reduced treatment frequency. These indirect benefits are especially relevant as, although Swiss hospitals are known for their relatively short waiting times[61], the country's ageing population might increase the prevalence of age-related diseases[62]. Fewer hospital visits not only reduce demands on physicians' time but also minimize the burden on patients and caregivers. Many patients with DMO are still of working age, and hospital visits often involve the presence of a caregiver. Therefore, each visit can result in productivity losses and opportunity costs, adding to the economic burden on society. Beyond the economic implications, it is worth mentioning that optimised regimens could also improve patient experience, and possibly treatment adherence. Therefore, for future studies, it would be interesting to investigate the more indirect impact of the more durable treatment regimens of anti-VEGFs.

There are several limitations to the study, primarily induced by the limited availability of real-world data and the reliance on indirect comparisons across randomized clinical trials. While efforts were made to select trials with comparable regimens and set-ups, differences in study protocols (e.g. loading phases, re-treatment criteria, and follow-up durations) and study structures may have influenced the reported injection frequencies, which are the main input for the outcomes of this analysis. Notably, the model assumes that treatment regimens reported in the trials and specified in the product labels are followed exactly as reported in a clinical trial setting. These trials and treatment labels support extended dosing intervals of up to 16 or 24 weeks for aflibercept 8 mg and faricimab[10,16,17,41]. Nevertheless, the real-world applicability of these newer, more durable treatment regimens remains uncertain, particularly

given their recent approval and limited long-term usage data. Real-world data often shows different patterns, which might not fully be captured in clinical trial designs. For example, a real-world study in Switzerland estimated that the number of injections and treatment benefits has increased between the pre-2012 and post-2013 periods[63] – a trend which would not be captured by clinical trials. The OWSA and break-even analysis show the sensitivity of the results to the injection frequency and can be used to inform stakeholders of the relative costs of the anti-VEGFs, when injection frequencies in real-world regimens appear to higher or lower.

Moreover, while trials studying these regimens met their primary non-inferiority endpoints based on mean BCVA, a proportion of patients experienced disease activity that required shorter dosing intervals. The analysis uses mean injection frequencies, which incorporate both patients who remained on extended intervals and those who required more frequent injections to maintain visual outcomes, accounting for the variance in the trial regimens. However, by excluding BCVA as a modelled outcome, this approach does not fully capture potential fluctuations in visual acuity caused by under treatment and their clinical impact. The implications of this limitation are expected to be limited, as the model uses a short-term time horizon and indirect comparisons showed non-significant differences between treatments.

Another limitation is that the study utilized TARMED data to estimate the costs related to administration, diagnosis, and monitoring. However, actual costs in real-life settings may vary, especially when patients are examined for bilateral involvement. However, at the time of this analysis, no real-world studies in Switzerland had examined the injection frequencies specific to each anti-VEGF therapy or provided comprehensive treatment cost data across all related procedures.

Additionally, the study did not include treatment adherence rates and treatment pathways over time, thus, again, outcomes may not reflect routine clinical practice. Treatment adherence rates may vary between patient groups, types of anti-VEGF therapies, and treatment regimens, potentially influencing treatment outcomes[63]. For example, a study from the United States, performed before the introduction of aflibercept 8 mg and faricimab, reported that extended injection frequencies were linked to increased treatment discontinuation[64]. Additionally, European studies have highlighted different patterns: a Dutch study observed more frequent switching among patients initially treated with off-label bevacizumab, while a French study noted a stronger preference for flexible treatment regimens by physicians[65,66]. These studies suggest that the impact of newer, more durable regimens on adherence and treatment pathways, and their effect on clinical outcomes, may differ from clinical trial results and depend on the healthcare context. As the current analysis assumed an equal treatment effect for all anti-VEGFs, treatment adherence and its impact on clinical outcomes could not be included. However, as more data become available on treatment adherence in the Swiss setting, particularly in relation to newer therapies, it will be important to revisit these assumptions and assess their implications for both clinical and economic outcomes.

Lastly, since the available data primarily covered a 2-year period, the study did not account for the potential to extend treatment intervals over a longer duration. Patients are often treated for more than two years[63], and under a flexible regimen, there is the possibility to progressively extend treatment intervals. By year two, the maximal treatment intervals may not yet have been reached. Incorporating longer-term data, once available, would provide valuable insights for further analysis.

This is the first study that calculates the healthcare costs of treatment with anti-VEGFs from a Swiss perspective. By incorporating cost data from hospital databases, it provides insights specific to the Swiss context, helping relevant stakeholders better understand the costs associated with 1- and 2-year anti-VEGF treatments. By focusing solely on treatment-related costs and excluding the equivalent treatment effect, the study remains straightforward, and results are easy to interpret in clinical practice. Moreover, the break-even analysis helps to account for possible changes in the treatment landscape, such as cheaper biosimilars entering the market.

In conclusion, this study shows that the injection frequency and treatment regimen have a considerable impact on the healthcare costs associated with anti-VEGF treatment in nAMD and DMO. Based on clinical trial outcomes, the more durable regimen of aflibercept 8 mg could reduce the injection frequency compared to other anti-VEGFs, which may result in the lowest estimated treatment costs in both nAMD and DMO from a Swiss healthcare payer's perspective.

Transparency

Declaration of funding

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Declaration of financial/other relationships

AA has received grants from Bayer and Roche, and has served as a consultant speaker for Abbvie, Apellis, Astellas, Roche, Novartis, and RetinAI. SWQ is an employee at Asc Academics and MB was employed there at the time of writing. SM is an employee at Bayer (Schweiz) AG, Switzerland. DB has a consultancy agreement with ALCON and has received study support from Novartis and Bayer in the past, with no ongoing payments.

Peer reviewers on this manuscript have received an honorarium from JME for their review work. One of the reviewers received honorary for consultation and lectures from Abbvie/Allergan, Bayer, Novartis and Roche/Genentech. Another of the reviewers has been a consultant for Bayer, Revana, Biogen, Regeneron.

Author contributions

AA contributed to manuscript writing, validation of input data, and evaluation of model assumptions. SWQ participated in manuscript writing. MB was responsible for model adaptation and manuscript writing. SM generated the cost inputs used in the analysis. DB contributed to the validation of input data and model assumptions. All authors have contributed to the concept and read and reviewed the final manuscript.

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