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SYSTEMATIC REVIEW

Use of Aflibercept 8 mg for the Treatment of Diabetic Macular Edema in Italy: A Cost-Minimisation Analysis Based on an Indirect Treatment Comparison

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ABSTRACT

Introduction: Despite the availability of various anti-vascular endothelial growth factor (anti-VEGF) therapies for diabetic macular edema (DME), high treatment burden remains a significant issue in many European countries, including Italy. This burden impacts healthcare costs, clinic capacities, and patient adherence. Aflibercept 8 mg was developed to reduce treatment burden by requiring only three monthly injections before allowing extended dosing intervals up to 6 months, without compromising efficacy and safety. This analysis aimed to evaluate the efficacy, safety, and treatment burden of aflibercept 8 mg regimens compared to other anti-VEGF options (aflibercept 2 mg, ranibizumab 0.5 mg, faricimab 6 mg, brolucizumab 6 mg, and bevacizumab 1.25 mg) in Italy.
Methods: A systematic literature review identified randomised controlled trials of anti-VEGF therapies for DME with a 2-year follow-up. This informed a Bayesian network meta-analysis (NMA) assessing efficacy, safety, and treatment burden. A cost-minimisation analysis (CMA) was conducted from the perspective of the Italian National Health System over a 2-year horizon.
Results: The NMA, involving nine studies, showed no significant differences in best-corrected visual acuity, anatomical outcomes, and safety between aflibercept 8 mg and the other anti-VEGF agents. Aflibercept 8 mg required fewer injections than the comparators, with a mean of 9.3 injections over 2 years for T&E (Q12) and 8.4 for T&E (Q16) regimens. Economically, aflibercept 8 mg was the least costly licensed and reimbursed anti-VEGF in Italy.
Conclusion: Aflibercept 8 mg may be the most advantageous anti-VEGF option for reducing treatment burden in Italian patients with DME, benefiting healthcare providers, clinics, and the

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healthcare system. Aflibercept 8 mg offers comparable efficacy and safety to other anti-VEGF therapies, with fewer injections and potentially lower overall costs.

PLAIN LANGUAGE SUMMARY

Diabetic macular edema is a common complication of diabetes that causes fluid build-up and vision loss in the central part of the retina. The most often used treatments block vascular endothelial growth factor, a protein that causes leaking blood vessels in the eye. These drugs work well, but patients often need frequent eye injections. Frequent injections increase costs for the healthcare system and patients too, clinic visits, and make it harder for patients to stick with treatment. We reviewed 2-year results from clinical trials of several anti-vascular endothelial growth factor drugs. We combined the trial data using a statistical method that lets us compare many treatments even when trials did not directly compare every option. We also compared 2-year healthcare costs from the Italian public health system perspective. The newest drug, aflibercept at an 8 mg dose, delivered vision and retinal outcomes similar to other available drugs. It showed similar safety. Patients receiving aflibercept 8 mg needed fewer injections over 2 years, about 8 to 9 injections in 2 years. In the cost analysis, aflibercept 8 mg was the least costly option among licensed and reimbursed drugs in Italy. All this means that aflibercept 8 mg may reduce the number of injections and clinic visits without sacrificing effectiveness or safety. This can lower strain on clinics, reduce costs for the health system, and make it easier for patients to stay on treatment.

Keywords: Diabetic macular edema; Aflibercept; Aflibercept 8 mg; Anti-VEGF; Treatment frequency; Intravitreal injection; Indirect treatment comparison; Network meta-analysis; Cost-minimisation

Key Summary Points

Diabetic macular edema (DME) causes vision loss in patients with diabetes and creates substantial clinical and economic burden in Italy, driven by the need for frequent intravitreal injections.

Anti-vascular endothelial growth factor (anti-VEGF) drugs are the first-line treatment for DME but their high treatment burden increases pressure on clinics, healthcare and patient costs, and risks of patient nonadherence.

This study asked whether aflibercept 8 mg, the most recently approved and reimbursed anti-VEGF, administered with three monthly loading doses and allowing extended dosing up to 6 months, delivers comparable efficacy and safety but fewer injections and lower costs than other available anti-VEGF therapies in Italy.

A Bayesian network meta-analysis of nine 2-year trials found no significant differences in visual acuity, retinal anatomy, or safety between aflibercept 8 mg and other anti-VEGF agents, while aflibercept 8 mg required the fewest injections (mean 8.4–9.3 injections over 2 years, depending on treatment regimen) and was the least costly licensed and reimbursed option in Italy (€10,883 per patient over 2 years).

Aflibercept 8 mg with extended dosing intervals could reduce treatment burden for patients and clinics without compromising outcomes and may produce cost savings for the Italian National Health Service, although real-world and longer-term studies are needed to confirm system level benefits.

INTRODUCTION

Diabetic macular edema (DME), a complication of diabetic retinopathy, is a leading cause of vision loss across all age groups with diabetes [1]. In 2010, the global prevalence was estimated at 21 million people, projected to rise to 33 million by 2030 due to increasing diabetes prevalence [2, 3]. In Europe, DME affects 3.7% of people with diabetes, with higher frequency in type 1 than type 2 diabetes [4]. In Italy, however, epidemiological data remain limited due to the absence of a national registry of diabetic retinopathy [5]. This gap highlights the need for further investigation, particularly given the substantial clinical, humanistic, and healthcare burden associated with DME [6].

Since 2012, anti-vascular endothelial growth factor (anti-VEGF) drugs have become the first-line therapy for DME, showing superiority over laser photocoagulation in preserving vision [7–11]. Intravitreal corticosteroids, such as dexamethasone, are generally considered a second-line option after inadequate response to anti-VEGF therapy [9, 12]. Ranibizumab was reimbursed in Italy in 2012 [13], followed by aflibercept 2 mg in 2015, faricimab in 2023, brolucizumab in 2024, and most recently aflibercept 8 mg in 2024 [14, 15]. Despite their effectiveness, anti-VEGF therapies require frequent injections and clinic visits, leading to patient nonadherence and suboptimal outcomes [16–20]. Extended regimens, such as pro re nata (PRN) and treat-and-extend (T&E) aim to reduce treatment burden but require durable therapies to avoid compromising therapeutic efficacy or patient safety [21, 22].

To address the unmet needs associated with treatment burden, 8 mg aflibercept was developed as a longer-durability therapy option. In the PHOTON phase 2/3 clinical trial, aflibercept 8 mg was studied in two flexible treatment arms: aflibercept 8 mg T&E (Q12) defined as 3 monthly injections followed by treatment every 12 weeks, which could be reduced in the first year and reduced or extended in 4-week increments up to 24 week intervals in the second year; and aflibercept 8 mg T&E (Q16) as 3 monthly injections followed by treatment every 16 weeks, which could be reduced in the first year and reduced or extended in 4-week increments up to 24 week intervals in the second year. On the comparator arm aflibercept 2 mg was administered in a fixed Q8 regimen after 5 monthly injections. Aflibercept 8 mg, administered at extended treatment intervals, demonstrated non-inferiority in visual outcomes compared with the current standard of care, aflibercept 2 mg. At 96 weeks, 71% of patients treated with aflibercept 8 mg had a last completed dosing interval of ≥ 16 weeks, and 44% had a last assigned dosing interval of ≥ 20 weeks [23]. However, PHOTON did not provide head-to-head comparisons with other anti-VEGFs or evaluate economic outcomes. Quist et al. compared the efficacy and safety of aflibercept 8 mg to other anti-VEGF agents in the treatment of DME, by performing a network meta-analysis (NMA) approach on data from randomised clinical trials with approx. 1 year duration [24]. Recently another NMA has been published focusing on the comparison of aflibercept 8 mg versus faricimab [25]. Both analyses suggested comparable efficacy and safety profiles of aflibercept 8 mg to other anti-VEGFs, while maintaining a lower injection burden. However, comparative evidence of all available anti-VEGF therapies on longer-term efficacy, safety, treatment burden, and economic implications are not still available. Using Italy as a case study, this analysis had two objectives. The first was to compare flexible treatment regimens of available anti-VEGF therapies in terms of efficacy, safety, and frequency of administration through an indirect treatment comparison (ITC) using 2-year clinical trial data. The second was to perform an economic analysis, informed by the ITC, to assess the potential cost differences between the available anti-VEGF drugs from the perspective of the Italian healthcare system.

METHODS

Study Identification and Inclusion

A systematic literature review (SLR) was conducted to identify randomised controlled trials (RCTs) suitable for inclusion in the ITC. Medline and Embase databases were searched on 22 September 2023, and Cochrane library and clinical trials registry ClinicalTrials.gov were searched on 25 September 2023. No restrictions were applied to the publication date.

The population of interest included patients with DME, either treatment-naïve or previously treated. Eligible interventions were aflibercept 8 mg, aflibercept 2 mg, bevacizumab, ranibizumab, brolucizumab, faricimab, and dexamethasone. The primary outcome of interest was the mean change in best corrected visual acuity (BCVA) from baseline, assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts as the gold standard [26]. Secondary outcomes of interest included central retinal thickness (CRT) or central subfield thickness (CST), safety outcomes, and frequency of intravitreal injections.

No restrictions were applied to the geographical setting, with results considered generalisable to Italy. Only RCTs enrolling ≥ 40 patients or eyes were included, to reduce publication bias and uncertainty associated with small sample sizes. Full eligibility criteria are reported in Supplementary Table S1.

Indirect Treatment Comparison

After identification of eligible studies in the SLR, further restrictions were applied to ensure suitability for the NMA informing the ITC. Studies were excluded if they lacked a relevant comparator or could not be connected to the PHOTON trial within the evidence network, with the ITC and subsequent cost comparisons focused exclusively on anti-VEGF therapies. Furthermore the findings of the SLR were supplemented with long-term clinical data on faricimab versus aflibercept 2 mg when the YOSEMITE and RHINE 2-year results were published in early 2024 [27, 28] and with 96-week data from the PHOTON trial studying aflibercept 8 mg compared to aflibercept 2 mg once the clinical study reports were generated internally (since published by Do et al. [23]).

The primary analysis was conducted using a Bayesian NMA with non-informative prior distributions, ensuring that results were driven solely by the input data. This approach is consistent with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good research practices [29]. Likelihood distributions were defined to relate the data to the parameters of the models. For continuous variable outcomes (BCVA change from baseline, CRT/CST change from baseline, CRT/CST percent change from baseline), a normal distribution identity link function was employed. For dichotomous outcomes (e.g. ocular adverse events, gaining/losing at least 15 letters BCVA), a binomial logit function was used. A flat prior distribution was adopted to minimise bias from prior assumptions, consistent with established practice [30].

Generation of the posterior distributions of the output parameters was based on a simulation process using the Markov chain Monte Carlo (MCMC) approach. Three independent chains of 100,000 iterations were generated, starting from randomly generated initial values. The first 25,000 iterations of each chain were discarded as burn-in. Both fixed- and random-effects models were used, following heterogeneity testing, with I^2 and deviance information criterion (DIC) values reported. Outputs were reported as tabular comparisons ("each vs each"), forest plots, and the surface under the cumulative ranking curve (SUCRA). For the primary outcomes (change in BCVA from baseline), a margin of 5 letters was considered non-inferior, reflecting the minimum clinically important difference reported in the literature [31].

The statistical analysis was implemented in R (version 4.3.2) [32] using the gemtc package [33]. The simulations were run in the background using JAGS, version 4.3.1 [34].

Economic Analysis

Differences in efficacy outcomes of anti-VEGF therapies were within the margin on non-inferiority in the current and previous analyses as well, and no significant differences in safety were registered [24, 35]. Therefore a cost-minimisation analysis (CMA) framework was applied to estimate the economic impact of aflibercept 8 mg compared with the alternative treatment options available in Italy for patients with DME (aflibercept 2 mg, ranibizumab, faricimab, brolucizumab, and bevacizumab [off-label use regulated by law 648]) [36]—in alignment with previously published economic analyses, including UK National Institute for Health and Care Excellence (NICE) assessments [24, 35]. The aflibercept 8 mg flexible T&E (Q12) regimen was selected as the reference treatment, representing a conservative approach that is less different than gradual treatment interval extensions typically utilized in clinical practice.

A previously developed cost-effectiveness model was adapted and modified to perform the CMA [24, 37]. This was a bilateral vision Markov state transition model which adopted a three-phase approach based on efficacy, maintenance, and rest-of life phase. Using a cost-comparison approach, all efficacy was considered equal to aflibercept 8 mg and utility inputs were removed. Consistent with previous health technology assessments [38, 39], the only differences in inputs across treatment regimens were drug costs, injection procedure cost, and costs of monitoring exams and visits. Given the comparable safety profiles of anti-VEGFs, no differences in AE rates were expected from this updated NMA—and therefore no safety costs were included in the economic analysis.

The analysis adopted the perspective of the Italian National Health system and a 2-year time-horizon, based on the follow-up of the studies included in the NMA.

The NMA estimated the frequency of injections within the available anti-VEGF regimens, which was used to assess drug consumption, and the number of injection administration processes performed. If a comparator was excluded from the current NMA of 2-year data, data from a previous 1-year indirect comparison were used.

For each treatment, the regimen associated with the lower number of injections, as estimated by the NMA, was selected. The number of monitoring appointments and visits for each treatment was reported based on NICE technology assessments TA799, TA824, and expert opinion (Supplementary Table S2).

The ex-factory Italian price with mandatory discount (– 5%) was used for calculating the treatment cost (Supplementary Table S3). The injection cost for the Italian setting was retrieved from the literature and set at €247 per injection [40]. Monitoring and exam costs included a routine monitoring visit, optical coherence tomography (OCT), and fluorescein angiography, based on Italian ambulatory tariff [40]. A one-way sensitivity analysis tested the effect of variability in key cost parameters on the observed cost differences.

Further, to test the impact of different drug costs on the economic impact associated with aflibercept 8 mg vs other licensed drug options, two-way sensitivity analyses were conducted assuming different discount rate for aflibercept 8 mg and each licensed drug. A threshold analysis was also performed to determine the level of discount required for aflibercept 8 mg to reach cost parity with bevacizumab PRN. Finally, the threshold analysis was also performed in an alternative scenario using the aflibercept 8 mg T&E (Q16) regimen instead of the T&E (Q12).

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Studies Included

After removal of duplications, a total of 6835 records were screened in the SLR, of which 6493 were excluded at the title and/or abstract stage. Of 342 full-text articles retrieved for review, 57 studies (reported in 77 publications) met the SLR inclusion criteria (Fig. 1). Following further assessment for suitability in the NMA, only 10 RCTs were deemed eligible (9 included in the base case).

The included studies varied in sample size, ranging from 65 to 951 patients. Baseline visual acuity also differed, with mean BCVA values ranging from 55.4 to 72.5 ETDRS letters. Similarly, mean baseline CRT/CST measurements ranged from 285.9 to 540.0 μm. The study characteristics are summarised in Table 1.

Indirect Treatment Comparison

The included studies enabled the construction of a polymodal NMA model (Fig. 2), including

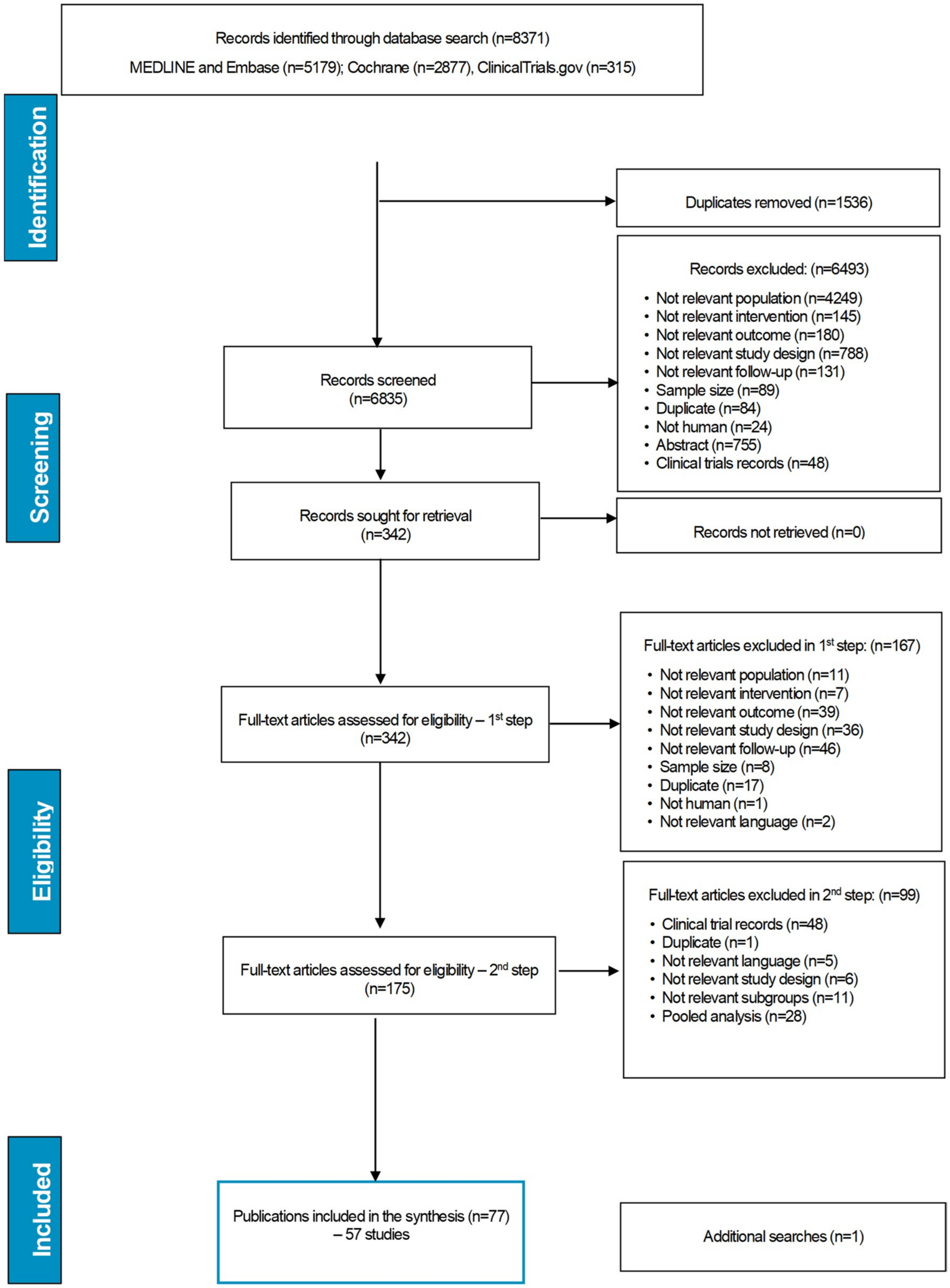

Fig. 1 PRISMA diagram of the search results of the SLR

aflibercept 2 mg, faricimab, brolucizumab, bevacizumab, and aflibercept 8 mg. Trials including ranibizumab arms could not be connected to the network and were therefore excluded from the comparative analyses on efficacy and safety. However, as the numbers of injections were estimated by a meta-analysis, ranibizumab studies could be included there. A random effects model

Table 1 Characteristics of the included studies

Study	Sample size*	Follow-up	Treatment arm	Baseline characteristics	
				BCVA mean (SD)	CRT [μm] mean (SD)
PHOTON [22]	328	2 years	AFL 8 mg T&E (Q12)	63.6 (10.1)	449.1 (127.4)
	163		AFL 8 mg T&E (Q16)	61.4 (11.8)	460.3 (117.8)
	167		AFL 2 mg Q8	61.5 (11.2)	457.2 (144.0)
BOLT [48]	37	2 years	BEV PRN	55.8 (9.7)	NR
	28		Laser PRN	55.4 (7.9)	NR
KESTREL [49]	189	100 weeks	BRO Q12/Q8	66.6 (9.7)	453.0 (123.0)[†]
	187		AFL 2 mg Q8	65.2 (12.4)	476.0 (136.0)[†]
KITE [49]	179	100 weeks	BRO Q12/Q8	66.0 (10.8)	481.0 (132.0)[†]
	181		AFL 2 mg Q8	63.7 (11.7)	484.0 (135.0)[†]
Protocol T [45]	201	104 weeks	AFL 2 mg PRN	69 (59; 74)[b]	411.0 (131.0)[†]
	185		BEV PRN	69 (60; 73)[b]	415.0 (134.0)[†]
RHINE [28]	315	2 years	AFL 2 mg Q8	62.1 (9.4)	477.3 (129.4)[†]
	317		FAR Q8	61.9 (10.1)	466.2 (119.4)[†]
	319		FAR T&E	62.5 (9.3)	471.3 (127.0)[†]
VIOLET[a] [50]	153	100 weeks	AFL 2 mg Q8	72.7 (10.4)	289.9 (66.8)
	152		AFL 2 mg T&E	72.5 (11.4)	285.9 (76.3)
	153		AFL 2 mg PRN	71.0 (10.9)	294.6 (81.0)
VISTA [51]	155	96 weeks	AFL 2 mg Q4	58.9 (10.8)	485.0 (157.0)
	152		AFL 2 mg Q8	59.4 (10.9)	479.0 (154.0)
	154		Laser PRN	59.7 (10.9)	483.0 (153.0)
VIVID [52]	136	96 weeks	AFL 2 mg Q4	60.8 (10.7)	502.0 (144.0)
	135		AFL 2 mg Q8	58.8 (11.2)	518.0 (147.0)
	133		Laser PRN	60.8 (10.6)	540.0 (152.0)
YOSEMITE [28]	312	2 years	AFL 2 mg Q8	62.2 (9.5)	484.5 (131.1)[†]
	315		FAR Q8	62.0 (9.9)	492.3 (135.8)[†]
	313		FAR T&E	61.9 (10.2)	485.8 (130.8)[†]

AFL aflibercept, *BCVA* best corrected visual acuity in ETDRS letters, *BEV* bevacizumab, *CRT* central retinal thickness, *FAR* faricimab, *NR* not reported, *PRN* pro re nata, *QX* every X weeks, *SD* standard deviation, *T&E* treat-and-extend

[a]VIOLET trial was excluded in the primary analysis but included in sensitivity analysis

[b]median (75th, 25th percentile)

*Only relevant treatment arms considered

[†]Central subfield thickness (CST) in μm

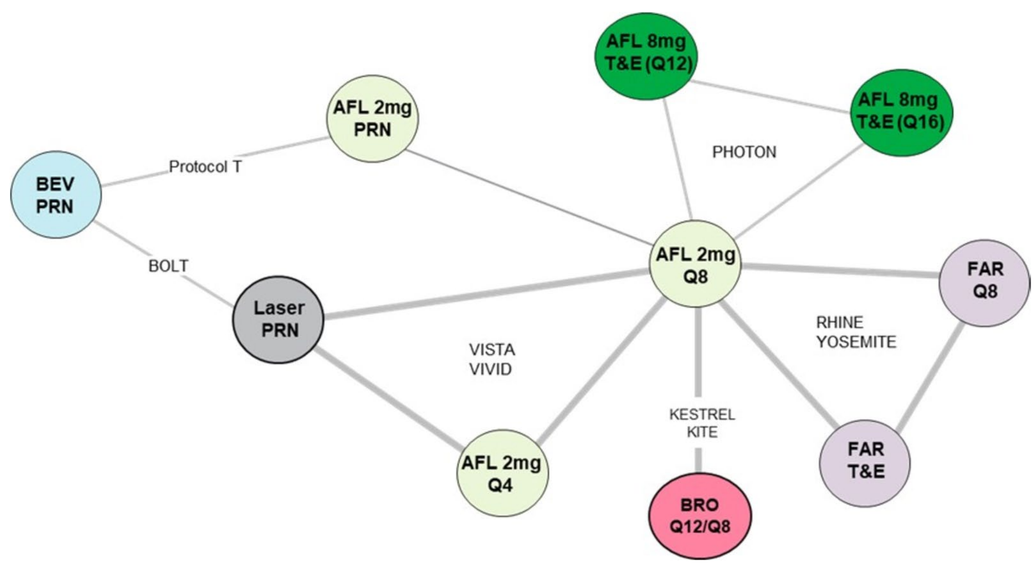

Fig. 2 Network of evidence for BCVA gain

was selected for the primary analysis due to evidence of study heterogeneity, with the I^2 value exceeding 30% under the fixed-effect model [41].

For the primary outcome, mean change in BCVA from baseline after 2 years of treatment, the NMA showed no significant differences between the two aflibercept 8 mg regimens or when compared with any of the other anti-VEGF therapies. In terms of point estimates, aflibercept 8 mg T&E (Q12) demonstrated favourable outcomes versus aflibercept 2 mg Q8, bevacizumab PRN, brolucizumab Q12/Q8, faricimab T&E, and faricimab PRN. Across most comparisons, observed differences were close to the prespecified non-inferiority margin, remaining within the minimum clinically important difference (MCID) of 5 letters [42].

Overall, fixed-effects model results were consistent with the random effects model; however, under the fixed-effects assumption, all estimates fell within the non-inferiority margin, except for bevacizumab PRN, which was associated with particularly wide credibility intervals (CrIs). The results are illustrated in Fig. 3.

The highest probability for being the most effective treatment was observed with aflibercept 2 mg PRN (50%), as illustrated by the SUCRA rankings (Fig. 4). Aflibercept 2 mg PRN ranked first, followed by aflibercept 2 mg Q4 and aflibercept 8 mg T&E (Q12). However, as these rankings do not account for the magnitude of estimates, and the differences between aflibercept 8 mg T&E (Q12) and aflibercept 2 mg PRN were not significant, the obtained probabilities should be interpreted with caution.

Aflibercept 8 mg T&E (Q12) was associated with a higher probability of being more effective compared with aflibercept 8 mg T&E (Q16) (0.81), aflibercept 2 mg Q8 (0.6), bevacizumab PRN and faricimab T&E (0.58), brolucizumab Q12/Q8 (0.53), and faricimab Q8 (0.51).

The NMA of anatomical outcomes (CRT or CST mean change from baseline, based on five trials) found no significant differences between aflibercept 8 mg and aflibercept 2 mg regimens. Similarly, no significant differences were observed when comparing aflibercept 8 mg with brolucizumab (Fig. 5). These findings were consistent in the analysis of mean percentage change from baseline analysis (Table 2).

Odds ratios (OR) for ocular adverse events were comparable between aflibercept 8 mg and other anti-VEGF therapies. Due to the wide confidence intervals in the comparison versus bevacizumab, no significant difference was demonstrated; however, the point estimate results may suggest a preference towards aflibercept 8 mg

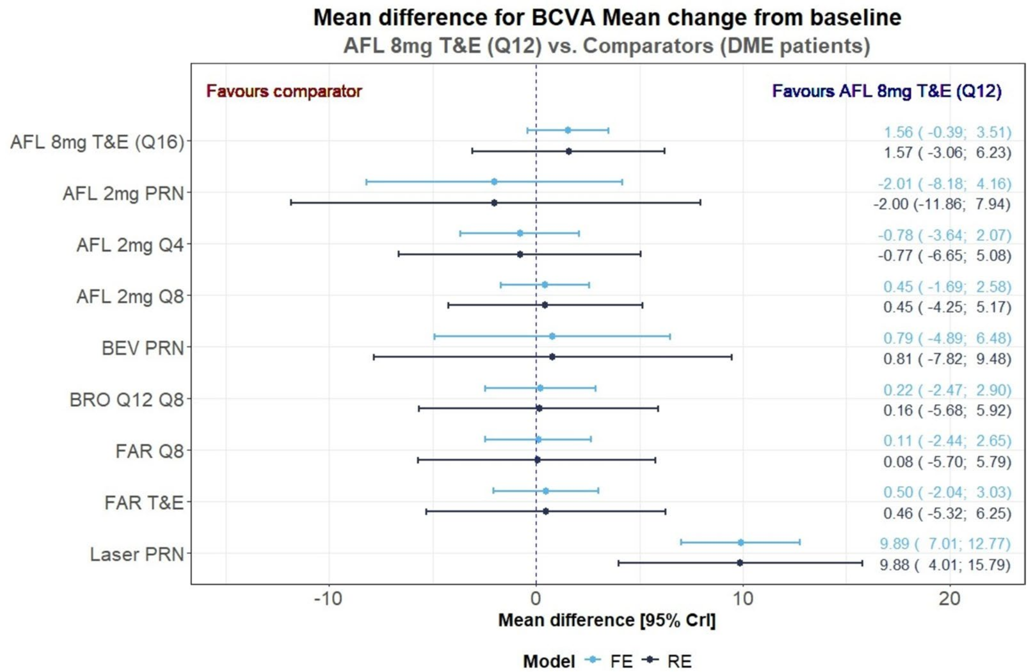

Fig. 3 Forest plot comparing AFL 8 mg Q12 vs comparators for BCVA mean change from baseline. *AFL* aflibercept, *BCVA* best corrected visual acuity in ETDRS letters, *BEV* bevacizumab, *BRO* brolucizumab, *CrI* credible interval, *FAR* faricimab, *FE* fixed effects, *PRN* pro re nata, *QX* every X weeks, *RE* random effects, *T&E* treat-and-extend

versus bevacizumab (Fig. 6). The OR of non-ocular adverse events were also comparable between aflibercept 8 mg and the three comparators for which data were available (Fig. 7).

The mean number of injections in a 2-year horizon was reported in eight of the included trials. The lowest mean number of injections was observed with the aflibercept 8 mg T&E (Q16) (8.37; 95% CI 8.09–8.64), followed by aflibercept 8 mg T&E (Q12) (9.33; 95% CI 9.07–9.59), and brolucizumab Q8/Q12 (10.74; 95% CI 10.40–11.07). In contrast, aflibercept 2 mg Q4 required the highest number of injections, with a mean of 22.84 (95% CI 21.49–24.20). These results are illustrated in Table 3.

Cost-Minimisation Analysis

Base Case

The base case analysis assessed the total per-patient cost of anti-VEGF treatments, using aflibercept 8 mg T&E (Q12) as the reference treatment. This analysis demonstrated that aflibercept 8 mg was the least costly licensed anti-VEGF option, with a total cost of €10,883 over 2 years. Compared to aflibercept 8 mg, aflibercept 2 mg was 44% more expensive (€4763 higher), ranibizumab 0.5 mg was 22% more expensive (€2400 higher), faricimab was 26% more expensive (€2805 higher), and brolucizumab was 9% more expensive (€944 higher).

Bevacizumab was the only treatment with a lower total cost (€4666); however, this remains an off-label treatment option (as currently no bevacizumab product is reimbursed in Italy with approved ophthalmologic indications and national guidelines recommend off-label use of Avastin).

Sensitivity Analysis

The one-way sensitivity analysis reporting drugs cost and administration costs as the main parameters which affect results (Supplementary Fig. S1).

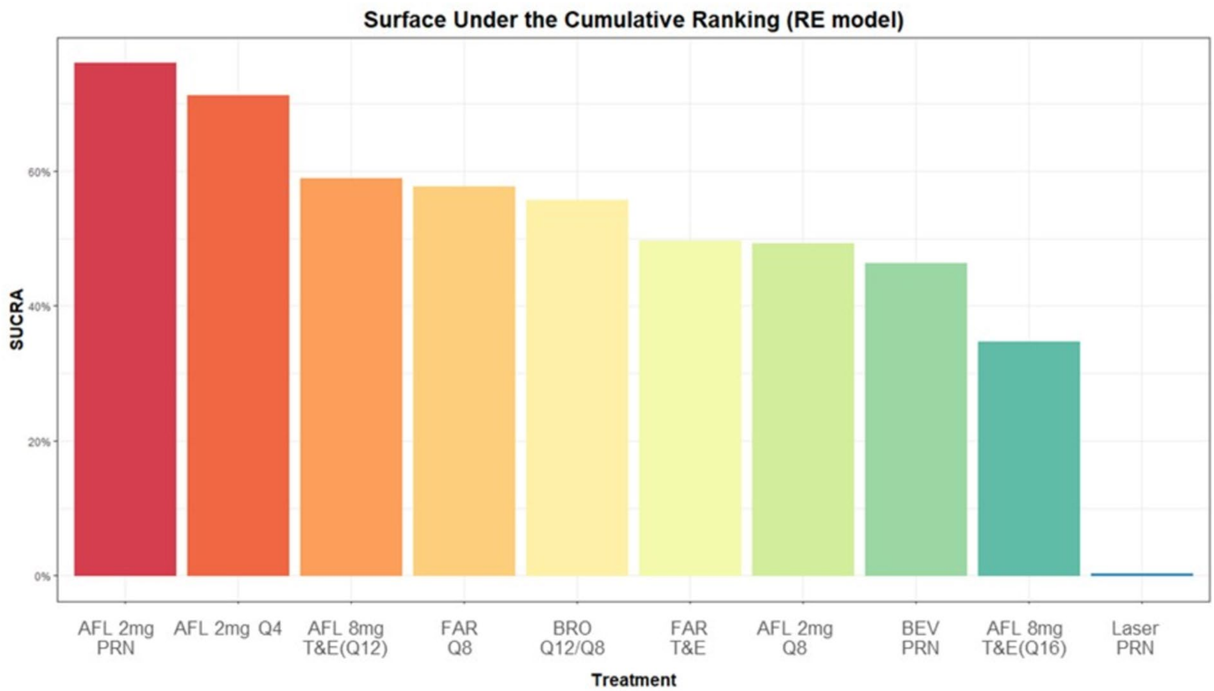

Fig. 4 Surface under the cumulative ranking (SUCRA) for BCVA mean change from baseline, primary analysis, random effects model. *AFL* aflibercept, *BCVA* best corrected visual acuity in ETDRS letters, *BEV* bevacizumab, *BRO* brolucizumab, *CrI* credible interval, *FAR* faricimab, *FE* fixed effects, *PRN* pro re nata, *QX* every X weeks, *RE* random effects, *T&E* treat-and-extend

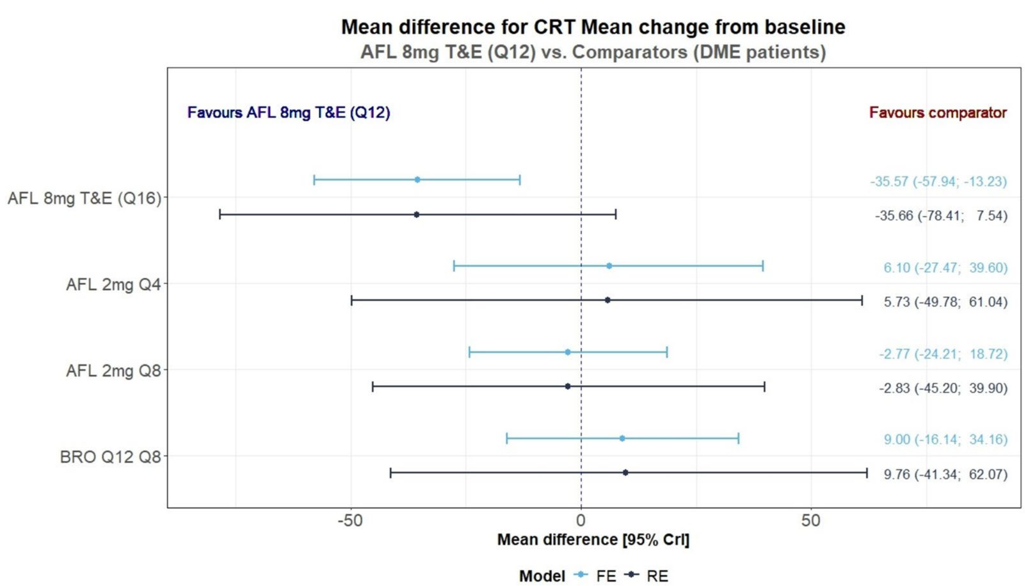

Fig. 5 Forest plot comparing AFL 8 mg Q12 vs comparators for CRT mean change from baseline. *AFL* aflibercept, *BRO* brolucizumab, *CrI* credible interval, *CRT* central retinal thickness, *FE* fixed effects, *QX* every X weeks, *RE* random effects, *T&E* treat-and-extend

Table 2 Cost-minimisation analysis results: cost per patient associated with each anti-VEGF and cost variation using aflibercept 8 mg as reference

	Drug			Healthcare resource use			Total		
	Cost	Δ cost	Δ %	Cost	Δ cost	Δ %	Total	Δ cost	Δ %
Aflibercept 8 mg T&E (Q12)	€ 8280	–	–	€ 2603	–	–	€ 10,883	–	–
Aflibercept 2 mg Q8	€ 11,920	€ 3640	44%	€ 3726	€ 1123	43%	€ 15,646	€ 4763	44%
Ranibizumab 0.5 mg PRN	€ 9713	€ 1433	17%	€ 3570	€ 967	37%	€ 13,283	€ 2400	22%
Faricimab 6 mg T&E	€ 10,290	€ 2010	24%	€ 3398	€ 795	31%	€ 13,688	€ 2805	26%
Brolucizumab 6 mg Q12/Q8	€ 8818	€ 538	7%	€ 3008	€ 405	16%	€ 11,827	€ 944	9%
Bevacizumab 1.25 mg PRN	€ 1429	− € 6851	− 83%	€ 4789	€ 2186	84%	€ 6218	− € 4666	− 43%

PRN pro re nata, *QX* every X weeks, *T&E* treat-and-extend

Two-way sensitivity analysis was conducted to assess the effect of variations in drug price discounts on the cost differences between anti-VEGF treatments (Fig. 8), suggesting that even a modest discount on aflibercept 8 mg price would require its comparators to decrease their prices significantly to attempt to balance savings associated with lower number of injections. In a scenario where a 15% discount is applied on the price of aflibercept 8 mg, the price of aflibercept 2 mg would need to be decreased by 50%, the price of ranibizumab by 38%, the price of brolucizumab by 26%, and the price of faricimab by 40% in order to achieve neutrality of total costs. These results provide insights for decision makers including treating physicians, pharmacists, and payers, on the extent to which cost reductions may or may not offset savings due to differences in injection frequency (Fig 9).

To further investigate the impact of price reductions, a threshold analysis was performed to determine the level of discount required for aflibercept 8 mg to reach cost parity with bevacizumab 1.25 mg PRN. In the conservative scenario of 8 mg T&E (Q12) regimen as base case, a discount rate of 55% was estimated to have a parity cost between aflibercept 8 mg and bevacizumab.

Scenario Analysis: Aflibercept 8 mg T&E (Q16)

Results of a scenario analysis with aflibercept 8 mg T&E (Q16) are reported in Supplementary Table S4. The savings with aflibercept 8 mg were higher in this scenario, reflecting the further reduction in injection frequency with this regimen: 58% cost reduction (€5775) vs aflibercept 2 mg, 38% cost reduction (€3798) vs faricimab, 34% cost reduction (€3393) vs ranibizumab, 20% cost reduction (€1936) vs brolucizumab.

In the threshold analysis performed for this alternative scenario a discount rate of 46% was estimated to have a parity cost between aflibercept 8 mg T&E (Q16) and bevacizumab (Supplementary Fig. S2).

DISCUSSION

Despite the availability of a number of anti-VEGF therapies, DME remains a significant clinical and economic burden in countries with developed healthcare systems [43]. The need for frequent intravitreal injections and regular monitoring imposes challenges for both patients and healthcare providers, often leading to suboptimal adherence and poorer long-term outcomes [44]. Aflibercept 8 mg—the only anti-VEGF injection requiring just three loading

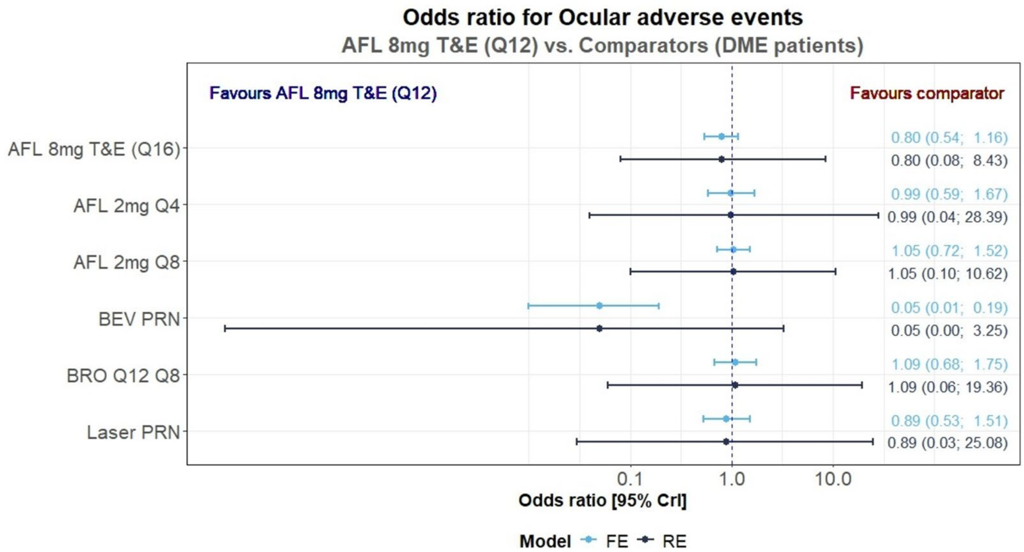

Fig. 6 Forest plot comparing AFL 8 mg Q12 vs comparators for ocular adverse events. *AFL* aflibercept, *BEV* bevacizumab, *BRO* brolucizumab, *CrI* credible interval, *FE* fixed effects, *PRN* pro re nata, *QX* every X weeks, *RE* random effects, *T&E* treat-and-extend

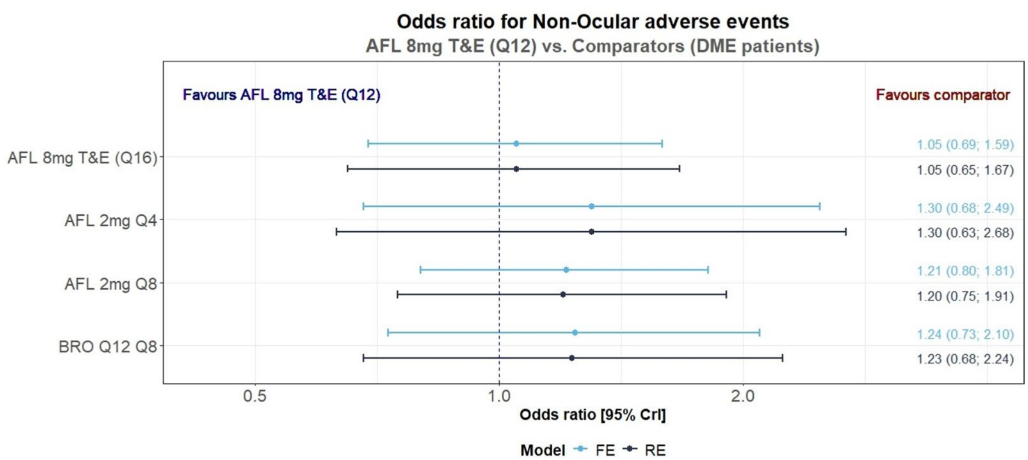

Fig. 7 Forest plot comparing AFL 8 mg Q12 vs comparators for non-ocular adverse events. *AFL* aflibercept, *BRO* brolucizumab, *CrI* credible interval, *FE* fixed effects, *QX* every X weeks, *RE* random effects, *T&E* treat-and-extend

doses and allowing treatment intervals of up to 6 months—offers a way to reduce treatment burden while maintaining vision. Italy, as a European G4 country with a well-developed national health service and number of treatment options for DME, represents an exemplar case study and provides a relevant model for other nations facing similar issues in DME management. The findings from this analysis, therefore, may be generalisable to other healthcare systems that prioritise both clinical efficacy and economic sustainability in treatment decision-making.

Table 3 Mean number of injections reported in studies

Treatment	Study	*N*	Number of injections in 2-year horizon Mean (95% CI)	Meta-Analysis results Mean (95% CI)
AFL 2 mg Q8	PHOTON	167	13.77 (13.36; 14.17)	13.39 (13.23; 13.56)
	KESTREL	187	13.00 (12.54; 13.46)	
	KITE	181	13.20 (12.75; 13.65)	
	VISTA	151	13.50 (13.04; 13.96)	
	VIVID	135	13.60 (13.11; 14.09)	
	YOSEMITE	312	13.30 (12.99; 13.61)	
	RHINE	315	13.40 (13.11; 13.69)	
AFL 8 mg T&E (Q12)	PHOTON	328	9.33 (9.07; 9.59)	9.33 (9.07; 9.59)
AFL 8 mg T&E (Q16)	PHOTON	163	8.37 (8.09; 8.64)	8.37 (8.09; 8.64)
AFL 2 mg Q4	VISTA	155	22.16 (21.21; 23.11)	22.84 (21.49; 24.20)
	VIVID	136	23.55 (22.53; 24.56)	
AFL 2 mg PRN	PROTOCOL T	201	14.20 (13.56; 14.84)	14.20 (13.56; 14.84)
BEV PRN	PROTOCOL T	185	15.30 (14.54; 16.06)	15.30 (14.54; 16.06)
BRO Q8/Q12	KESTREL	189	10.92 (10.48; 11.36)	10.74 (10.40; 11.07)
	KITE	179	10.58 (10.15; 11.00)	
FAR T&E	RHINE	319	12.41 (11.95; 12.87)	12.09 (11.48; 12.71)
	YOSEMITE	315	11.78 (11.33; 12.23)	
FAR Q8	YOSEMITE	315	14.42 (14.08; 14.76)	14.38 (14.14; 14.62)
	RHINE	317	14.34 (14.00; 14.68)	
RBZ T&E	RETAIN	126	12.8 (3.7)*	12.8 (3.7)
RBZ PRN	RETAIN	118	10.7 (5.6)*	10.7 (5.6)

*Mean (SD) [53]

This analysis demonstrated that aflibercept 8 mg, administered at extended dosing intervals, provides comparable efficacy and safety to other anti-VEGF agents for the treatment of DME, while reducing injection frequency and being the least costly licensed option in Italy. These findings suggest that aflibercept 8 mg can preserve clinical outcomes while alleviating treatment burden for patients and healthcare systems. It should also be noted that the base-case scenario, which used the aflibercept 8 mg T&E (Q12) regimen as the reference, represents a conservative approach. Even greater reductions in injection frequency and costs could be achieved with the T&E (Q16) regimen, as shown in the scenario analysis.

The analysis suggests that aflibercept 8 mg can be comparable to aflibercept 2 mg,

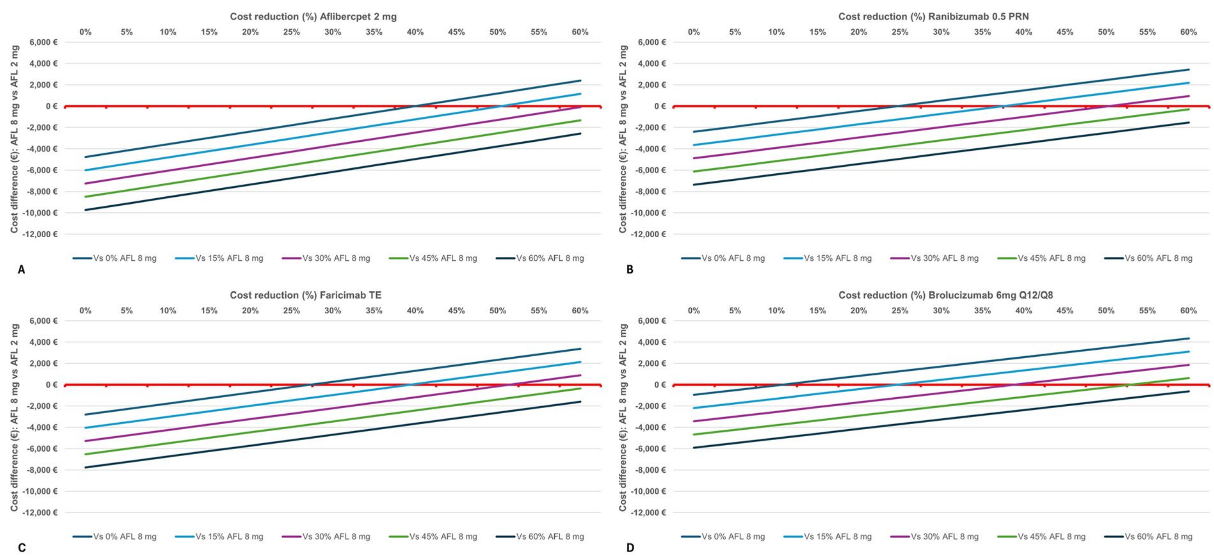

Fig. 8 Two-way sensitivity analysis: cost difference variation applying increasing reduction to drug cost. **a** Aflibercept 8 mg vs aflibercept 2 mg; **b** aflibercept 8 mg vs ranibizumab; c aflibercept 8 mg vs faricimab; **d** aflibercept 8 mg vs brolucizumab

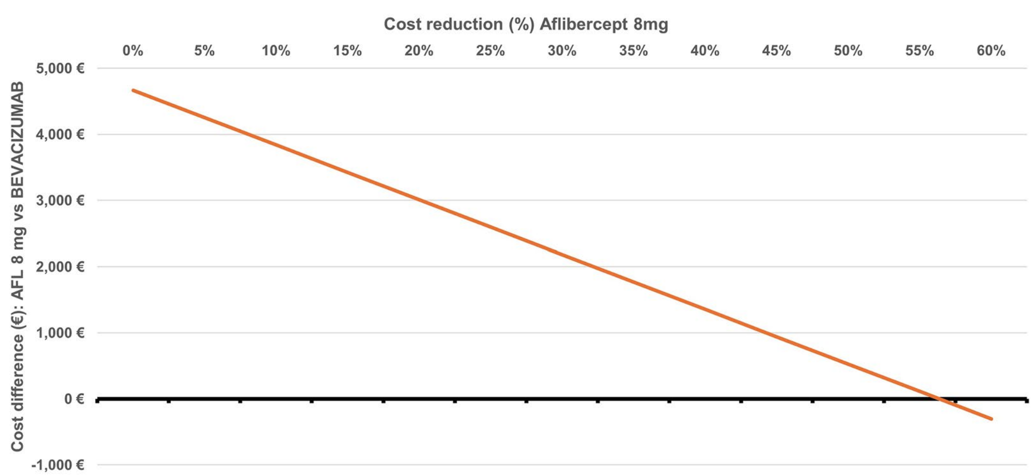

Fig. 9 Impact of aflibercept 8 mg price variation on the cost difference compared with bevacizumab

faricimab, brolucizumab, and bevacizumab in terms of BCVA improvements, with estimated differences remaining within the predefined non-inferiority margin (MCID of 5 letters). From a Bayesian perspective, the NMA showed no significant differences in BCVA change from baseline, in line with previously conducted analyses. In addition to visual outcomes, anatomical endpoints (CRT/CST) showed no meaningful differences between aflibercept 8 mg and the comparator anti-VEGF therapies, supporting the overall conclusion of comparable efficacy. Similarly, ocular adverse events were comparable between aflibercept 8 mg and other anti-VEGF therapies. These results provide further evidence that less frequent injections of aflibercept 8 mg do not compromise treatment efficacy or safety, reinforcing the reliability of extended dosing regimens beyond 16-weekly doses.

To understand the economic impact of the different treatment approaches, cost-minimisation analysis was used to estimate the costs associated with each strategy. We found that aflibercept 8 mg was the least costly licenced and reimbursed anti-VEGF option, with a total per-patient cost of €10,883 over 2 years. This cost advantage was primarily achieved through lower drug administration and reduced procedural expenses. Other on-label anti-VEGF therapies, including aflibercept 2 mg, ranibizumab, faricimab, and brolucizumab, all incurred higher overall treatment costs than aflibercept 8 mg. Bevacizumab PRN was the only treatment with a lower total cost; however, this remains an off-label treatment option. Moreover, in DME indication, the *Nota 98*, issued by the Italian regulatory authority (AIFA), defines a difference in efficacy among patients with low or better baseline visual acuity. Specifically, off label Avastin (bevacizumab) is allowed only in the subset of patients with better baseline visual acuity, whereas the *Nota 98* states that in patients with low visual acuity (20/50 or worse, equivalent to 4/10 or worse), the treatment with aflibercept is significantly superior to bevacizumab at 1 and 2 years [45].

Furthermore, the larger cost advantage observed for bevacizumab reflects the use of ex-factory prices of the approved therapies in the base case.

A two-way sensitivity analysis was conducted to explore the impact of potential price discounts on the relative costs of treatments. This analysis demonstrated that even under varying discount scenarios, aflibercept 8 mg consistently remained the least costly licensed anti-VEGF option. Further, the economic benefit of aflibercept 8 mg resulted even higher in the scenario assessing the T&E (Q16) regimen.

All the economic benefits were assessed using a conservative approach that did not include the patients' and caregivers' points of view and the potentially high indirect costs associated with the time and productivity loss for the administration of anti-VEGF treatments [46]. Considering the lower number of injections associated with aflibercept 8 mg, an analysis from Italian societal perspective, incorporating the costs associated with productivity loss, could result in an even more favourable economic impact associated with aflibercept 8 mg compared to other anti-VEGF, as previously shown in an analysis in the Netherlands [24].

These findings are consistent with those reported in a recent Bayesian NMA of aflibercept 8 mg in neovascular age-related macular degeneration (nAMD), which also showed comparable efficacy and safety to other anti-VEGF agents, with the added benefit of fewer injections [47]. While that analysis focused on nAMD and a 1-year horizon, this study is the first to apply a similar framework in DME over a 2-year period, with the additional step of linking clinical outcomes to an economic evaluation in the Italian healthcare context. Together, these results reinforce the evidence that aflibercept 8 mg maintains non-inferiority to standard regimens across retinal diseases, while offering the potential for reduced treatment burden and improved efficiency.

The key strength of this study lies in the robust methodological approach used in the ITC, which was conducted in line with health technology assessment standards, helping to ensure that the findings are relevant for decision-making in healthcare systems. The ITC was based on an SLR of RCTs identified to be of low risk of bias. Furthermore, non-inferiority was established using the strictest predefined MCID criteria, which was conservative, reinforcing confidence in the statistical and clinical validity of the results. The CMA incorporated real-world treatment frequencies to provide a transparent assessment of overall cost differences across anti-VEGF options.

However, as with any ITC and resultant economic analysis, certain limitations are acknowledged. While NMA enables comparisons between treatments that have not been directly evaluated in head-to-head trials, it remains an indirect form of evidence synthesis. Differences in trial populations, study designs, and treatment protocols may introduce variability that cannot be fully accounted for, even with rigorous adjustments. In this case, there was evidence in heterogeneity in the baseline BCVA and CRT/CST that could have introduced confounding. Furthermore, the NMA included a relatively small number of trials (nine in the base case), leading to wide credibility intervals for some comparisons. The NMA also lacked the data to inform subgroup-specific analyses, so the analysis could not be performed on an Italian cohort only. While RCTs are among the most robust sources regarding efficacy and safety of therapies, they carry limitations when it comes to measuring the burden of treatment. Dosing regimens and their potential modification criteria are often predefined in the study protocol and might differ from real-world treatment practices. For these reasons, the number of injections were not statistically contrasted in this analysis. The relatively low injection frequency reported for ranibizumab PRN (10.7 injections over 2 years) should be interpreted with caution, as first-generation agents are generally associated with more frequent dosing requirements than more recent anti-VEGF options. Failure to adhere to appropriate treatment intensity may result in irreversible loss of visual function. Finally, while the CMA provided a clear cost comparison based on equivalent efficacy, it did not capture long-term cost differences related to patient adherence, disease progression, or quality of life improvements, which may further enhance the value proposition of extended dosing intervals.

CONCLUSION

Aflibercept 8 mg has shown comparable efficacy and safety profile to other anti-VEGF therapies used in clinical practice, such as aflibercept 2 mg, faricimab, and brolucizumab. These results were achieved with fewer injections, and from an economic perspective aflibercept 8 mg was the least costly licensed anti-VEGF option in Italy. These findings suggest that aflibercept 8 mg with extended dosing intervals has the potential to improve the management of patients with DME while reducing the burden on patients and healthcare systems.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of Interest. Prof. Francesco Bandello consults for Abbvie, Adverum Biotechnologies Inc., Alimera, Apellis, Bayer, Boehringer Ingelheim, Breye Therapeutics A.p.S., Fidia Sooft, Hoffmann-La Roche, Outlook Therapeutics, Novartis, NTC Pharma, Oxurion NV, 4D Molecular Therapeutics Inc., SIFI. Prof. Paolo Angelo Cortesi has received grants and personal fees from Hoffmann-La Roche, Almirall, Otsuka, Novartis, Daiichi Sankyo, Boehringer Ingelheim, and Bayer. Izabella Lunk, Mario Fazzi D'Orsi, and Monica Zurria are employees of Bayer. Marwa Mezghani and Mohammed Alshaikheid declare that they were employed by Putnam at the time the research was conducted, a company which received funds from Bayer to conduct this research.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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