BMJ Open Ophthalmology

Randomised, double-masked trial to compare the efficacy, safety and immunogenicity of the biosimilar aflibercept FYB203 with reference aflibercept in patients with neovascular age-related macular degeneration

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To cite: Balser S, Capsius B, Hole R, *et al*. Randomised, double-masked trial to compare the efficacy, safety and immunogenicity of the biosimilar aflibercept FYB203 with reference aflibercept in patients with neovascular age-related macular degeneration. *BMJ Open Ophthalmology* 2026;**11**:e002398. doi:10.1136/bmjophth-2025-002398

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjophth-2025-002398).

Received 6 August 2025
Accepted 17 December 2025

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ABSTRACT

Objective Biosimilars are helping to reduce the cost burden of treatment and widen patient access to therapies. This multicentre trial compared the efficacy, safety and immunogenicity of the biosimilar aflibercept FYB203 with reference aflibercept in patients with neovascular age-related macular degeneration (nAMD).

Methods and analysis Patients aged ≥50 years with newly diagnosed nAMD and a best-corrected visual acuity (BCVA) between 20/40 and 20/200 Snellen equivalent were randomised (1:1) to double-masked treatment with 2 mg FYB203 or EU-approved reference aflibercept by intravitreal injection every 4 weeks for three doses (baseline, weeks 4 and 8) then every 8 weeks up to week 48. The primary efficacy endpoint was the change from baseline in BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 8 in the study eye. Therapeutic equivalence of FYB203 and reference aflibercept was demonstrated if, depending on the regulatory requirement with respect to the significance level, the two-sided 90.4% and 95.2% CIs were within the predefined equivalence interval of (−3.5 to 3.5) ETDRS letters.

Results A total of 433 patients received treatment with FYB203 (n=215) or reference aflibercept (n=218). Mean improvement in BCVA from baseline to week 8 was 6.6 ETDRS letters with FYB203 and 5.6 ETDRS letters with reference aflibercept, with an estimated mean treatment difference of 1.0 and the two-sided 90.4% CI (−0.3 to 2.2) and 95.2% CI (−0.6 to 2.5) fully contained within the pre-defined equivalence margins, confirming therapeutic equivalence between FYB203 and reference aflibercept. Safety and immunogenicity profiles were similar between groups.

Conclusion Although conducted during the COVID-19 pandemic in a potentially vulnerable elderly population and affected by geopolitical disruption in Ukraine, mitigation measures minimised the overall impact of these events. FYB203 demonstrated therapeutic equivalence to reference aflibercept in patients with nAMD, supporting similar clinical performance across all approved indications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The high cost of treatments, increasing patient numbers in ageing populations, and the long-term chronic nature of the disease represent significant challenges in the management of neovascular age-related macular degeneration (nAMD). Biosimilars may help address some of these challenges by reducing the cost burden of therapies and widening patient access to treatment.

WHAT THIS STUDY ADDS

⇒ The biosimilar aflibercept FYB203 demonstrated therapeutic equivalence to reference aflibercept in patients with nAMD in this randomised, double-masked, phase 3 study, with comparable safety and immunogenicity profiles.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on this therapeutic equivalence, together with established high similarity in quality attributes, similar clinical performance of FYB203 and reference aflibercept is assumed across all approved indications.

Trial registration number Clinicaltrials.gov: NCT04522167; EudraCT: 2019-003923-39.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) can result in substantial vision impairment with a profound detrimental impact on quality of life.[1] It has an acute onset and rapid progression, typically affecting individuals over 50 years of age, and is the leading cause of visual loss in older people in developed countries.[2 3] nAMD occurs due to pathologic choroidal neovascularisation

(CNV) and exudation of blood and/or fluid into the macula, leading to retinal oedema and thickening. Vascular endothelial growth factor (VEGF), a growth factor that stimulates angiogenesis and increases vascular permeability, is a major factor in nAMD pathophysiology.[4]

The standard of care for nAMD is intravitreal injections with VEGF inhibitors, including ranibizumab, aflibercept, brolucizumab, faricimab and the off-label use of bevacizumab.[5 6] However, anti-VEGF treatment for nAMD can represent a substantial economic burden for patients, caregivers and healthcare systems.[7 8] The high cost of drugs, increasing patient numbers in ageing populations and the long-term chronic nature of the disease represent significant challenges in the management of nAMD.

Biosimilars may help address some of these challenges by reducing the cost burden of therapies and widening patient access to treatment.[9] Biosimilars of both ranibizumab and aflibercept have shown similar efficacy and safety to their respective reference products and have been approved for the treatment of nAMD and other ocular conditions for which the reference products are indicated.[10–12]

Regulatory approval of biosimilars requires a totality of evidence approach that shows the molecule is highly similar to the reference product in terms of structure, function, clinical efficacy and safety. This multicentre, randomised trial compared the efficacy, safety and immunogenicity of the biosimilar aflibercept FYB203 with reference aflibercept in patients with subfoveal nAMD.

METHODS

This was a randomised, double-masked, phase 3 study (MAGELLAN-AMD), conducted between 21 July 2020 and 18 May 2023 at 72 sites in Bulgaria, Czech Republic, Hungary, Israel, Italy, Japan, Poland, Russia and Ukraine (NCT04522167, EudraCT 2019-003923-39). The aim of the study was to show therapeutic equivalence of FYB203 and reference aflibercept and to compare safety, systemic exposure and immunogenicity. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines, and in compliance with all local or regional regulatory requirements. The study protocol was reviewed and approved by the independent ethics committee or institutional review board for each centre (online supplemental table S1). An independent data and safety monitoring board reviewed safety and tolerability data.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study. Patients were only involved as study participants.

Participants

Eligible patients were ≥50 years old at screening with a newly diagnosed (within 6 months of screening) treatment-naïve angiographically documented CNV lesion secondary to nAMD (subfoveal or juxtafoveal with subfoveal component related to CNV activity). The total area of the whole lesion in the study eye had to be ≤9 disc areas with total CNV area ≥50% of total lesion area based on fluorescein angiography (FA), including all subtypes of nAMD. Patients also had to have a best-corrected visual acuity (BCVA) between 20/40 and 20/200 Snellen equivalent and foveal centre point (FCP) retinal thickness of between ≥300 µm and <800 µm. A BCVA of at least 20/200 Snellen equivalent was required in the fellow eye.

Patients were excluded if they had prior or current ocular treatment, including any prior treatment of AMD with anti-VEGF or any investigational product in either eye; any investigational treatment of ocular disease other than nAMD within 30 days or 5 half-lives prior to randomisation; medical history of vitrectomy, macular surgery or other surgical intervention for AMD in the study eye; history of intravitreal treatment with corticosteroids or device implantation in the study eye within 6 months prior to randomisation; prior treatment with photodynamic therapy or focal laser photocoagulation in the study eye; or any other intraocular surgery including cataract surgery in the study eye within 3 months prior to randomisation. Patients were also excluded based on particular CNV lesion characteristics or current ocular conditions or if they had any diagnosis and signs of nAMD, requiring intravitreal treatment with an anti-VEGF agent within the screening period or throughout the study in the fellow eye. Full eligibility criteria are listed in online supplemental table S2.

As a part of the screening process, retinal images were evaluated by a central reading centre (GRADE Reading Center, Bonn, Germany) to provide an independent assessment of patient eligibility regarding FCP, lesion classification, lesion size and area of CNV (total lesion area).

Procedures

Patients were randomised (1:1) to double-masked treatment with biosimilar aflibercept FYB203 or EU-approved reference aflibercept (both at a dose of 2 mg, 0.05 mL of a 40 mg/mL solution) by intravitreal injection every 4 weeks for three doses (baseline, week 4 and week 8) followed by 2 mg once every 8 weeks up to week 48. A safety follow-up occurred at week 56. The trial design is shown in online supplemental figure 1.

Patients were randomly assigned to treatment groups in accordance with the randomisation schedules generated using permuted block randomisation. Randomisation was stratified by country and participation in a pharmacokinetic (PK) analysis subgroup (yes/no). Patients and investigators were masked to the study intervention assignment. Due to the differing appearances of the two trial treatments, injections were administered by an unmasked independent ophthalmologist at each site. This unmasked ophthalmologist could also perform tonometry preintravitreal and postintravitreal injection

and the postdose safety check for light perception, according to the clinical practice of the study site. Any adverse events noted by the unmasked ophthalmologist were assessed for relationship to study treatment by the masked investigator. All other assessments were done by the masked investigator (and/or masked study team) except for refraction and visual acuity measurements, which were done by a visual acuity examiner who was also masked to treatment.

Refraction and visual acuity testing were assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart prior to any ophthalmic assessments. Visual acuity examiners and lanes at study sites were certified to ensure consistent measurement of BCVA. Patients had to use the same chart consistently from screening to week 56. Other assessments included ophthalmological examination, which consisted of an external examination of the eye and adnexa, routine screening for eyelid/pupil responsiveness (including but not limited to blepharoptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light and afferent pupillary defect), slit lamp exam, indirect ophthalmoscopy and tonometry intraocular pressure (IOP) measurements. Colour fundus photography and FA were also conducted, and morphologic changes of FCP retinal thickness, foveal central subfield (FCS) retinal thickness and fluid-free macula were evaluated by spectral domain optical coherence tomography.

Endpoints

The primary efficacy endpoint was change from baseline in BCVA by ETDRS letters at week 8. Change from baseline in FCP retinal thickness at week 4 was a key secondary endpoint. Other secondary endpoints were changes from baseline in FCP and FCS retinal thickness, BCVA by ETDRS letters and total lesion size at weeks 24, 40 and 56. The proportion of patients who gained or lost ≥5, 10 or 15 ETDRS letters from baseline to weeks 24, 40 and 56 and percentage of patients with fluid-free macula at each visit were also assessed as secondary endpoints. Vision-related functioning and well-being were also assessed using the National Eye Institute Visual Function Questionnaire (NEI VFQ)−25 at weeks 24, 40 and 56.

Safety assessments included adverse events, serious adverse events, adverse events of special interests, clinical safety laboratory assessments, vital signs and physical examination.

Antidrug antibodies (ADAs) to aflibercept were evaluated in serum samples collected from all randomised patients. In case of confirmed ADAs, the ADA titre and neutralising antibodies (NAbs) were evaluated. Additional ADA sampling and evaluation was performed in patients experiencing signals of unexpected ocular inflammation. ADA positivity was based solely on a positive result from the ADA confirmatory assay, which was performed after the ADA screening result gave a positive signal. Only ADA/NAb evaluable patients, defined as patients who had at least one valid assessment both prior and post-first study treatment administration, were included in the immunogenicity analyses.

Systemic exposure based on total and free aflibercept was compared at baseline prior to first dose, and close to maximum concentration (C_{max}) at 48 hours after first and third doses in a PK subgroup of 60 patients at selected study sites. Total and free aflibercept were measured in plasma to avoid the release of VEGF from platelets because quantification in serum may underestimate systemic levels.

Statistical analysis

The sample size was calculated based on a 1:1 randomisation and an SD of 9.0 ETDRS letters in BCVA. An equivalence test of means using two one-sided tests with sample sizes of 180 in each treatment group (360 patients in total) achieves 90% power at a 2.5% significance level when no difference between the means is assumed, the SD is 9.0 letters, and the equivalence interval is (−3.5 to 3.5) letters. Given that approximately 10% of patients might drop out and/or would be non-evaluable, a total sample size of 400 patients was planned. The sample size was based on the fixed. As there had been uncertainty about the assumed SD of 9.0 letters at the time of initial sample size calculation, a masked sample size review was performed after the first 200 treated patients had completed week 8 and revealed that the observed overall variability did not require an increase in sample size to maintain the intended statistical power.

The full analysis set included all patients who received ≥1 injection of study medication in the study eye, with patients analysed according to the treatment to which they were randomised. The safety analysis set (SAF) included all patients who received ≥1 injection of study medication in the study eye, with patients analysed according to the treatment they actually received irrespective of their randomised treatment. The PK set included patients who were in the SAF and had ≥1 valid postdose plasma concentration measurement.

A mixed model repeated measurements (MMRM) was used for the analyses of the primary efficacy endpoint including BCVA at baseline as covariate and region (Japan vs Rest of World), visit, randomised treatment group, baseline-by-visit interaction and the treatment-by-visit interaction as fixed effects. All intercurrent events were handled according to a treatment policy estimand, that is, all values of interest were analysed irrespective of intercurrent events (treatment or study discontinuation, or major protocol deviation which impacted the BCVA assessment at week 8).

For the primary endpoint of change from baseline in BCVA by ETDRS letters at week 8, two different analyses were conducted to comply with the different regulatory requirements of the European Medicines Agency (EU-specific analysis) and the US Food and Drug Administration (US-specific analysis). The difference between the least squares (LS) means of the treatment groups (FYB203—reference aflibercept) was estimated from

the MMRM, as were corresponding two-sided 90.4% CIs for the US-specific analysis and two-sided 95.2% CI for the EU-specific analysis. The significance level alpha was reduced from 0.5 to 0.48 and from 0.025 to 0.024 for the US-specific and EU-specific analyses, respectively, to control the overall type 1 error in the light of the masked sample size review. If the respective CI was completely contained in the interval (−3.5 to 3.5) ETDRS letters, therapeutic equivalence of FYB203 and reference aflibercept could be concluded. A hierarchical test strategy was applied with the EU-specific analysis only performed if the US-specific analysis had already shown equivalence. Various supportive sensitivity analyses and supplemental estimands for the primary efficacy endpoint were preplanned and are described in online supplemental table S3. Subgroup analyses of the primary efficacy endpoint analysis including those based on sex, use of an ancillary chart, ADA status, total lesion area, lesion type, syringe use and region were also preplanned and performed if the subgroup size allowed the calculation of meaningful CIs.

The EU-specific analysis key secondary endpoint of change in FCP retinal thickness between baseline and week 4 used a similar MMRM model as specified for the primary efficacy endpoint with a two-sided 95.2% CI and equivalence interval of (−45 to 45) µm. For the US-specific analysis, there was no key secondary endpoint and the change from baseline in FCP retinal thickness at week 4 was analysed with the same MMRM as described above to derive 95.0% CIs, but without formal hypothesis testing. Continuous secondary efficacy endpoints were analysed similarly to the primary efficacy endpoint, using corresponding MMRMs but reporting descriptive two-sided 95% CIs for the difference between the treatment groups.

RESULTS

A total of 712 patients were screened, of whom 434 were randomised to FYB203 (n=215) or reference aflibercept (n=219); one patient in the reference aflibercept group withdrew consent before receiving treatment. Nineteen (8.8%) patients in the FYB203 group and 12 (5.5%) patients in the reference aflibercept group prematurely discontinued. A total of 196 (91.2%) patients in the FYB203 group and 206 (94.1%) patients in the reference aflibercept group completed the study. Disposition of patients is shown in figure 1.

Baseline demographics and ophthalmologic characteristics were well-balanced between treatment groups; overall, 57.3% were female, 91.9% were white and mean (SD) age was 73.5 (7.7) years. Mean (SD) baseline BCVA was 57.9 (11.3) letters, FCP retinal thickness was 476.6 (154.6) µm, FCS retinal thickness was 504.1 (139.3) µm, screening total lesion area was 9.6 (5.8) mm² and IOP was 15.3 (2.7) mm Hg (table 1).

Efficacy

For the primary efficacy endpoint, least-squares mean improvement in BCVA from baseline to week 8 was 6.6 ETDRS letters in patients treated with FYB203 and 5.6 ETDRS letters in patients treated with reference aflibercept. The estimated least-squares mean treatment difference was 1.0 and the two-sided 90.4% CI (−0.3 to 2.2) (US analysis) and 95.2% CI (−0.6 to 2.5) (EU

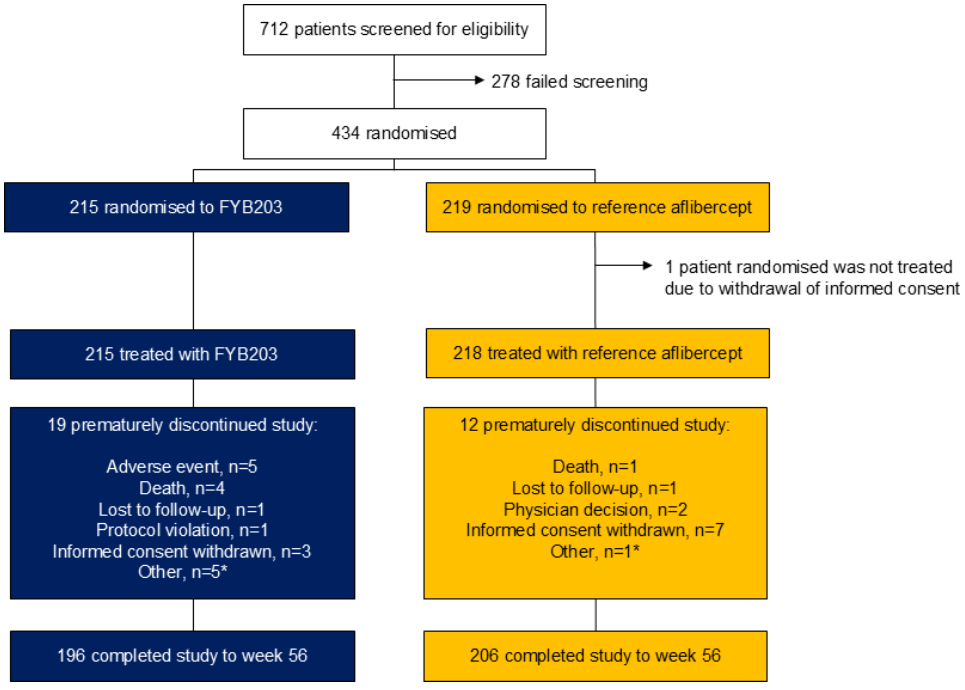

Figure 1 Study disposition *Other: four patients treated with FYB203 and one treated with reference aflibercept discontinued the study due to other reasons related to the geopolitical situation in Ukraine. One patient treated with FYB203 refused to participate in the continuation of the study due to improvement of vision.

Table 1 Baseline demographics and clinical characteristics (full analysis set)

	FYB2023 (N=215)	Reference aflibercept (N=218)
Male/female, n (%)	94 (43.7%)/121 (56.3%)	91 (41.7%)/127 (58.3%)
Age (years)*	73.7±7.7	73.3±7.7
Race:		
White	197 (91.6%)	201 (92.2%)
Asian	17 (7.9%)	16 (7.3%)
Study eye, Snellen equivalent, n (%):		
20/40	39 (18.1%)	40 (18.3%)
20/50	50 (23.3%)	46 (21.1%)
20/63	32 (14.9%)	33 (15.1%)
20/80	32 (14.9%)	35 (16.1%)
20/100	23 (10.7%)	17 (7.8%)
20/125	5 (2.3%)	15 (6.9%)
20/160	13 (6.0%)	13 (6.0%)
20/200	21 (9.8%)	19 (8.7%)
Lesion type in study eye, n (%):		
Type 1 MNV	71 (33.0%)	72 (33.0%)
Type 2 MNV	49 (22.8%)	51 (23.4%)
Mixed type 1 and 2 MNV	74 (34.4%)	76 (34.9%)
Type 3 MNV	19 (8.8%)	19 (8.7%)
Time since first diagnosis (days)	55±102	53±109
BCVA (ETDRS letters)	58.0±11.4	57.8±11.2
FCP retinal thickness (µm)	465.9±157.1	487.0±151.7
FCS retinal thickness (µm)	493.5±140.5	514.5±137.7
Total lesion area (mm^2)*	9.5±5.7	9.6±6.0
IOP (mm Hg)	15.0±2.6	15.6±2.7

All data mean±SD unless otherwise stated.
*At screening.
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; FCP, foveal centre point; FCS, foveal central subfield; IOP, intraocular pressure; MNV, macular neovascularisation.

analysis) were fully contained within the predefined equivalence margins, confirming therapeutic equivalence between FYB203 and reference aflibercept (figure 2A).

Sensitivity and supplementary analyses for the primary endpoint supported the result of the primary analysis (online supplemental table S4). Subgroup analyses also supported the primary analysis (online supplemental figure 2).

Equivalence in the key secondary efficacy endpoint of change from baseline in FCP retinal thickness at week 4 was shown with an estimated least-squares mean change of −171.4 µm with FYB203 and −166.9 µm with reference aflibercept. The estimated least-squares treatment difference was −4.5 µm (95.2% CI −24.4 to 15.4) and was therefore within the predefined equivalence range (−45 to 45) (figure 2B). All other secondary efficacy endpoints showed similar improvements for both groups and were sustained until week 56 (table 2, online supplemental figures S3–S5). Quality of life assessment using the NEI VFQ-25 showed stabilisation of disease for both treatments (online supplemental figure S6).

Safety

Both treatments were well tolerated, and the safety profiles were comparable between groups, with 498 events reported in 165 (76.7%) patients treated with FYB203 vs 536 events in 158 (72.5%) patients treated with reference aflibercept (table 3, online supplemental table S5). Most adverse events were of mild or moderate intensity, with severe events observed in 10 (4.7%) patients treated with FYB203 and 15 (6.9%) patients treated with reference aflibercept.

Ocular adverse events in the study eye were comparable between groups, with 125 events in 67 (31.2%) patients treated with FYB203 versus 157 events in 75 (34.4%) patients treated with reference aflibercept. The most frequent ocular event was conjunctival haemorrhage (4 events in 4 (1.9%) patients treated with FYB203 vs 24 events in 14 (6.4%) patients treated with reference aflibercept). Adverse events in the fellow eye were also comparable between groups. Systemic (non-ocular) adverse events were also reported in similar frequencies between the groups.

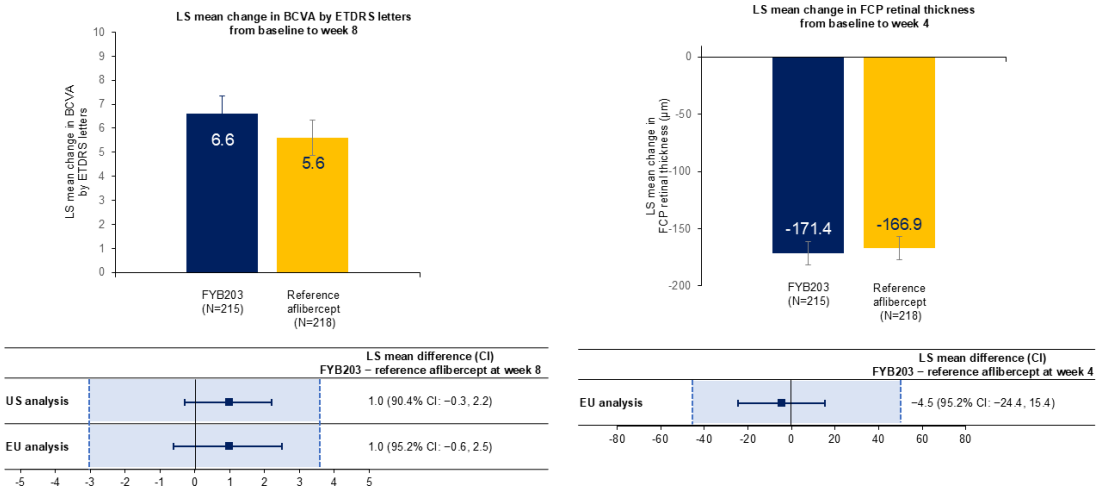

Figure 2 (A) Primary efficacy endpoint: change from baseline in BCVA by ETDRS letters at week 8; (B) key secondary efficacy endpoint: change from baseline in FCP retinal thickness at week 4. *Key secondary efficacy endpoint for EU analysis only. For the US analysis, change from baseline in FCP to week 4 was analysed with the same MMRM but without formal hypothesis testing. BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; FCP, foveal centre point; LS, least squares; MMRM, mixed model repeated measurements.

Treatment-related adverse events were similar in both groups, with 34 events in 20 (9.3%) patients treated with FYB203 and 32 events in 16 (7.3%) patients treated with reference aflibercept. Adverse events related to the study procedure were also similar between groups (55 events in 28 (13.0%) patients treated with FYB203 versus 93 events in 37 [17.0%] patients treated with reference aflibercept.

A total of 38 serious adverse events were reported in 19 (8.8%) patients treated with FYB203 and 40 events were reported in 28 (12.8%) patients treated with reference aflibercept. Most serious adverse events were systemic (FYB203, 35 events in 17 (7.9%) patients; reference aflibercept, 35 events in 23 (10.6%) patients). For the study eye, serious adverse events were reported in two patients in the FYB203 group (iridocyclitis and uveitis; rhegmatogenous retinal detachment) and two patients in the reference aflibercept group (visual impairment; corneal dystrophy). For the fellow eye, serious adverse events were reported in three patients in the reference aflibercept group (nAMD; retinal degeneration; glaucoma). No serious adverse events were reported in the fellow eye in the FYB203 group.

Five patients randomised to treatment died during the study, four patients treated with FYB203 (pulmonary fibrosis and cardiac failure; COVID-19, COVID-19 pneumonia and cardiac failure; toxic shock syndrome and ileus; acute myeloid leukaemia) and one patient treated with reference aflibercept (cardiac failure). None was judged as related to the study treatment or procedure.

Eighteen events in 10 (4.7%) patients treated with FYB203 and 2 events in 2 (0.9%) patients with reference aflibercept led to discontinuation of treatment (online supplemental table S5). These included five ocular adverse events in three patients in the FYB203 group (macular hole, rhegmatogenous retinal detachment (three events in one patient) and subretinal fluid, all in study eye) and in one patient in the reference aflibercept group (undefined eye disorder, green spot in field of view of the study eye). None was judged as related to the study treatment. Adverse events leading to study treatment interruption showed similar frequencies in both groups: 23 events in 20 (9.3%) patients treated with FYB203 and 27 events in 22 (10.1%) patients with reference aflibercept. Study treatment interruptions were due to ocular adverse events in three patients in the FYB203 group (two events each of iridocyclitis and keratitis) and in one patient in the reference aflibercept group (chalazion).

Other safety assessments resulting from ophthalmological examinations and tonometry, as well as laboratory assessments, vital signs and physical examination, were also well balanced between the two treatment groups and no relevant safety-related differences were identified.

Immunogenicity

Four (1.9%) patients in the FYB203 group and 3 (1.5%) patients in the reference aflibercept group tested positive for ADAs prefirst dose; none was NAb-reactive. Until week 56 (post-treatment only), four (1.9%) patients in the FYB203 group and two (1.0%) patients in the reference aflibercept group tested positive for ADAs. Three (1.4%) patients in the FYB203 group were NAb-reactive. None was NAb-reactive in the reference aflibercept group.

Systemic exposure

Three patients had positive total aflibercept concentrations at baseline and were excluded from the PK analysis population, which consisted of 57 patients (FYB203, n=31; reference aflibercept, n=26). Aflibercept plasma concentrations (total and free) were similar in the FYB203 and reference aflibercept groups 48 hours after the third dose at week 8, the time of predicted maximum concentration (C_{max}). At 48 hours after the first dose of study treatment,

Table 2 Other secondary efficacy endpoints (full analysis set)

	FYB2023 (N=215)	Reference aflibercept (N=218)	Treatment difference (95% CI)
Change in FCP retinal thickness (µm)			
Week 24	−172 (−195 to −149)	−164 (−187 to −140)	−8 (−34 to 17)
Week 40	−194 (−216 to −171)	−186 (−208 to −164)	−8 (−32 to 16)
Week 56	−208 (−229 to −187)	−203 (−224 to −182)	−5 (−28 to 17)
Change in FCS retinal thickness (µm)			
Week 4	−164 (−182 to −145)	−157 (−176 to −138)	−6 (−24 to 12)
Week 24	−159 (−180 to −138)	−153 (−174 to −132)	−6 (−29 to 16)
Week 40	−181 (−201 to −161)	−177 (−197 to −157)	−4 (−25 to 18)
Week 56	−193 (−212 to −174)	−192 (−212 to −173)	−1 (−21 to 19)
Change in BCVA by ETDRS letters			
Week 24	6.5 (4.9, 8.2)	6.2 (4.6, 7.8)	0.3 (−1.5 to 2.2)
Week 40	7.7 (5.9, 9.4)	6.3 (4.6, 8.0)	1.4 (−0.6 to 3.4)
Week 56	7.5 (5.7, 9.3)	6.2 (4.4, 8.0)	1.3 (−0.9 to 3.5)
Gain or loss of ≥15 ETDRS letters, n (%)			
Week 24			
≥15 letter gain	45 (22.4%)	38 (18.7%)	–
≥15 letter loss	4 (2.0%)	6 (3.0%)	–
Week 40			
≥15 letter gain	48 (25.1%)	43 (21.5%)	–
≥15 letter loss	4 (2.1%)	5 (2.5%)	–
Week 56			
≥15 letter gain	52 (27.7%)	49 (24.4%)	–
≥15 letter loss	2 (1.1%)	9 (4.5%)	–
Patients with fluid-free macula, n (%)			
Week 4	85/215 (39.5%)	87/214 (40.7%)	−1.12 (−10.36 to 8.14)
Week 24	71/198 (35.9%)	65/200 (32.5%)	3.36 (−5.96 to 12.64)
Week 40	73/188 (38,8%)	86/197 (43.7%)	−4.83 (−14.57 to 5.02)
Week 56	79/187 (42.2%)	100/198 (50.5%)	−8.26 (−18.07 to 1.72)
Total lesion size (mm^2)			
Week 24	−1.1 (−2.0, −0.2)	−1.4 (−2.3, −0.6)	0.3 (−0.5 to 1.2)
Week 40	−0.9 (−1.8, 0.0)	−1.2 (−2.0, −0.3)	0.2 (-0.7 to 1.1)
Week 56	−1.4 (−2.3, 0.4)	−1.5 (−2.4, −0.6)	0.1 (-0.8 to 1.1)

All data LS mean (95% CI) unless otherwise stated. The two-sided 95% CI was based on normal approximation. For the calculation of LS means based on the MMRM, all patients with missing and non-missing week 24/week/week 40/week/week 56 assessments were considered if they had at least one post-baseline value until week 24/week/week 56/week/week 56.
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; FCP, foveal centre point; FCS, foveal central subfield; MMRM, mixed model repeated measurements.

aflibercept plasma concentrations tended to be slightly higher in the FYB203 group compared with the reference aflibercept group, but this was not considered relevant given the variability and comparing the 95% CIs of the geometric means.

DISCUSSION

FYB203 was shown to be equivalent to reference aflibercept with the mean improvement from baseline in BCVA by ETDRS letters at week 8 within predefined equivalence intervals for both the US-specific and EU-specific analyses. Extensive sensitivity and subgroup analyses supported the primary analysis.

The primary endpoint of improvement in BCVA by ETDRS letters from baseline to week 8 was measured consistently at study sites using certified study lanes by certified masked examiners. BCVA improved by 6.6 letters in the FYB203 group and 5.6 ETDRS letters in the reference aflibercept group. Relevant CIs for the difference between the two treatments of 1.0 letter were completely contained in the predefined equivalence margin of (−3.5; 3.5) ETDRS letters. This improvement in BCVA is consistent with the previous studies of reference aflibercept[13] as well as other aflibercept biosimilars.[14–17]

Use of change in BCVA at week 8 as the primary efficacy endpoint has been endorsed by regulatory authorities[18]

Table 3 Adverse events (safety analysis set)

n (%)	FYB2023 (N=215)	Reference aflibercept (N=218)
Any AE:	165 (76.7%)	158 (72.5%)
In the study eye	67 (31.2%)	75 (34.4%)
In the fellow eye	45 (20.9%)	48 (22.0%)
Systemic	124 (57.7%)	113 (51.8%)
Ocular AE in study eye (≥2% in either group):		
Conjunctival haemorrhage	4 (1.9%)	14 (6.4%)
Increased IOP	7 (3.3%)	9 (4.1%)
Cataract	8 (3.7%)	7 (3.2%)
nAMD	7 (3.3%)	7 (3.2%)
Eye pain	6 (2.8%)	6 (2.8%)
Reduced visual acuity	7 (3.3%)	4 (1.8%)
Conjunctivitis	5 (2.3%)	6 (2.8%)
Blurred vision	6 (2.8%)	3 (1.4%)
Impaired vision	3 (1.4%)	5 (2.3%)
Ocular AE in fellow eye (≥2% in either group):		
nAMD	22 (10.2%)	24 (11.0%)
Cataract	7 (3.3%)	4 (1.8%)
Conjunctivitis	5 (2.3%)	0
Serious AE:	19 (8.8%)	28 (12.8%)
In the study eye	2 (0.9%)	2 (0.9%)
In the fellow eye	0	3 (1.4%)
Systemic	17 (7.9%)	23 (10.6%)
AE related to study treatment	20 (9.3%)	16 (7.3%)
AE related to IVT injection	28 (13.0%)	37 (17.0%)
AE leading to withdrawal of treatment	10 (4.7%)	2 (0.9%)
AEs leading to study discontinuation	9 (4.2%)	1 (0.5%)
Deaths*	4 (1.9%)	1 (0.5%)

*Two additional patients who were screening failures died during the course of the study.
AE, adverse event; IOP, intraocular pressure; IVT, intravitreal; nAMD, neovascular age-related macular degeneration.

and is consistent with previous biosimilar studies of anti-VEGF inhibitors.[15–17 19–21] This timing was chosen because aflibercept is typically associated with a rapid initial improvement in visual acuity; however, the maximum effect on BCVA is not yet reached at this point. Thus, week 8 is still within the steep part of the dose–response curve and therefore represents the most sensitive time-point to detect any potential efficacy differences between FYB203 and reference aflibercept.

Improvements in BCVA from baseline were stable and sustained until week 56 in both treatment groups. At week 56, 27.7% of patients in the FYB203 group and 24.4% of patients in the reference aflibercept group gained BCVA by 15 or more ETDRS letters. In addition, 22.9% of patients in the FYB203 group and 17.9% of patients in the reference aflibercept group gained BCVA by 10 to 14 ETDRS letters. Smaller changes in BCVA by ETDRS letters were also similar in the two groups. Improvements in other endpoints assessed at week 56 were also sustained and similar between groups.

Similarity between FYB203 and reference aflibercept was also shown for change in FCP retinal thickness from baseline to week 4. All other secondary efficacy endpoints were also similar between treatments, with improved functional and morphological signs of nAMD in both groups, with no clinically or statistically significant between-group differences. Quality of life as assessed by the NEI VFQ-25 showed stable disease for both treatments.

Intravitreal injections of both FYB203 and reference aflibercept were well tolerated. Overall, 9.3% of patients treated with FYB203 and 7.3% of patients treated with reference aflibercept had at least one adverse event related to the study treatment, and 13% of patients treated with FYB203 and 17% of patients treated with reference aflibercept had at least one adverse event related to the study procedure. The proportion of patients affected by local AEs in the study eye and fellow eye was similar for the two groups. The fellow eye events were mostly AMD and other eye complications, not related to the treatment of the study eye. Safety findings in the study eye were consistent with the reported safety profile of reference aflibercept.[13 22]

Incidence of ADAs and NAbs was also similar between both groups. The low incidence and minimal ADA titres detected indicate the absence of clinically impactful ADA or NAb formation for either FYB203 or reference

aflibercept, consistent with previous experience.[23] The treatment-emergent ADAs had no impact on safety and efficacy.

Systemic concentrations of total and free aflibercept close to maximum exposure after the first and third dose were low and comparable between both treatment groups with no sign of accumulation.

Limitations of the study included that it was conducted during the later stages of the COVID-19 pandemic in a potentially vulnerable elderly population. However, the impact on the conduct of the study was limited, with patients and study site staff generally able and willing to adhere to the study schedule and assessments. Another limitation was the geopolitical situation in Ukraine, with eight study sites there at the start of the war; however, mitigation measures, such as the use of local instead of central laboratories, meant the study could mostly be conducted as planned. Another limitation was the lack of racial and ethnic diversity among participants, over 90% of whom were White.

The mode of action of aflibercept across the intended indications is based on its inhibition of VEGF-A, with the inhibitory effect of aflibercept on vascular permeability and angiogenesis exerted locally in the same tissue compartments of the choroid and retinal vessels. As such, therapeutic equivalence in nAMD allows for extrapolation to other indications. Studies of other aflibercept biosimilars which were evaluated in patients with diabetic macular oedema rather than nAMD have also shown therapeutic equivalence to their reference product.[24 25]

In this study, the biosimilar aflibercept FYB203 demonstrated therapeutic equivalence to reference aflibercept in patients with nAMD, with comparable safety and immunogenicity profiles. Together with the established high similarity in quality attributes, similar clinical performance of FYB203 and reference aflibercept is assumed across all approved indications.

Acknowledgements The authors would like to thank the patients and study personnel involved in this study. Medical writing and editorial support were provided by Andy Bond of Felt Medical Communications Ltd, funded by Formycon AG.

Contributors SB, BC, RH, NP, AR and TT contributed to the study design. AP collected study data. All authors contributed to data analysis or interpretation, reviewed and critically revised the manuscript, provided final approval of the version to be published, and agreed to be accountable for accuracy and integrity. SB and AR agreed to be guarantors.

Funding This trial was originally funded by Bioeq GmbH, which has since been acquired by Formycon AG. Formycon AG funded medical writing and editorial support for the preparation of this manuscript.

Competing interests AP: grants or contracts from Annexon, Apobiologics/Apotex, Altos Biologics, Alvotech, Amgen, Bayer, Bioeq, Celltrion Inc, Chengdu Kanghong, Clearside Biomedical, Eyebiotech Ltd, Formycon AG, Genentech, Intas Pharmaceuticals, Kodiak Sciences, Novartis, Ocular Therapeutics, Oculis, Ophthea, Ophthotech/Iveric Bio, Qilu, Regeneron, Roche, SamChunDang Pharm. Co. Ltd, Samsung Bioepis, Sanghai Henlius Biotech Inc and Xbrain. Consulting fees from Akceso Advisors, Bayer, Guidepoint Advisors, Formycon AG, Novartis, Ocular Therapeutics, Roche and TEVA. Payment or honouraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Apobiologics/Apotex, Bayer, Novartis and Roche. Support for attending meetings and/or travel from Novartis and Roche; Data Safety Monitoring Board or Advisory Board participation for Bayer, Novartis, Ocular Therapeutics and Roche; Leadership role – Past president of the Retina Section of the Hungarian Ophthalmic Society. SB, BC, RH, NP, AR and TT are employees of Formycon AG.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Approval was obtained from the EC of the Coordinating Investigator (Medical Research Council Ethics Committee for Clinical Pharmacology, Budapest, Hungary; approval number OGYÉI/6311-7/2020) as well as from all other local ECs. The complete list has been included within online supplemental material. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data supporting the findings of this study are available within the paper and its Supplementary Information.

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