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BRIEF REPORT

Therapeutic Equivalence of Eyluxvi (Aflibercept) to Eylea in Neovascular Age-Related Macular Degeneration: ALTERA Trial (Randomized)

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ABSTRACT

***Introduction*:** This study aimed to evaluate the efficacy and safety of Eyluxvi, an aflibercept biosimilar, compared with reference Eylea in patients with neovascular age-related macular degeneration (nAMD).

***Methods*:** This phase 3, multicenter, randomized, double-masked, parallel-group study enrolled 431 patients at 79 sites across 12 countries. Patients were randomized 1:1 to receive intravitreal Eyluxvi or Eylea (2 mg) every 4 weeks through week 12, then every 8 weeks through week 48. The primary endpoint was change from baseline in best corrected visual acuity (BCVA) at week 8.

***Results*:** The week 8 least-squares mean BCVA change was 5.771 letters with Eyluxvi vs 7.863 letters with Eylea (difference −2.092 [95% confidence interval (CI) −3.431 to −0.753]). This equivalence was maintained through week 52. Week 52 adjusted mean changes were comparable for central subfield thickness (CST) (difference −4.742 µm [95% CI −22.006 to 12.521]) and choroidal neovascularization (CNV) area

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(difference 0.233 mm^2 [95% CI −0.724 to 1.191]). Safety profiles and immunogenicity were similar between groups.
Conclusion: This study demonstrated therapeutic equivalence between Eyluxvi and Eylea in nAMD treatment, with comparable anatomical outcomes and safety profiles. These findings support the development of Eyluxvi as an aflibercept biosimilar, potentially increasing treatment accessibility for patients with nAMD.
Trial Registration: EudraCT Identifier 2021-004530-11.

Keywords: Aflibercept; Biosimilar; Neovascular age-related macular degeneration; Anti-vascular endothelial growth factor therapy; Therapeutic equivalence; Randomized controlled trial; Eyluxvi; Eylea

Key Summary Points

Why carry out this study?

Neovascular age-related macular degeneration (nAMD) is a leading cause of vision loss with a growing global disease burden and substantial economic impact affecting healthcare systems and patients.

The study aimed to evaluate the therapeutic equivalence of Eyluxvi, an aflibercept biosimilar, to the reference product Eylea in patients with nAMD.

What was learned from the study?

Eyluxvi demonstrated equivalent efficacy and safety compared to Eylea in improving best corrected visual acuity over 52 weeks.

These results support Eyluxvi as a clinically interchangeable and cost-effective alternative to Eylea.

Wider use of biosimilars like Eyluxvi may improve patient access to effective treatments and reduce the economic burden of nAMD globally.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible vision loss globally [1, 2]. This condition significantly impacts patients' quality of life, increasing the risk of falls, depression, reduced daily activities, and need for long-term care, particularly among older adults with existing comorbidities [3]. Current management relies on intravitreal anti-vascular endothelial growth factor (VEGF) therapies, which have revolutionized treatment outcomes but pose significant economic challenges [4–6]. Aflibercept, a recombinant fusion protein that binds VEGF-A, VEGF-B, and placental growth factor, ranks among the most effective anti-VEGF agents for nAMD [7, 8]. Eyluxvi is a biosimilar to Eylea with high structural and functional similarity demonstrated in preclinical studies.

This phase 3 study aimed to compare the efficacy, safety, and immunogenicity of Eyluxvi to Eylea in patients with nAMD, with the primary objective of demonstrating equivalence in best corrected visual acuity (BCVA) at week 8—a critical evaluation as the need for cost-effective AMD treatments grows increasingly urgent alongside the aging global population and rising disease burden [1, 3].

METHODS

Study Design and Participants

This phase 3, randomized, double-masked, parallel-group study was conducted at 79 sites in Korea, Japan, and 10 countries in Europe from June 2022 to February 2024. Key inclusion criteria were age ≥ 50 years, active subfoveal or juxtafoveal choroidal neovascularization (CNV) secondary to AMD, and BCVA of 20/40 to 20/200. Key exclusion criteria were prior anti-VEGF treatment, active intraocular inflammation, and ocular conditions other than nAMD that could affect vision. Institutional review boards of each site approved the study protocol and subsequent amendments. The study was conducted in compliance with the International Council for Harmonisation and Good

Clinical Practice guidelines and Declaration of Helsinki of 1964 and its later amendments. Written informed consent was obtained before participation. Participants did not receive a stipend; however, their travel expenses were reimbursed. Additional consent was obtained for the pharmacokinetics substudy. The study protocol and subsequent amendments were approved by the institutional review boards/ethics committees at each participating site. A complete list of ethics committees and approval reference numbers is provided in Table S5.

Randomization and Interventions

Patients were randomized in a 1:1 ratio using a permuted block design via an Interactive Response Technology (IRT) system to receive 2 mg Eyluxvi or 2 mg Eylea intravitreally every 4 weeks for 8 weeks (3 loading doses), followed by dosing every 8 weeks through week 48. Randomization was stratified by baseline BCVA (≥ 64 vs < 64 ETDRS, Early Treatment Diabetic Retinopathy Study, letters), central subfield thickness (CST at screening ≥ 300 vs < 300 µm), and geographic region (Europe vs Asia Pacific). The randomization scheme was generated by an independent biostatistician and remained masked until database lock. All participants, investigators, and study staff were masked to treatment assignment.

Ophthalmological examinations, including BCVA assessment, slit-lamp examination (SLE), intraocular pressure (IOP) measurement, dilated fundus examination (DFE), and spectral domain-optical coherence tomography (SD-OCT), were performed at each visit. BCVA was measured using ETDRS charts by certified, masked assessors according to standardized procedures. SD-OCT was performed by trained technicians after BCVA assessment and before study drug administration. Color fundus photography and fluorescein angiography were performed at screening, week 32 and 52 visits. A masked central reading center (CRC) determined central subfield thickness (CST) and choroidal neovascularization (CNV) area and active CNV leakage was determined from the images.

Outcomes and Assessment

The primary efficacy endpoint was change from baseline in BCVA (ETDRS letter score) at week 8. Secondary efficacy endpoints included change from baseline in BCVA, CST, and CNV area over time, as well as the proportion of participants gaining or losing ≥ 5, 10, and 15 letters.

Safety assessments included adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs): vital signs, physical examinations, ophthalmological examinations, clinical laboratory assessments (routine hematology, clinical chemistry, and urinalysis), immunogenicity testing, and monitoring and recording of the type, frequency, relatedness, and severity of all AEs and injection-site reactions. Immunogenicity was evaluated by measuring anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) in blood samples collected on day 1 and at week 4, 8, 16, 32, and 52.

Statistical Analysis

The primary analysis tested the equivalence of Eyluxvi and Eylea in the intention-to-treat (ITT) set using an analysis of covariance (ANCOVA) model with treatment group and stratification factors as fixed effects. Equivalence was declared if the two-sided 90% CI (US Food and Drug Administration, FDA) or 95% CI (other agencies) for the between-group difference in least squares mean (LSM) change from baseline BCVA at week 8 was within ± 3.49 letters. Sample size was based on 90% power to demonstrate equivalence with an equivalence margin of ± 3.49 letters and an assumed SD of 9.5 for Eylea, requiring 194 evaluable participants per arm (total 388). Accounting for 5% dropout rate, 410 participants (205 per arm) were planned for randomization.

RESULTS

Participants

The patient flow is shown in Fig. 1. Of 642 participants screened between June 2022 and February 2023, 216 were randomized to Eyluxvi and 215 to

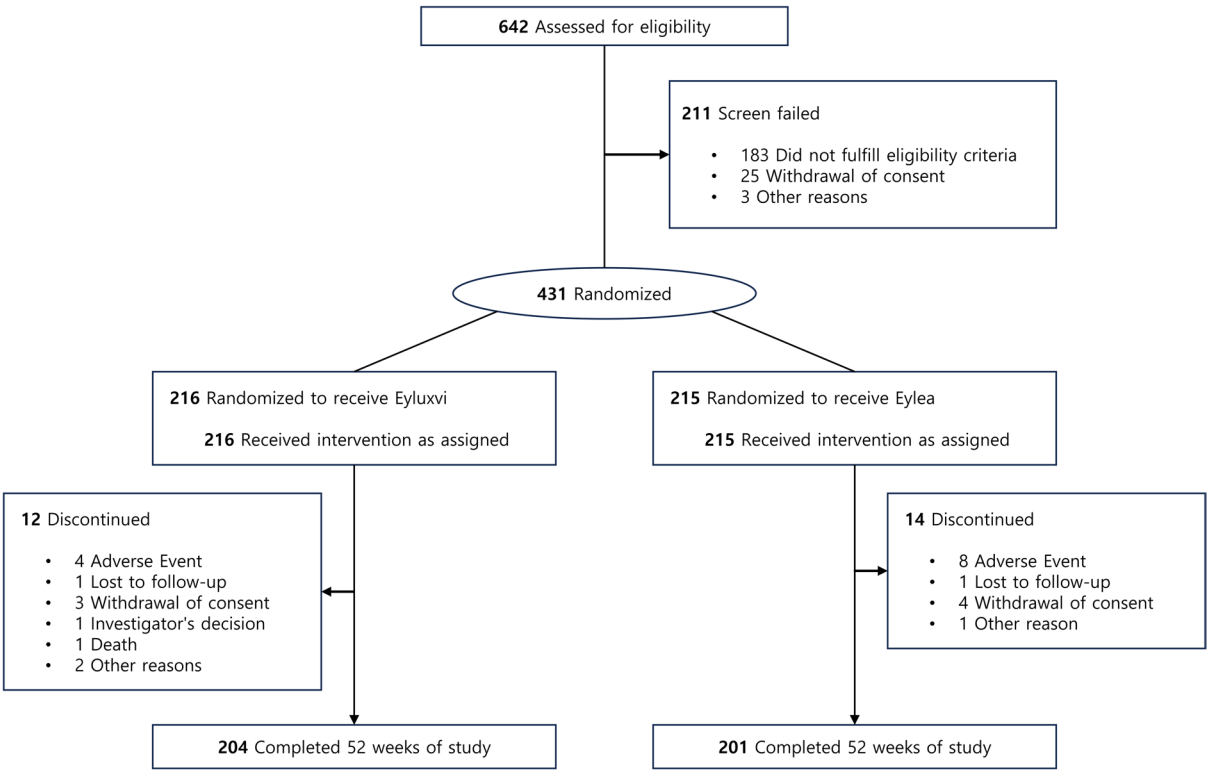


Fig. 1 CONSORT diagram of patients' flow through the trial

Eylea at 79 participating sites. Study completion rates were high, with 405 patients (94%; Eyluxvi 204, Eylea 201) completing week 52. The most common reasons for discontinuation were adverse events (12; Eyluxvi 4, Eylea 8) and withdrawal of consent (7; Eyluxvi 3, Eylea 4).

Demographics and baseline disease characteristics were well balanced between groups (Table 1). The mean age was 74 years. Slightly more female than male patients participated. The study population was white (83.3%) and Asian (16.7%). BCVA at baseline was categorized by letter score with similar distribution between groups. CST measurements at screening were also comparable between the groups.

Efficacy

Primary Outcome

The study met its primary endpoint, demonstrating equivalence between Eyluxvi and Eylea. The LSM for adjusted change from baseline in BCVA at week 8 was 5.771 letters for Eyluxvi and 7.863 letters for Eylea (difference −2.092; 90% CI −3.216 to −0.968; 95% CI −3.431 to −0.753). As both CIs were entirely within the ± 3.49-letter margin, equivalence was established for US FDA (90% CI) and other agencies (95% CI). Sensitivity analyses supported the primary analysis.

Secondary Outcomes

Equivalence was maintained through week 52, with the LSM (SE) for the adjusted change from baseline in BCVA being 7.315 (0.7871) letters for Eyluxvi and 9.259 (0.8018) letters for Eylea (LSM difference [95% CI] −1.944 [−3.781 to −0.107]) (Table 2; Fig. 2a). Changes from baseline in BCVA at each assessment timepoint throughout the study period are presented in Table S1. CST decreased significantly in both groups, with LSM difference (95% CI) of −4.742 µm (−22.006 to

Table 1 Demographics and baseline characteristics (ITT set)

	Eyluxvi (*N* = 216)	Eylea (*N* = 215)	Total (*N* = 431)
Age, mean (SD), years	74.4 (7.83)	73.9 (7.97)	74.2 (7.90)
Age group, *n* (%)			
< 75 years	103 (47.7)	104 (48.4)	207 (48.0)
≥ 75 years	113 (52.3)	111 (51.6)	224 (52.0)
Sex, *n* (%)			
Male	84 (38.9)	89 (41.4)	173 (40.1)
Female	132 (61.1)	126 (58.6)	258 (59.9)
Race, *n* (%)			
White	178 (82.4)	181 (84.2)	359 (83.3)
Asian	38 (17.6)	34 (15.8)	72 (16.7)
Ethnicity, *n* (%)			
Not Hispanic or Latino	216 (100)	215 (100)	431 (100)
Region, *n* (%)			
Europe	178 (82.4)	181 (84.2)	359 (83.3)
Asia Pacific	38 (17.6)	34 (15.8)	72 (16.7)
Height, mean (SD), cm	165.08 (7.931)	165.49 (8.734)	165.29 (8.334)
Weight, mean (SD), kg	75.187 (15.8315)	74.242 (14.5711)	74.715 (15.2055)
BMI*, mean (SD), kg/m^2	27.481 (4.8294)	27.054 (4.6254)	27.268 (4.7280)
Study eye, *n* (%)			
OS	104 (48.1)	119 (55.3)	223 (51.7)
OD	112 (51.9)	96 (44.7)	208 (48.3)
Fellow eye treatment at baseline, *n* (%)			
Yes	8 (3.7)	3 (1.4)	11 (2.6)
No	208 (96.3)	212 (98.6)	420 (97.4)
BCVA at baseline, *n* (%), ETDRS letter score			
< 64 letter score	124 (57.4)	123 (57.2)	247 (57.3)
≥ 64 letter score	92 (42.6)	92 (42.8)	184 (42.7)
CST at screening, *n* (%), μm			
< 300 μm	77 (35.6)	76 (35.3)	153 (35.5)
≥ 300 μm	139 (64.4)	139 (64.7)	278 (64.5)

Abbreviations: *BCVA* best corrected visual acuity, *BMI* body mass index, *CST* central subfield thickness, *ETDRS* Early Treatment Diabetic Retinopathy Study, *ITT* intention-to-treat, *N* number of participants in the ITT set for each treatment group, *n* number of participants with available data, *OD* oculus dexter (right eye), *OS* oculus sinister (left eye), *SD* standard deviation

Percentage was based on the number of participants in the ITT set

*BMI (kg/m^2) = Weight (kg)/[Height (m)^2]

Table 2 Primary and secondary efficacy endpoints measurements

Primary endpoint at week 8 (analysis set)	Treatment	Adjusted change from baseline, LSM (SE)[†]	Difference (Eyluxvi − Eylea)		
			LSM difference	SE	95% CI
BCVA (letters)* (ITT set)	Eyluxvi ($N=216$)	5.771 (0.5821)	− 2.092	0.6834	− 3.431 to − 0.753
	Eylea ($N=215$)	7.863 (0.5888)			

Secondary endpoints at week 52 (analysis set)	Treatment	Adjusted change from baseline, LSM (SE)[†]	Difference (Eyluxvi − Eylea)		
			LSM difference	SE	95% CI
BCVA (letters)* (ITT set)	Eyluxvi ($N=216$)	7.315 (0.7871)	− 1.944	0.9373	− 3.781 to − 0.107
	Eylea ($N=215$)	9.259 (0.8018)			
CST (μm)* (ITT set)	Eyluxvi ($N=216$)	− 116.023 (7.4471)	− 4.742	8.808	− 22.006 to 12.521
	Eylea ($N=215$)	− 111.281 (7.5733)			
Total Size of CNV Area (mm^2)* (ITT set)	Eyluxvi ($N=216$)	− 1.890 (0.4174)	0.233	0.4887	− 0.724 to 1.191
	Eylea ($N=215$)	− 2.123 (0.4188)			

Secondary endpoints at week 52 (analysis set)	Treatment	Adjusted proportion (%)[§]	Difference (Eyluxvi − Eylea)		
			Risk difference	SE	95% CI
Participants who lost ≥ 5 letters in BCVA compared with baseline[‡] (ITT set)	Eyluxvi ($N=216$)	10.6	6.7	2.53	1.8–11.7
	Eylea ($N=215$)	4.0			
Participants who lost ≥ 10 letters in BCVA compared with baseline[‡] (ITT set)	Eyluxvi ($N=216$)	6.4	4.4	1.96	0.6–8.3
	Eylea ($N=215$)	2.0			
Participants who lost ≥ 15 letters in BCVA compared with baseline[‡] (ITT set)	Eyluxvi ($N=216$)	3.4	2.5	1.43	− 0.3 to 5.3
	Eylea ($N=215$)	1.0			

Table 2 continued

Secondary endpoints at week 52 (analysis set)	Treatment	Adjusted proportion (%)§	Difference (Eyluxvi − Eylea)		
			Risk difference	SE	95% CI
Participants who gained ≥ 5 letters in BCVA compared with baseline‡ (ITT set)	Eyluxvi (*N* = 216)	68.8	− 4.2	4.52	− 13.1 to 4.7
	Eylea (*N* = 215)	72.9			
Participants who gained ≥ 10 letters in BCVA compared with baseline‡ (ITT set)	Eyluxvi (*N* = 216)	41.5	− 3.3	5.05	− 13.2 to 6.6
	Eylea (*N* = 215)	44.6			
Participants who gained ≥ 15 letters in BCVA compared with baseline‡ (ITT set)	Eyluxvi (*N* = 216)	19.2	− 3.0	3.93	− 10.7 to 4.7
	Eylea (*N* = 215)	21.8			
Participants with intraretinal or subretinal fluid‡ (ITT set)	Eyluxvi (*N* = 216)	39.7	0.9	4.78	− 8.5 to 10.2
	Eylea (*N* = 215)	39.1			
Participants with active CNV leakage‡¶ (ITT set)	Eyluxvi (*N* = 216)	61.7	6.7	4.95	− 3.0 to 16.4
	Eylea (*N* = 215)	55.1			

Abbreviations: *BCVA* best corrected visual acuity, *CI* confidence interval, *CNV* choroidal neovascularization, *CST* central subfield thickness, *ITT* intention-to-treat, *n* number of participants with available data at week 52, *LSM* least squared mean, *N* number of participants in the ITT set for each treatment group, *SE* standard error

*Analysis of covariance model was applied with treatment arm (Eyluxvi vs Eylea) and geographic region of enrollment (Europe vs Asia Pacific), baseline BCVA (< 64 letters vs ≥ 64 letters), and screening CST (< 300 μm vs ≥ 300 μm) as fixed factors in the model

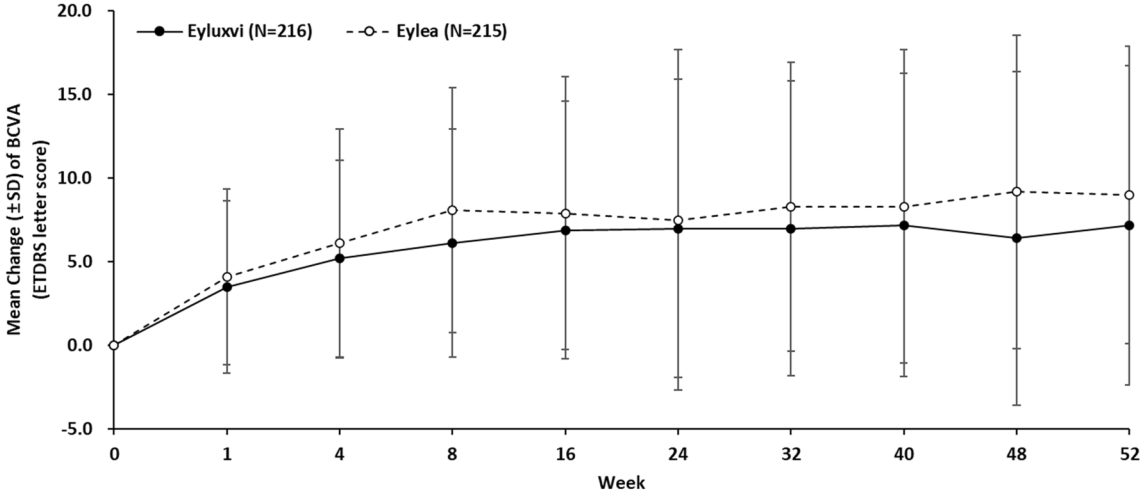
†Adjusted change was presented for primary estimand (400 imputations) based on the mean change across all imputations

‡Cochran–Mantel–Haenszel test was applied with treatment arm (Eyluxvi vs Eylea) adjusted for the randomization strata (geographic region at enrollment [Europe vs Asia Pacific], baseline BCVA [< 64 letters vs ≥ 64 letters], and screening CST [< 300 μm vs ≥ 300 μm])

§Adjusted proportion was presented for the primary estimand (400 imputations) based on the proportion across all imputations. Proportion was based on imputed data

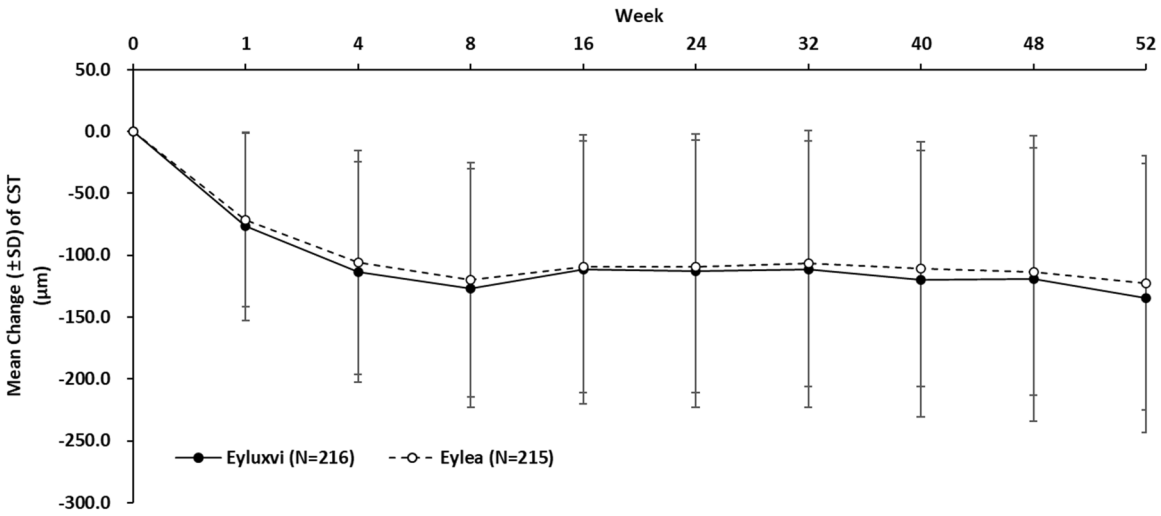
¶The result > 0 (mm^2) was counted as active CNV leakage

A



Week	0	1	4	8	16	24	32	40	48	52
Eyluxvi (n)	216	213	214	213	210	210	208	206	206	204
Eylea (n)	215	211	215	214	213	210	208	206	205	201

B



Week	0	1	4	8	16	24	32	40	48	52
Eyluxvi (n)	216	212	213	211	205	207	207	205	205	203
Eylea (n)	215	209	213	212	207	207	203	205	204	195

Fig. 2 Change from baseline in **a** BCVA and **b** CST at each timepoint through week 52 in the ITT set

12.521) at week 52 (Table 2; Fig. 2b). Complete CST measurements at each timepoint are provided in Table S2. CNV area also decreased, with LSM difference (95% CI) of 0.233 mm^2 (−0.724 to 1.191) at week 52 (Table 2).

Vision Gains and Losses and CNV leakage

The proportion of participants gaining ≥ 15 letters at week 52 was 19.2% for Eyluxvi and 21.8% for Eylea (risk difference [95% CI] −3.0% [−10.7 to 4.7%]), while those losing ≥ 15 letters were 3.4% and 1.0%, respectively (risk difference [95% CI] 2.5% [−0.3 to 5.3%]) (Table 2). The proportions of participants with ≥ 15 letter changes in BCVA and showing active CNV leakage are illustrated in Fig. S1. Additional data on participants achieving ≥ 5 and ≥ 10 letter changes can be found in Table 2.

Changes from baseline in BCVA at each assessment timepoint throughout the study period are presented in Table S1. The proportion of participants with BCVA change and active CNV leakage is shown in Fig. S1. The full dataset for CST changes over time is available in Table S2, and the proportion of participants with intraretinal or subretinal fluid at each visit is shown in Table S3. Figure S2 shows the proportion of participants with intraretinal or subretinal in the ITT set.

Safety

The incidence of treatment-emergent adverse events (TEAEs) including SAEs and TEAEs leading to study drug discontinuation and death through week 52 was comparable between treatment groups: 152 (70.4%) and 142 (66.0%) (Table 3). Non-ocular TEAEs occurred in 116 (53.7%) participants with Eyluxvi and 112 (52.1%) with Eylea. The incidence of ocular TEAEs in the study eye was similar between Eyluxvi (61 [28.2%]) and Eylea (53 [24.7%]) groups. Serious ocular TEAEs were rare: three SAEs of non-drug-related endophthalmitis (Eyluxvi, 1 [0.5%]; Eylea, 2 [0.9%]).

AESIs, which included arterial thromboembolic events, non-ocular hemorrhages, and IVT injection-related reactions, occurred in 13 (6.0%) participants in the Eyluxvi group and 22 (10.2%) participants in the Eylea group.

One death (unrelated to study drug) occurred during the study due to a cystic glial tumor. No significant trend was observed for laboratory parameters, vital signs, physical examination, and ophthalmic examinations. Thus, the safety profile in both the treatment groups was similar.

Pharmacokinetics and Immunogenicity

Systemic exposure was evaluated in the pharmacokinetics substudy population (Eyluxvi, $n = 25$; Eylea, $n = 21$). Mean plasma concentrations were comparable between treatment arms across all timepoints, as detailed in Table S4, and mean plasma concentration profiles are shown in Fig. S3. No evidence of free aflibercept accumulation was observed after repeated dosing.

At baseline, anti-drug antibody (ADA) status was positive for two participants each in both the treatment groups. Overall, the proportion of participants with ADA-induced or ADA-boosted and positive neutralizing antibodies (NAbs) were comparable between the treatment groups. Of the ADA-positive participants, the proportion of participants with positive NAbs was > 70% in both treatment groups at every visit except for the baseline visit.

In the Eyluxvi group, an ADA titer of 20 was reported in four participants at week 52. In the Eylea group, an ADA titre of 20 was reported in one participant each at weeks 8, 32, and 52, and ADA titer of 40 was reported in one participant at week 32. All other participants had titers of ≤ 10.

DISCUSSION

Clinical Equivalence and Outcomes

This phase 3 study demonstrated therapeutic equivalence between Eyluxvi and Eylea in nAMD treatment. The confidence interval of difference in BCVA at week 8 fell well within predefined equivalence margins and this equivalence was maintained through week 52. Comparable anatomical outcome, including CST and CNV

Table 3 Summary of adverse events up to week 52

	Eyluxvi (*N* = 216) ***n*** **(%)**	**Eylea (*N* = 215)** ***n*** **(%)**
TEAEs		
Any TEAE	152 (70.4)	142 (66.0)
Ocular TEAEs in the study eye	61 (28.2)	53 (24.7)
Ocular TEAEs in the fellow eye	51 (23.6)	37 (17.2)
Non-ocular TEAEs	116 (53.7)	112 (52.1)
Related TEAEs	3 (1.4)	5 (2.3)
Serious TEAE (SAEs, all unrelated)	26 (12.0)	27 (12.6)
TEAEs by maximum severity		
Mild TEAEs	123 (56.9)	111 (51.6)
Moderate TEAEs	71 (32.9)	61 (28.4)
Severe TEAEs	11 (5.1)	17 (7.9)
Most common ocular TEAEs (reported in > 2% of the participants overall, by preferred term)		
Neovascular age-related macular degeneration	23 (10.6)	13 (6.0)
Visual acuity reduced	12 (5.6)	10 (4.7)
Cataract	8 (3.7)	4 (1.9)
Subretinal fluid	6 (2.8)	4 (1.9)
Serious ocular AE in the study eye (by preferred term)		
Any ocular SAE in the study eye	1 (0.5)	3 (1.4)
Endophthalmitis	1 (0.5)	2 (0.9)
Blindness	0 (0.0)	1 (0.5)
AESI*	13 (6.0)	22 (10.2)
TEAEs leading to IP discontinuation		
Any TEAEs leading to IP discontinuation	3 (1.4)	9 (4.2)
Ocular TEAEs in the study eye leading to IP discontinuation	1 (0.5)	2 (0.9)
Ocular TEAEs in the fellow eye leading to IP discontinuation	0 (0.0)	0 (0.0)
Non-ocular TEAEs leading to IP discontinuation	2 (0.9)	7 (3.3)
Deaths	1 (0.5)	0 (0.0)

Abbreviations: *AE* adverse event, *AESI* adverse event of special interest, *IP* investigational product, *n* number of participants with event, *N* total number of participants, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

Percentages are based on the number of participants in the safety set

Adverse events were coded to system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary Version 26.1

A treatment-emergent AE (TEAE) is defined as any event not present prior to the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment

*The adverse events of special interests (AESIs) included arterial thromboembolic events, non-ocular hemorrhages, and all AEs related to IVT injection-related reactions

Events recorded as OU (oculus uterque) are counted separately under the study eye and fellow eye

area, provide additional confirmation of biosimilarity. These findings align with the structural and functional similarity demonstrated in preclinical studies and support Eyluxvi as a viable alternative to Eylea.

Safety and Immunogenicity Profile

The safety and immunogenicity profile of Eyluxvi closely matched that of Eylea, with comparable TEAE and ADA rates and a similarly low incidence of serious ocular adverse events.

Global Disease Burden and Access to Care

Age-related macular degeneration (AMD), particularly its neovascular form, nAMD, is a leading cause of irreversible vision loss worldwide. The global prevalence of AMD is projected to increase from approximately 200 million cases in 2020 to nearly 300 million by 2040, primarily driven by aging populations [1, 2]. Significant geographic and socioeconomic disparities exist: regions with lower socioeconomic development have higher age-standardized AMD rates yet face profound challenges in accessing anti-VEGF therapies [3–5].

The consequences of vision loss due to nAMD extend beyond reduced visual acuity, with higher risks of falls, depression, loss of independence, and long-term care needs, particularly among older adults with coexisting chronic conditions [2, 6, 7]. These clinical and psychosocial effects impose substantial societal and economic burdens [6, 7].

Anti-VEGF agents such as aflibercept (Eylea) have revolutionized nAMD management by improving vision and reducing disease progression [8–10]. However, the substantial cost of these biologics strains healthcare budgets and limits patient access, especially in resource-constrained settings [8–10]. Consequently, the development and adoption of biosimilars like Eyluxvi, with demonstrated structural and functional equivalence to the reference product, offer promising avenues to improve treatment affordability and accessibility and may help mitigate global disparities in nAMD care [11].

Study Strengths and Limitations

Key strengths of this study include the large multinational population (431 patients), comprehensive evaluation of efficacy and safety parameters, and high retention rates (94%). The inclusion of multiple efficacy endpoints beyond the primary BCVA measure provides robust evidence for therapeutic equivalence. Limitations include the 52-week follow-up period, which, although consistent with other phase 3 biosimilar anti-VEGF trials, may be insufficient to fully characterize long-term outcomes for a chronic condition like nAMD. Additionally, the predominantly white study population (>80%) limits generalizability to other ethnic groups, particularly relevant given known ethnic variations in AMD prevalence.

Future Perspectives

The introduction of biosimilars like Eyluxvi represents a promising strategy to improve treatment affordability and accessibility globally [11]. Future research should include longer-term follow-up studies, real-world effectiveness evaluations across diverse healthcare settings, pharmacoeconomic analyses in different healthcare systems, and comparative studies with emerging longer-acting anti-VEGF agents. Additionally, exploration of extended dosing intervals could further enhance the value proposition of Eyluxvi by reducing treatment burden while maintaining efficacy.

CONCLUSION

This study aimed to demonstrate the therapeutic equivalence of Eyluxvi, an aflibercept biosimilar, to the reference product Eylea in patients with nAMD. The results confirmed the hypothesis by showing comparable improvements in BCVA, anatomical outcomes, and safety profiles maintained through 52 weeks of treatment. These findings support the use of Eyluxvi as a clinically interchangeable alternative, potentially expanding patient access to effective, affordable

anti-VEGF therapy amid the growing global burden of nAMD.

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Data Availability. The datasets are available in the EudraCT repository, EudraCT Identifier 2021-004530-11.

Declarations

Conflict of Interest. Dorota Raczynska, Jan Ernest, Kristine Baumane, Min Sagong, Kunihiko Akiyama, Attila Vajas, Agnieszka Nowosielska, Jaroslava Dusova, Nora Majtnov, Piotr Oleksy, Irina Kuneva, Miklos Resch, Natalia Lange, Eliza Briede, Beta Bajdik, Areum Jeong, Barbara Kozub, and Andras Papp received research grants/investigator fees from Alteogen Biologics Inc. for conducting this study. Winrich Rauschning received consulting fees from Alteogen Biologics Inc. No other conflicts of interest exist.

Ethical Approval. This study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments. All participants provided written informed consent before participation. The study protocol and subsequent amendments were approved by the institutional review boards/ethics committees at each participating site. Participants did not receive a stipend; however, their travel expenses were reimbursed. Additional consent was obtained for the pharmacokinetics substudy.A complete list of ethics committees and approval reference numbers is provided in Table S5.

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