Efficacy and safety outcomes at 5 years of age from the FIREFLEYE next study in children treated with intravitreal aflibercept 0.4 mg versus laser for retinopathy of prematurity in the randomized FIREFLEYE study

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Disclosures

- **Andreas Stahl** reported receiving consultant fees from Bayer AG during the conduct of the study and outside the submitted work; and receiving consultant fees from AbbVie, Apellis, Bayer, Novartis, Roche and Sandoz outside the submitted work.
    - **DL** reported receiving consultant fees from Bayer AG during the conduct of the study and outside the submitted work and receiving consultant fees from Novartis outside the submitted work. **HN, NA,** and **CJ** reported receiving honoraria fees from Bayer AG during the conduct of the study and outside the submitted work. **W-CW** reported receiving consultant fees from Bayer AG during the conduct of the study and outside the submitted work and receiving consultant fees from Allegan, Novartis, and Roche outside the submitted work**. AA** is an employee of Regeneron Pharmaceutics, Inc**. SS, KB,** and **TN** are employees of Bayer AG. **SL** is an employee, stockholder and patent holder at Bayer Consumer Care AG. **TM** is an employee of Bayer US, LLC. **AF** reported receiving consultant fees from Bayer AG during the conduct of the study and outside the submitted work and receiving consultant fees from Novartis outside the submitted work.
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- This study included research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
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FIREFLEYE next (NCT04015180) Study Design and Baseline Characteristics

FIREFLEYE next was the first multinational, Phase 3b study to assess ocular and further clinical outcomes, including growth and neurodevelopmental outcomes, **through 5 years of age** following treatment of acute-phase ROP with intravitreal aflibercept 0.4 mg per eye versus laser photocoagulation in the **24-week, Phase 3 FIREFLEYE study**[1]

Treated in FIREFLEYE after **2:1 randomization** at baseline

Very/extremely preterm or very/extremely low birth weight neonates (gestational age ≤32 weeks or birth weight ≤1500 g)

- **Aflibercept 0.4 mg** group **N=75 (146 eyes)**
- **Laser** group **N=38 (72 eyes)**

Total N=113

Followed in FIREFLEYE next

Enrolled in **FIREFLEYE next**[a]

- **Aflibercept 0.4 mg** group **N=66 (128 eyes)**
- **Laser** group **N=34 (64 eyes)**

Total N=100[b]

Completed visit at **5 years of age**

- **Aflibercept 0.4 mg** group **N=59 (114 eyes)**
- **Laser** group **N=30 (58 eyes)**

Total N=89

Endpoints (5 years of age[c])

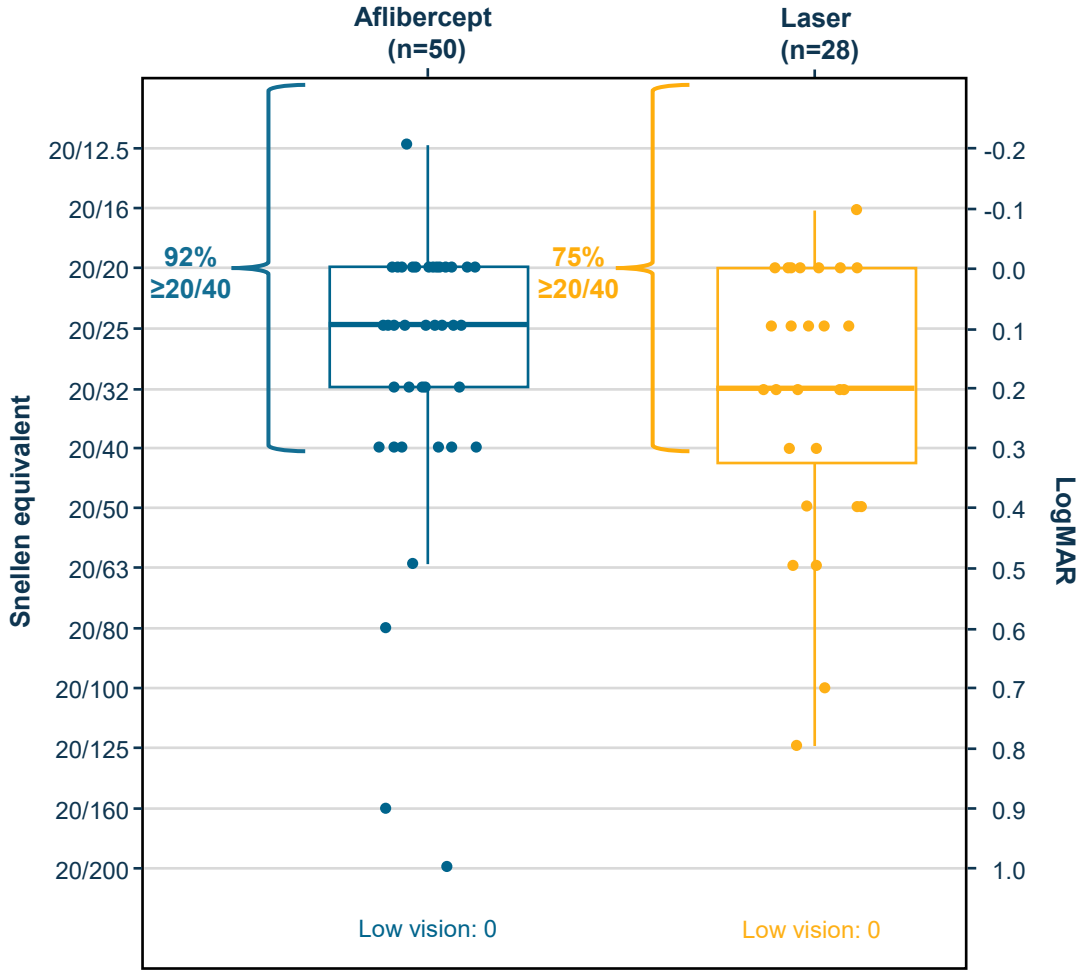
- **Primary endpoint:** Binocular **BCVA** (Snellen equivalent) at 5 years of age
- **Secondary endpoints:** Ocular and systemic **AEs** and **SAEs;** Absence of **active ROP**; Absence of **unfavorable structural outcomes**; **ROP recurrence; BCVA** in each eye; **Treatment need** for ROP complications; **Refractive spherical equivalent**; Outcomes of **neurodevelopmental tests** (i.a., WPPSI-IV, VABS-II)
- **Exploratory endpoints (i.a.):** Completion of **retinal vascularization;** Ability to **fix and follow a 5-cm toy**; **Growth outcomes**

	Aflibercept 0.4 mg (N=66)	Laser (N=34)	Total (N=100)
Male, %	**54.5**	**50.0**	**53.0**
Gestational age, w	**26w 4d** ±2.1	**26w 0d** ±1.7	**26w 3d** ±1.9
Birth weight, g	**882.2** ±286.9	**819.5** ±238.6	**860.9** ±271.9
Body weight at baseline treatment in FIREFLEYE, g	**2045.8** ±675.8	**1843.8** ±569.2	**1977.1** ±645.8
Body weight at baseline in FIREFLEYE next, kg	**6.7** ±1.2	**6.4** ±1.2	**6.6** ±1.2
Age at FIREFLEYE next entry, months	**9.0** ±1.6	**9.1** ±1.7	**9.0** ±1.6

Data are mean ±standard deviation unless stated otherwise. [a]Constituting the analysis set. [b]Three study treatment-unrelated deaths occurred in FIREFLEYE, and the parents/carers of 10 children (aflibercept 0.4 mg, 6; laser, 4) did not consent to enrollment in FIREFLEYE next. **AE**, adverse event; [C]Refers to "chronological age" unless indicated otherwise. **BCVA**, best-corrected visual acuity; **d,** day; **g**, gram; **kg**, kilogram; **ROP**, retinopathy of prematurity; **SAE**, serious adverse event; **VABS-II**, Vineland Adaptive Behavior Scales, Second Edition; **w**, week; **WPPSI-IV**, Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition. 1. Stahl A, et al. JAMA 2022;328:348–59.

Primary Endpoint: Binocular and Monocular BCVA at 5 Years of Age

Binocular BCVA[a]



Monocular BCVA[b]



Primary Estimand: The estimated probability that treatment initiation with aflibercept resulted in better binocular BCVA at 5 years of age than with laser was 62.4% (95% CI: 49.3–74.2%), where a value above or below 50% indicate an advantage for aflibercept or laser

All enrolled patients. Low vision outcomes included BCVA values of <20/200, light perception, and no light perception. [a]Results for binocular BCVA are reported by patient. [b]Results for monocular BCVA are reported per treated eye.
BCVA, best-corrected visual acuity; **CI**, confidence interval; **logMAR**, the logarithm of the minimum angle of resolution.

Unfavorable Structural Outcomes and the Need for ROP Treatment in FIREFLEYE next

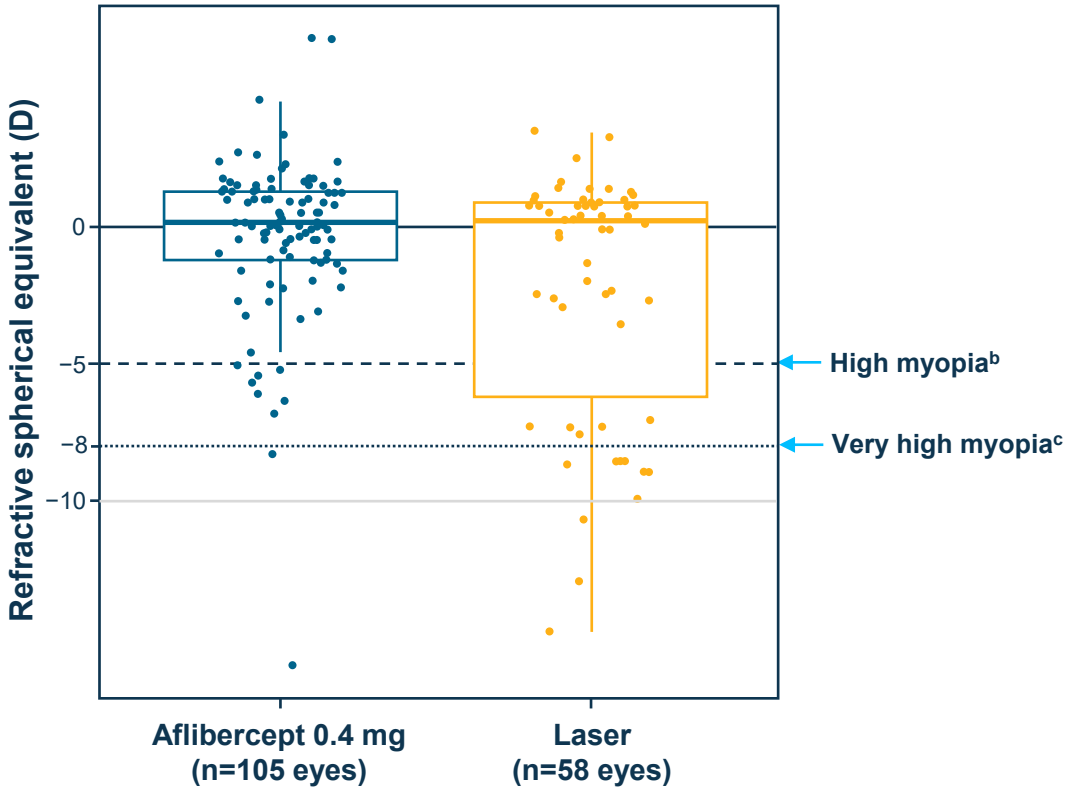
	Aflibercept 0.4 mg (N=66)			Laser (N=34)		
Unfavorable structural outcomes	**Between treatment and 2 years of age**	**Between treatment and 3 years of age**	**Between treatment and 5 years of age**	**Between treatment and 2 years of age**	**Between treatment and 3 years of age**	**Between treatment and 5 years of age**
Proportion of children, %						
None	**93.9**	**93.9**	**93.9**	**94.1**	**94.1**	**94.1**
Retinal detachment	**4.5**	**6.1**	**6.1**	**2.9**	**2.9**	**2.9**
Macular dragging	**1.5**	**1.5**	**1.5**	**2.9**	**2.9**	**2.9**
Macular fold	**1.5**	**1.5**	**1.5**	0	0	0
Retrolental opacity	**1.5**	**1.5**	**1.5**	0	0	0
Any unfavorable structural outcome	**6.1**	**6.1**	**6.1**	**5.9**	**5.9**	**5.9**
Proportion of treated eyes,[a] %						
None	**94.5**	**94.5**	**94.5**	**95.3**	**95.3**	**95.3**
Retinal detachment	**3.9**	**4.7**	**4.7**	**1.6**	**1.6**	**1.6**
Macular dragging	**1.6**	**1.6**	**1.6**	**3.1**	**3.1**	**3.1**
Macular fold	**1.6**	**1.6**	**1.6**	0	0	0
Retrolental opacity	**1.6**	**1.6**	**1.6**	0	0	0
Any unfavorable structural outcome	**5.5**	**5.5**	**5.5**	**4.7**	**4.7**	**4.7**
Reactivation of ROP after entry into FIREFLEYE next[b]	**Between entry and 2 years of age**	**Between entry and 3 years of age**	**Between entry and 5 years of age**	**Between entry and 2 years of age**	**Between entry and 3 years of age**	**Between entry and 5 years of age**
Infants evaluated, n	66	66	66	34	34	34
Reactivation, %	**1.5**	**1.5**	**1.5**	**0**	**0**	**0**

- **No disease reactivation** occurred after 50 weeks of age
  - 1 patient (laser) had ROP with sequelae of stage 4b from FIREFLEYE next screening through 5 years
- In total, **4 children** (aflibercept 0.4 mg) received treatment for ROP complications after entry into FIREFLEYE next (including 2 children with pre-existing bilateral retinal detachment, 1 with reactivated plus disease[c], and 1 with retinal neovascularization not further specified[d])
  - 1 child showed retinal detachment at age 3 (in the progression of macular fold reported at ages 1 and 2 years)

[a]Number of eyes, aflibercept 0.4 mg, 128; laser, 64. [b]A child was considered as having ROP recurrence if: the inclusion criteria of FIREFLEYE (or worse) were reported and a previous assessment (either in FIREFLEYE or in FIREFLEYE next) of ROP not requiring treatment (according to the inclusion criteria) was available.[c]Zone I, both eyes, treated at ~43 weeks of age. [d]Treated at ~50 weeks of age.

Ophthalmic Outcomes at 5 Years of Age

No./Total No. (%)	Aflibercept 0.4 mg	Laser
Ocular findings, patients		
Nystagmus	1/56 (**1.8**)	1/30 (**3.3**)
Manifest strabismus	10/56 (**17.9**)	4/30 (**13.3**)
Ocular findings, eyes		
Cataract	1/108 (**0.9**)	0/58 (**0**)
Optic nerve atrophy	3/108 (**2.8**)	0/58 (**0**)
Eyes with complete retinal vascularization[a]		
At 1 year of age	89/128 (**69.5**)	N/A
At 2 years of age	97/121 (**80.2**)	N/A
At 3 years of age	89/111 (**80.2**)	N/A
At 4 years of age	87/109 (**79.8**)	N/A
At 5 years of age	91/107 (**85.0**)	N/A



Myopia

Mild in both groups and
less pronounced with aflibercept 0.4 mg[d]

Aflibercept 0.4 mg, **−0.3 [2.9] D**;
Laser, −2.2 [4.5] D

Eyes with high myopia ≤ −5 D

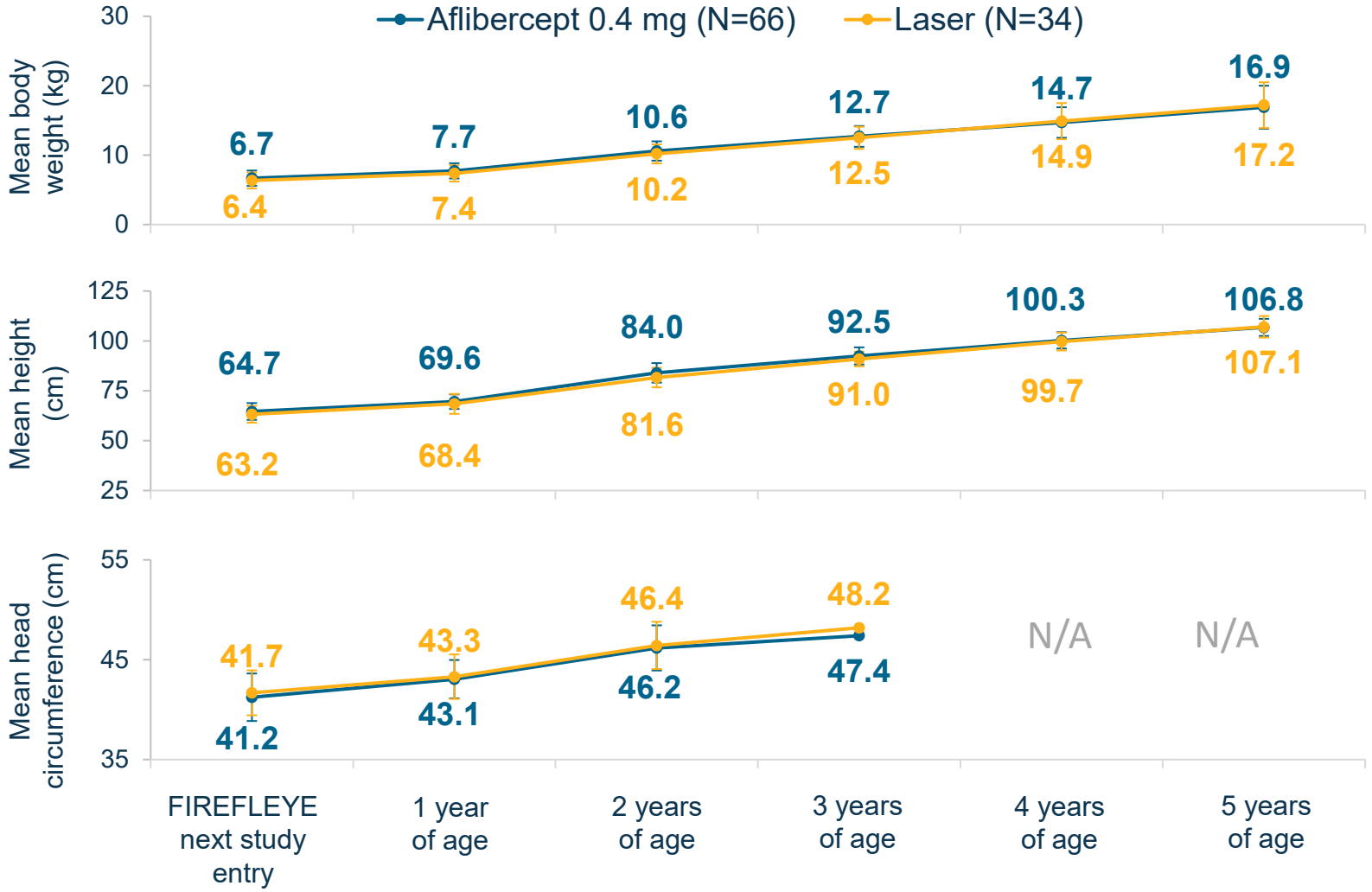
Aflibercept 0.4 mg **9 eyes** (**9%**);
Laser **15 eyes** (**26%**)

Eyes with very high myopia ≤ −8 D

Aflibercept 0.4 mg **2 eyes** (**2%**);
Laser **10 eyes** (**17%**)

[a]Retinal vessels had to be within 1 disc cm of ora serrata for the vascularization to be deemed complete. Analysis of complete vascularization in eyes receiving laser therapy is not reported, as laser scars prevent physiologic vascularization of the peripheral retina. [b]High myopia was defined as −5 D or worse. [c]Very high myopia was defined as −8 D or worse. [d]Mean [standard deviation] refractive spherical equivalent. **D**, diopter.

Growth Parameters up to 5 Years of Age

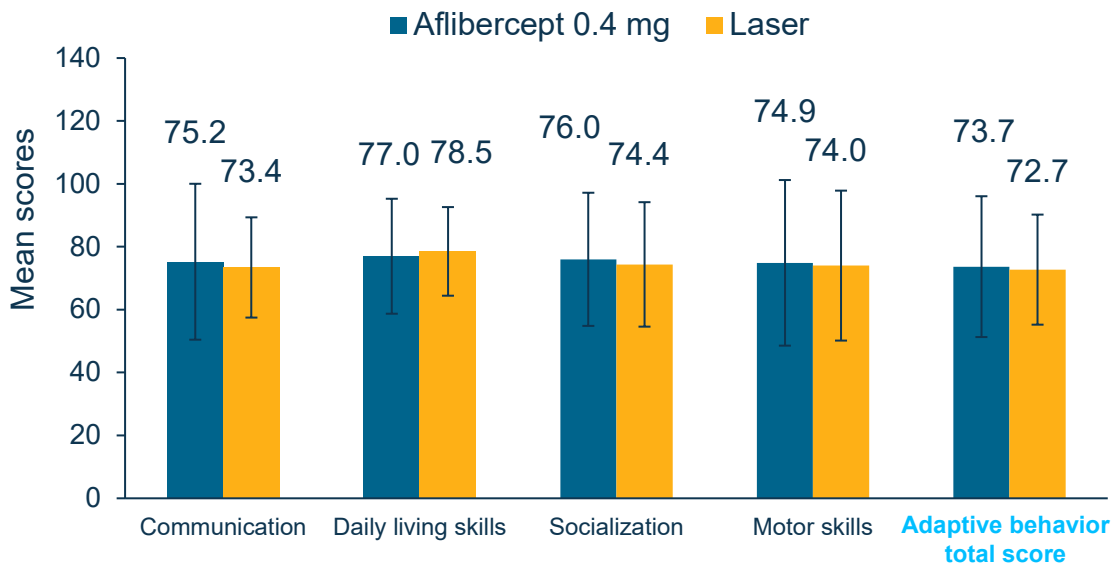


No clinically relevant differences in growth parameters were observed between groups up to 5 years of age, and results are in line with **what is expected** in this population of children born prematurely

Head circumference was not assessed at 4 and 5 years of age. Bars represent standard deviation.

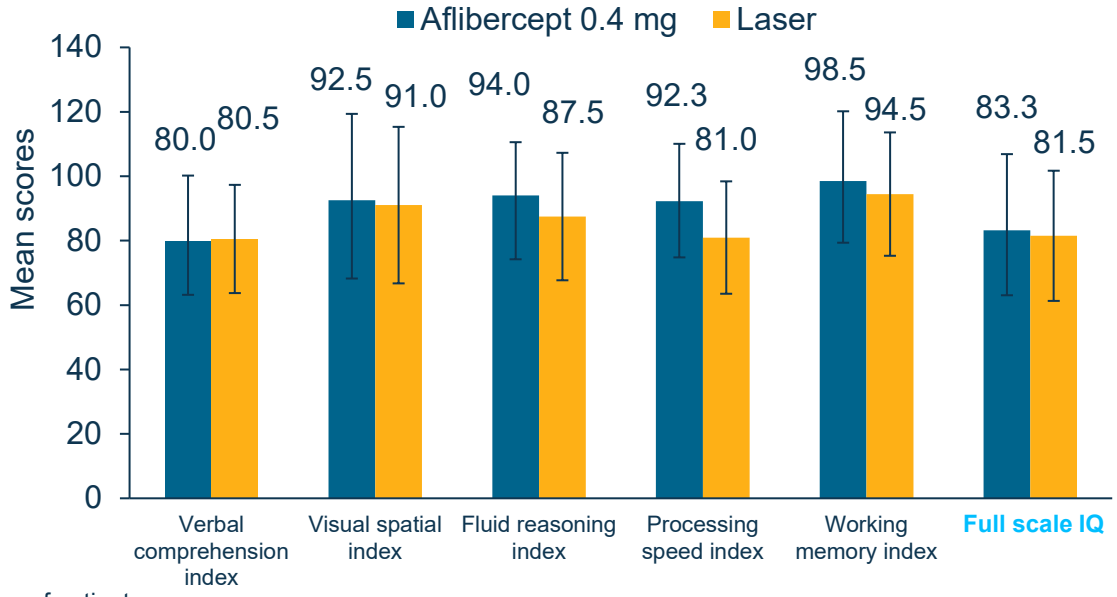
Neurodevelopmental Test Outcomes (VABS-II and WPPSI-IV) at 5 Years of Age

Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II) scores



Number of patients					
Aflibercept 0.4 mg	52	52	52	52	52
Laser	29	29	29	29	29

Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) scores



Number of patients						
Aflibercept 0.4 mg	46	48	41	40	43	48
Laser	29	30	29	27	29	30

- No relevant differences in domain and total scores were observed between the two groups

Bars represent standard deviation. **VABS-II**, Vineland Adaptive Behavior Scales, Second Edition; **WPPSI-IV**, Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

Adverse Events During FIREFLEYE next Through 5 Years of Age

	Aflibercept 0.4 mg (n=66)	Laser (n=34)
Any AE, n (%)	62 (**93.9**)	29 (**85.3**)
Ocular AEs	35 (53.0)	16 (47.1)
Ocular AEs in treated eye	34 (51.5)	15 (44.1)
Ocular AEs in untreated eye	2 (3.0)	1 (2.9)
Systemic AEs	59 (89.4)	29 (85.3)
AEs related to aflibercept 0.4 mg	2 (3.0)	1 (2.9)
AEs related to laser treatment	3 (4.5)	5 (14.7)
Any SAE, n (%)	25 (**37.9**)	16 (**47.1**)
Any ocular SAE	6 (9.1)	0
Ocular AEs in treated eye	6 (9.1)	0
Ocular AEs in untreated eye	0	0
Systemic SAEs	23 (34.8)	16 (47.1)
SAEs related to aflibercept 0.4 mg	1 (1.5)	0
SAEs related to laser treatment	0	0

The observed frequencies of AEs or SAEs were **comparable between the two groups**

AE, adverse event; **SAE**, serious adverse event.

Conclusions

FIREFLEYE next is the **first prospective, controlled, Phase 3b study** evaluating **long-term efficacy and safety outcomes** after treatment of **acute-phase ROP with aflibercept 0.4 mg versus laser photocoagulation**

Through 5 years of age, **efficacy outcomes were well sustained**, and **no ocular or systemic safety concerns were identified:**

Efficacy

- At 5 years of age, **92% of children treated with aflibercept 0.4 mg versus 75% of children treated with laser** had binocular **BCVA ≥20/40**
- In both treatment groups, approximately **94% of children** had **no unfavorable structural outcomes** through 5 years
- **No disease reactivation occurred** after 50 weeks of age. One patient (aflibercept 0.4 mg) showed retinal detachment at age 3 years in the progression of macular fold reported at ages 1 and 2 years of age
- Myopia was **less frequent** and **less severe** if treatment was initiated with aflibercept compared to laser

Safety

- **No clinically relevant differences** in **neurodevelopmental** or **growth outcomes** were identified
- No ocular or systemic safety concerns through 5 years of age were identified

Overall, aflibercept 0.4 mg injection therapy in very/extremely preterm or very/extremely low birthweight patients with acute-phase ROP (as approved[a]) was **effective and generally well tolerated through 5 years of age**

[a]Aflibercept has been approved for treatment of ROP in Japan (September 2022),[1] the European Union (December 2022),[2] Switzerland,[3] the USA (February 2023),[4] and Brazil (April 2023).[5]

1. Bayer, 2023. Available at: https://www.bayer.com/media/en-us/eylea-approved-in-japan-for-treatment-of-preterm-infants-with-retinopathy-of-prematurity/ [Accessed Nov 2025]; 2. Bayer AG, 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf (Accessed Nov 2025) 3. Aflibercept RMP Summary, 2025. Available at: https://www.swissmedic.ch/dam/swissmedic/en/dokumente/marktueberwachung/rmp/aflibercept_eylea_rmp-summary.pdf.download.pdf/Aflibercept_Eylea_SwissRMPSummary_v1_EURMP_32.2_20230220.pdf (Accessed Nov 2025); 4. Regeneron Pharmaceuticals, 2023. Available at:https://www.regeneron.com/downloads/eylea_fpi.pdf [Accessed Nov 2025]; 5. Anvisa NHSA, 2023. Available at: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/eylia-aflibercepte-nova-indicacao (Accessed Nov 2025).