Two-year outcomes from FIREFLEYE Next, a prospective follow-up study to evaluate long-term efficacy and safety of patients treated with intravitreal aflibercept or laser photocoagulation for ROP in the FIREFLEYE study

Noriyuki Azuma,[1] Andreas Stahl,[2] Domenico Lepore,[3] Hidehiko Nakanishi,[4] Wei-Chi Wu,[5] Carlos Jacas,[6] Robert Vitti,[7] Aditya Athanikar,[7] Karen Chu,[7] Pablo Iveli,[8] Fei Zhao,[9] Sergio Leal,[10] Thomas Schmelter,[11] Thomas Miller,[12] Evra Köfüncü,[11] Alistair Fielder,[13] on behalf of the FIREFLEYE Next investigators

[1]Department of Developmental and Regenerative Biology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan; [2]Department of Ophthalmology, University Medicine Greifswald, Greifswald, Germany; [3]Department of Neuroscience, Sensory Organs and Thorax, Catholic University of the Sacred Heart, A. Gemelli Foundation IRCCS, Rome, Italy [4]Research and Development Center for New Medical Frontiers, Department of Advanced Medicine, Division of Neonatal Intensive Care Medicine, Kitasato University School of Medicine, Sagamihara, Japan; [5]Department of Ophthalmology, Linkou Chang Gung Memorial Hospital, and College of Medicine, Chang Gung University, Taoyuan City, Taiwan; [6]Department of Psychiatry, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [7]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [8]Bayer AG, Wuppertal, Germany; [9]Bayer Inc., Mississauga, Ontario, Canada; [10]Bayer Consumer Care AG, Basel, Switzerland; [11]Bayer AG, Berlin, Germany; [12]Bayer Healthcare, LLC, Whippany, NJ, USA; [13]Department of Optometry and Visual Science, City, University London, London, UK

Presented at the 77th Annual Congress of Japan Clinical Ophthalmology (JCO), Tokyo, Japan, October 6–9, 2023

Disclosures

Presenting Author

Noriyuki Azuma: Not applicable to COI disclosure criteria

Co-author group

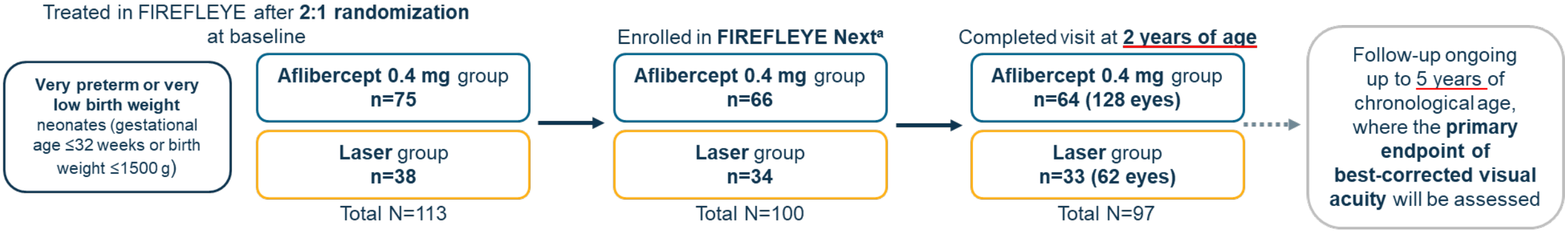
AS, DL, HN, W-CW and CJ: Not applicable to COI disclosure criteria; **RV, AA & KC:** Employees of Regeneron (E); **PI, FZ, SL, TS, TM & EK:** Employees of Bayer (E); **AF:** Not applicable to COI disclosure criteria

Previously presented at the European Society of Retina Specialists (EURETINA) Congress, Amsterdam, Netherlands, October 5–8, 2023

As per JCO conflict of interest (COI) disclosure criteria, only Class IV conflicts of interest are disclosed.

FIREFLEYE Next (NCT04015180) study design

FIREFLEYE Next is the first multinational, ongoing, phase 3b study assessing 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 vs. laser photocoagulation in the **24-week, Phase 3 FIREFLEYE study**[1]



Endpoints included in exploratory interim analysis (2 years of chronological age)

- Absence of **active ROP**
- Absence of **unfavorable structural outcomes**
- **Completion of retinal vascularization**
- **Treatment need** for ROP complications
- **Refractive spherical equivalent**
- Ability to **fix and follow a 5-cm toy**
- Outcomes of **growth**, and **neurodevelopmental tests** (BSID-III, VABS-II)

[a]Three study treatment-unrelated deaths in FIREFLEYE and the parents/carers of 10 children (aflibercept 0.4 mg, six; laser, four) did not consent to enrollment in FIREFLEYE Next.
BSID-III, Bayley Scales of Toddler and Infant Development, Third Edition; **ROP**, retinopathy of prematurity; **VABS-II**, Vineland Adaptive Behavior Scales, Second Edition.
1. Stahl et al. *JAMA* 2022;328(4):348–59.

Baseline characteristics

	Aflibercept 0.4 mg (n=66)	Laser (n=34)	Total (n=100)
Male, n (%)	36 (**54.5**)	17 (**50.0**)	53 (**53.0**)
Gestational age, w and d	**26w 4d** ±2.1	**26w 0d** ±1.7	**26w 3d** ±1.9
Gestational age group, n (%)			
<24 weeks	3 (**4.5**)	3 (**8.8**)	6 (**6.0**)
≥24 to <27 weeks	39 (**59.1**)	22 (**64.7**)	61 (**61.0**)
≥27 weeks	24 (**36.4**)	9 (**26.5**)	33 (**33.0**)
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
Chronological age at FIREFLEYE Next entry, months	**9.0** (1.6)	**9.1** (1.7)	**9.0** (1.6)

84% of children had **no ROP** at FIREFLEYE Next study entry

Detailed ROP classification by investigator, n (%)	At FIREFLEYE study entry			At FIREFLEYE Next study entry		
	Aflibercept 0.4 mg (n=75)	Laser (n=38)	Total (n=113)	Aflibercept 0.4 mg (n=66)	Laser (n=34)	Total (n=100)
Absence of ROP	0	0	0	55 (83.3)	29 (85.3)	84 (84.0)
Zone I (excluding AP-ROP)	15 (20.0)	7 (18.4)	22 (19.5)	3 (4.5)	3 (8.8)	6 (6.0)
Stage 1	1 (1.3)	0	1 (0.9)	1 (1.5)	1 (2.9)	2 (2.0)
Stage 2	2 (2.7)	2 (5.3)	4 (3.5)	0	0	0
Stage 3	3 (4.5)	1 (2.6)	4 (3.5)	0	0	0
Stage 3+	9 (12.0)	4 (10.5)	13 (11.5)	0	0	0
Stage 4A	0	0	0	1 (1.5)	0	1 (1.0)
Stage 4B	0	0	0	1 (1.5)	1 (2.9)	2 (2.0)
Missing	0	0	0	0	1 (2.9)	1 (1.0)
Zone II (excluding AP-ROP)	46 (61.3)	26 (68.4)	72 (63.7)	4 (6.1)	2 (5.9)	6 (6.0)
Stage 1	0	0	0	1 (1.5)	1 (2.9)	2 (2.0)
Stage 2	0	1 (2.6)	1 (0.9)	2 (3.0)	0	2 (2.0)
Stage 2+	7 (9.3)	4 (13.2)	12 (10.6)	0	0	0
Stage 3+	39 (52.0)	20 (52.6)	59 (52.2)	0	0	0
Missing	0	0	0	1 (1.5)	1 (2.9)	2 (2.0)
Zone III (excluding AP-ROP)	0	0	0	4 (6.1)	0	4 (4.0)
Stage 1	0	0	0	3 (4.5)	0	3 (3.0)
Missing	0	0	0	1 (1.5)	0	1 (1.0)
AP-ROP	14 (18.7)	5 (13.2)	19 (16.8)	0	0	0
Zone I	12 (16.0)	4 (10.5)	16 (14.2)	0	0	0
Zone II	2 (2.7)	1 (2.6)	3 (2.7)	0	0	0

Data are mean ±SD unless stated otherwise. **AP-ROP**, aggressive-posterior retinopathy of prematurity; **n**, number; **SD**, standard deviation

Unfavorable structural outcomes, ROP recurrence, and treatment for ROP complications in FIREFLEYE Next

	Aflibercept 0.4 mg (n=66)		Laser (n=34)	
Unfavorable structural outcomes	At any time until 1 year of chronological age	At any time until 2 years of chronological age	At any time until 1 year of chronological age	At any time until 2 years of chronological age
Number of children, n (%)	66 (100.0)	66 (100.0)	34 (100.0)	34 (100.0)
None	62 (**93.9**)	62 (**93.9**)	32 (**94.1**)	32 (**94.1**)
Retinal detachment	3 (**4.5**)	3 (**4.5**)	1 (**2.9**)	1 (**2.9**)
Macular dragging	1 (**1.5**)	1 (**1.5**)	1 (**2.9**)	1 (**2.9**)
Macular fold	1 (**1.5**)	1 (**1.5**)	0	0
Retrolental opacity	1 (**1.5**)	1 (**1.5**)	0	0
Any unfavorable structural outcome	4 (**6.1**)	4 (**6.1**)	2 (**5.9**)	2 (**5.9**)
Number of treated eyes, n (%)	128 (100.0)	128 (100.0)	64 (100.0)	64 (100.0)
None	121 (**94.5**)	121 (**94.5**)	61 (**95.3**)	61 (**95.3**)
Retinal detachment	5 (**3.9**)	5 (**3.9**)	1 (**1.6**)	1 (**1.6**)
Macular dragging	2 (**1.6**)	2 (**1.6**)	2 (**3.1**)	2 (**3.1**)
Macular fold	2 (**1.6**)	2 (**1.6**)	0	0
Retrolental opacity	2 (**1.6**)	2 (**1.6**)	0	0
Any unfavorable structural outcome	7 (**5.5**)	7 (**5.5**)	3 (**4.7**)	3 (**4.7**)
Recurrence of ROP after entry into FIREFLEYE Next[a]	Between entry and 1 year of age	Between entry and 2 years of age	Between entry and 1 year of age	Between entry and 2 years of age
n	66	64	34	32
Recurrence, n (%)	1 (**1.5**)	**0**	**0**	**0**

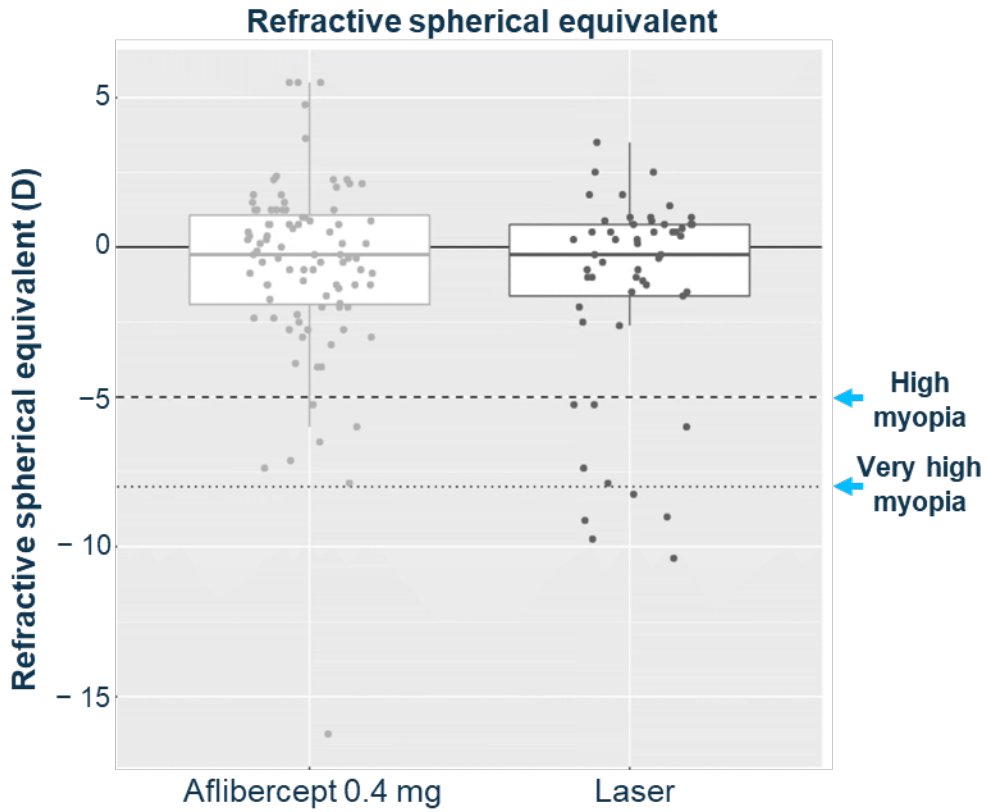
In total, **4 patients were treated** after entry into FIREFLEYE Next for ROP complications, all before 1 year of age (including 2 patients with pre-existing bilateral retinal detachment, 1 each with reactivated plus disease[b] and retinal neovascularization not further specified[c])[d]

[a]Post hoc analysis. 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. [b]Zone I, both eyes, treated at around 43 weeks of age. [c]Treated around 50 weeks of chronological age. [d]None of the 4 children were considered as having recurrence of ROP as per study protocol.

Ophthalmic outcomes at 2 years of age

	Aflibercept 0.4 mg (122 eyes)	Laser (63 eyes)
Ocular findings at 2 years of chronological age, n (%)		
Nystagmus	6 (**4.9**)	4 (**6.3**)
Manifest strabismus	28 (**23.0**)	12 (**19.0**)
Amblyopia	**0**	**0**
Cataract	1 (**0.8**)	**0**
Optic nerve atrophy	2 (**1.6**)	**0**
Ability to fix and follow a 5-cm toy	118 (**96.7**)	62 (**98.4**)
Eyes with complete retinal vascularization, n (%)[a]		
At 1 year of chronological age	91 (**71.1**)	-
At 2 years of chronological age	97 (**80.2**)	-

Retinal vascularization in the aflibercept 0.4 mg group **continued beyond 1 year of age**



Most eyes (aflibercept 0.4 mg, **97%**; laser, **98%**) **were able to fix and follow a 5-cm toy**

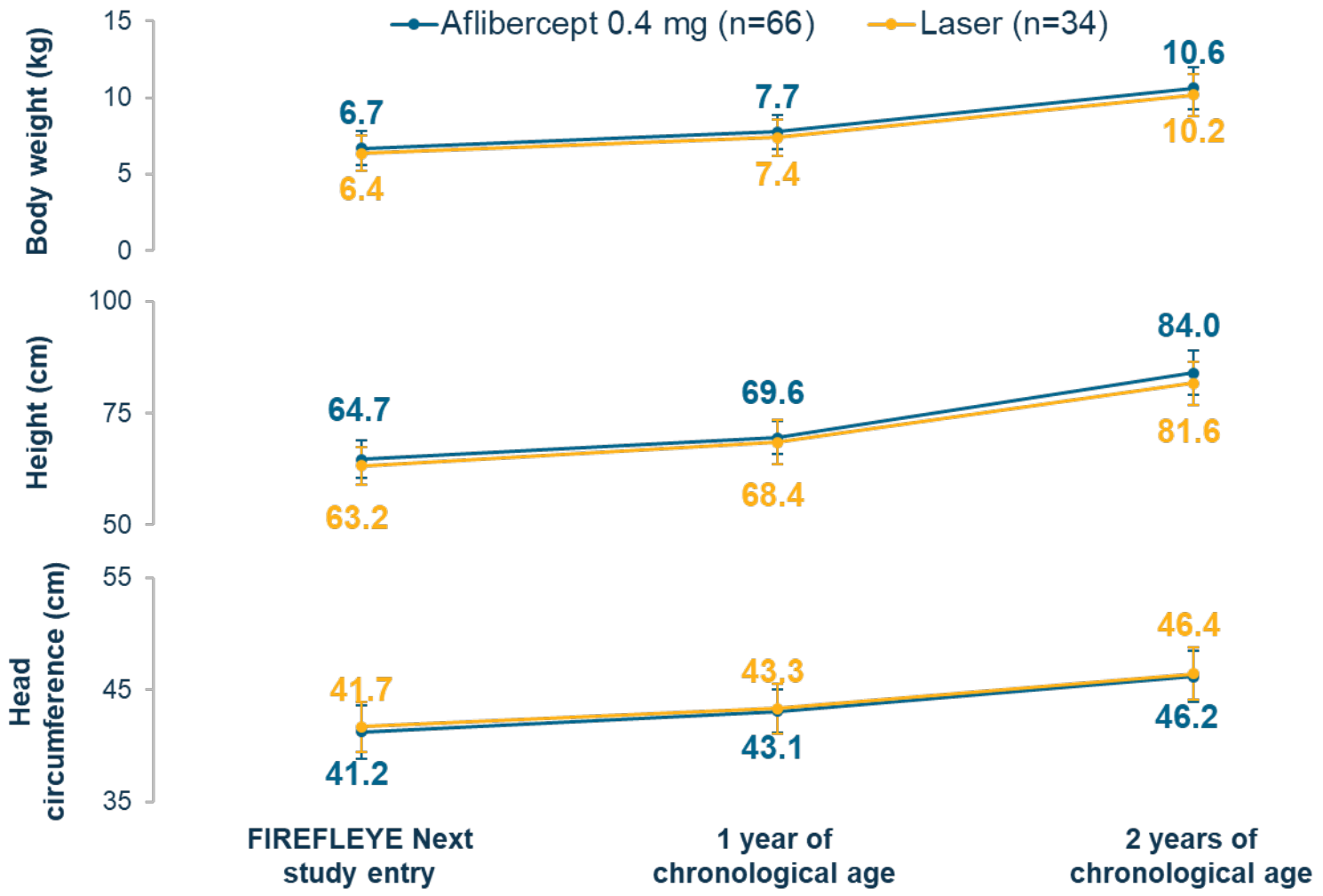
Myopia was mild in both groups and **less pronounced in the aflibercept 0.4 mg group** (aflibercept 0.4 mg, −0.6 [3.1] D; laser, −1.4 [3.4] D).

High myopia was present in **7 eyes** (**8%**) in the aflibercept 0.4 mg group and **10 eyes** (**19%**) in the laser group

Very high myopia was present in **1 eye** (**1%**) in the aflibercept 0.4 mg group and **5 eyes** (**9%**) in the laser group

[a]Analysis of complete vascularization in eyes receiving laser therapy is not reported, as laser scars prevent physiologic vascularization of the peripheral retina. **D**, diopter

Growth parameters up to 2 years of age

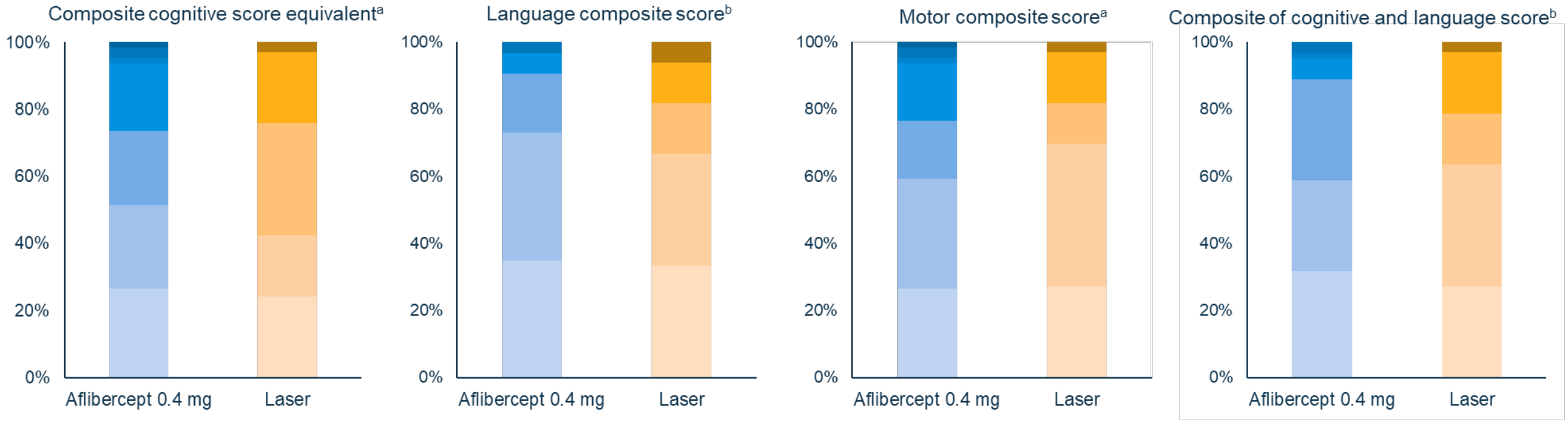


No clinically relevant differences in growth parameters were observed between both groups at 1 and 2 years of age, and results are in line with **what is expected in this prematurely born** pediatric population

Error bars represent SD

Neurodevelopmental test outcomes at 2 years of age

Bayley Scales of Toddler and Infant Development, 3rd Edition (BSID-III) scores



Composite scores for BSID-III and **VABS-II** (not shown) at 2 years of age were comparable across both groups. Small numerical differences in both directions can likely be attributed to sample size

[a]Aflibercept 0.4 mg, n=64; Laser, n=34. [b]Aflibercept 0.4 mg, n=63; Laser, n=33.

Adverse events (during FIREFLEYE Next through 2 years of age)

	Aflibercept 0.4 mg (n=66)	Laser (n=34)
Any AE, n (%)	53 (**80.3**)	27 (**79.4**)
Ocular AEs	30 (45.5)	9 (26.5)
Ocular AEs in eyes formerly treated in FIREFLEYE	29 (43.9)	9 (26.5)
Systemic AEs	49 (74.2)	24 (70.6)
AEs related to aflibercept 0.4 mg	1 (1.5)	1 (2.9)
AEs related to laser treatment	1 (1.5)	5 (14.7)
Ocular AEs in eyes formerly treated in FIREFLEYE (≥5% occurrence in any group), n (%)		
Astigmatism	9 (13.6)	4 (11.8)
Myopia	9 (13.6)	5 (14.7)
Strabismus[a]	9 (13.6)	2 (5.9)
Conjunctivitis	1 (1.5)	2 (5.9)
Any SAE, n (%)	17 (**25.8**)	10 (**29.4**)
Ocular SAEs in eyes formerly treated in FIREFLEYE	6 (9.1)	0
Systemic SAEs	15 (22.7)	10 (29.4)
SAEs related to aflibercept 0.4 mg	1 (1.5)	0
Death	0	0
Ocular SAEs, n (%)		
Optic atrophy	1 (1.5)	0
Retinal detachment	2 (3.0)	0
Retinal neovascularization	2 (3.0)	0
Retinopathy of prematurity	1 (1.5)	0
Vitreous opacities	1 (1.5)	0
Retinoblastoma	1 (1.5)	0
Systemic SAEs (≥5% occurrence in any arm), n (%)		
Cerebral palsy	2 (3.0)	2 (5.9)
Bronchospasm	0	2 (5.9)

Ocular and systemic AEs **were consistent with those expected** in children born preterm **with severe ROP,** and no new safety concerns were identified

[a]Reported as an adverse event. No imbalance of "manifest strabismus" (reported as an efficacy parameter) between 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 vs. laser photocoagulation** (final results through 5 years of age expected for 2026)

Through 2 years of chronological age, **efficacy outcomes were well sustained**, and **no ocular or systemic safety concerns**, including outcomes of growth and neurodevelopmental testing, **were identified:**

Efficacy

- **No late retinal detachment,** and **disease reactivation** after aflibercept 0.4 mg **was rare**
- No patient received treatment in the post-acute phase later than 50 weeks of chronological age
- **Retinal vascularization** after aflibercept 0.4 mg **continued beyond 1 year** of chronological age
- **Visual function was age-appropriate**, and **myopia** was rarer and **less severe in the aflibercept 0.4 mg group** than the laser group

Safety

- **No ROP treatment-specific effects** on **growth** outcomes through 2 years of age and **neurodevelopmental test** performance at 2 years of age
- No ocular or systemic safety concerns through 2 years of age were identified

Overall, aflibercept 0.4 mg injection therapy in very preterm/very low birthweight patients with acute-phase ROP (as approved[a]) was **effective and generally well-tolerated through 2 years of age**

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

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 July 2023]; **2.** Bayer AG, 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf [Accessed July 2023]; **3.** Regeneron Pharmaceuticals, 2023. Available at: https://www.regeneron.com/downloads/eylea_fpi.pdf. [Accessed July 2023]; **4.** Anvisa NHSA, 2023. Available at: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/eylia-aflibercepte-nova-indicacao [Accessed July 2023].

Thank you to all FIREFLEYE Next patients and investigators

For more information, please contact:

Noriyuki Azuma
azuma-nkt@yacht.ocn.ne.jp

Acknowledgments

The ongoing FIREFLEYE Next study is sponsored by Bayer AG (Leverkusen, Germany).The sponsor participated in the design and conduct of the study, analysis of the data, and preparation of this abstract. Medical writing support, under the direction of the author, was provided by ApotheCom and funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP) guidelines (*Ann Intern Med* 2022;175:1298–1304).

World map showing FIREFLEYE Next study site countries.