Efficacy and safety outcomes from the FIREFLEYE next study of children 3 years of age with retinopathy of prematurity (ROP) treated with intravitreal aflibercept versus laser in the randomized FIREFLEYE study

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Disclosures

- **Domenico Lepore:** Consultant for Bayer and Novartis
  - **AS:** Speaker for Allergan, Bayer, Novartis, and Roche; attended advisory boards: Apellis, Bayer, Novartis, and Roche; research: Bayer and Novartis; contributed to clinical trials: Bayer and Novartis; board of directors: SemaThera Inc. **HN, NA,** and **CJ:** Received honoraria from Bayer. **W-CW:** Consultant for Allergan, Bayer, Novartis, and Roche. **AA, RV, and KC:** Employees of Regeneron Pharmaceuticals Inc. **SS, EK, and KB:** Employees of Bayer AG. **PI:** Former employee of Bayer AG. **FZ:** Employee of Bayer Inc. **SL:** Employee of Bayer Consumer Care AG. **TM:** Employee of Bayer U.S. LLC. **AF:** Consultant for Bayer and Novartis.
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- This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
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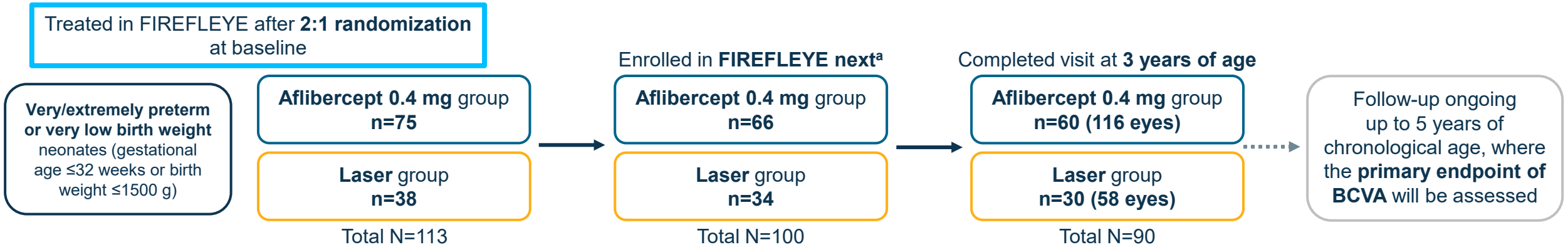
FIREFLEYE next (NCT04015180) study design

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 pre-planned interim analysis (3 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**
- **BCVA function** (Snellen equivalent)
- Ability to **fix and follow a 5-cm toy**
- Outcomes of **growth** and **neurodevelopmental tests** (optional [WPPSI-IV, VABS-II])

[a]Three study treatment-unrelated deaths in FIREFLEYE and the parents/carers of 10 children (aflibercept 0.4 mg, 6; laser, 4) did not consent to enrollment in FIREFLEYE next.
BCVA, best corrected visual acuity; **n**, number; **ROP**, retinopathy of prematurity; **VABS-II**, Vineland Adaptive Behavior Scales, Second Edition; **WPPSI-IV**, Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition. 1. Stahl A, et al. JAMA 2022;328:348–59.

Baseline characteristics

	Aflibercept 0.4 mg (n=66)	Laser (n=34)	Total (N=100)
Male, %	**54.5**	**50.0**	**53.0**
Gestational age, w and d	**26w 4d** ±2.1	**26w 0d** ±1.7	**26w 3d** ±1.9
Gestational age group, %			
<24 weeks	**4.5**	**8.8**	**6.0**
≥24 to <27 weeks	**59.1**	**64.7**	**61.0**
≥27 weeks	**36.4**	**26.5**	**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, %	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	83.3	85.3	84.0
Zone I (excluding AP-ROP)	20.0	18.4	19.5	4.5	8.8	6.0
Stage 1	1.3	0	0.9	1.5	2.9	2.0
Stage 2	2.7	5.3	3.5	0	0	0
Stage 3	4.0	2.6	3.5	0	0	0
Stage 3+	12.0	10.5	11.5	0	0	0
Stage 4A	0	0	0	1.5	0	1.0
Stage 4B	0	0	0	1.5	2.9	2.0
Missing	0	0	0	0	2.9	1.0
Zone II (excluding AP-ROP)	61.3	68.4	63.7	6.1	5.9	6.0
Stage 1	0	0	0	1.5	2.9	2.0
Stage 2	0	2.6	0.9	3.0	0	2.0
Stage 2+	9.3	13.2	10.6	0	0	0
Stage 3+	52.0	52.6	52.2	0	0	0
Missing	0	0	0	1.5	2.9	2.0
Zone III (excluding AP-ROP)	0	0	0	6.1	0	4.0
Stage 1	0	0	0	4.5	0	3.0
Missing	0	0	0	1.5	0	1.0
AP-ROP	18.7	13.2	16.8	0	0	0
Zone I	16.0	10.5	14.2	0	0	0
Zone II	2.7	2.6	2.7	0	0	0

Data are mean ±SD unless stated otherwise. **AP-ROP**, aggressive-posterior retinopathy of prematurity; **d**, day; **w**, week.

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 2 years of chronological age**	**At any time until 3 years of chronological age**	**At any time until 2 years of chronological age**	**At any time until 3 years of chronological age**
Number of children, %	100.0	100.0	100.0	100.0
None	**93.9**	**93.9**	**94.1**	**94.1**
Retinal detachment	**4.5**	**6.1**	**2.9**	**2.9**
Macular dragging	**1.5**	**1.5**	**2.9**	**2.9**
Macular fold	**1.5**	**1.5**	0	0
Retrolental opacity	**1.5**	**1.5**	0	0
Any unfavorable structural outcome	**6.1**	**6.1**	**5.9**	**5.9**
Number of treated eyes, %	100.0	100.0	100.0	100.0
None	**94.5**	**94.5**	**95.3**	**95.3**
Retinal detachment	**3.9**	**4.7**	**1.6**	**1.6**
Macular dragging	**1.6**	**1.6**	**3.1**	**3.1**
Macular fold	**1.6**	**1.6**	0	0
Retrolental opacity	**1.6**	**1.6**	0	0
Any unfavorable structural outcome	**5.5**	**5.5**	**4.7**	**4.7**
Recurrence of ROP after entry into FIREFLEYE next[a]	Between entry and 2 years of age	Between entry and 3 years of age	Between entry and 2 years of age	Between entry and 3 years of age
n	64	60	32	30
Recurrence, %	**1.5**	**1.7**	**0**	**0**

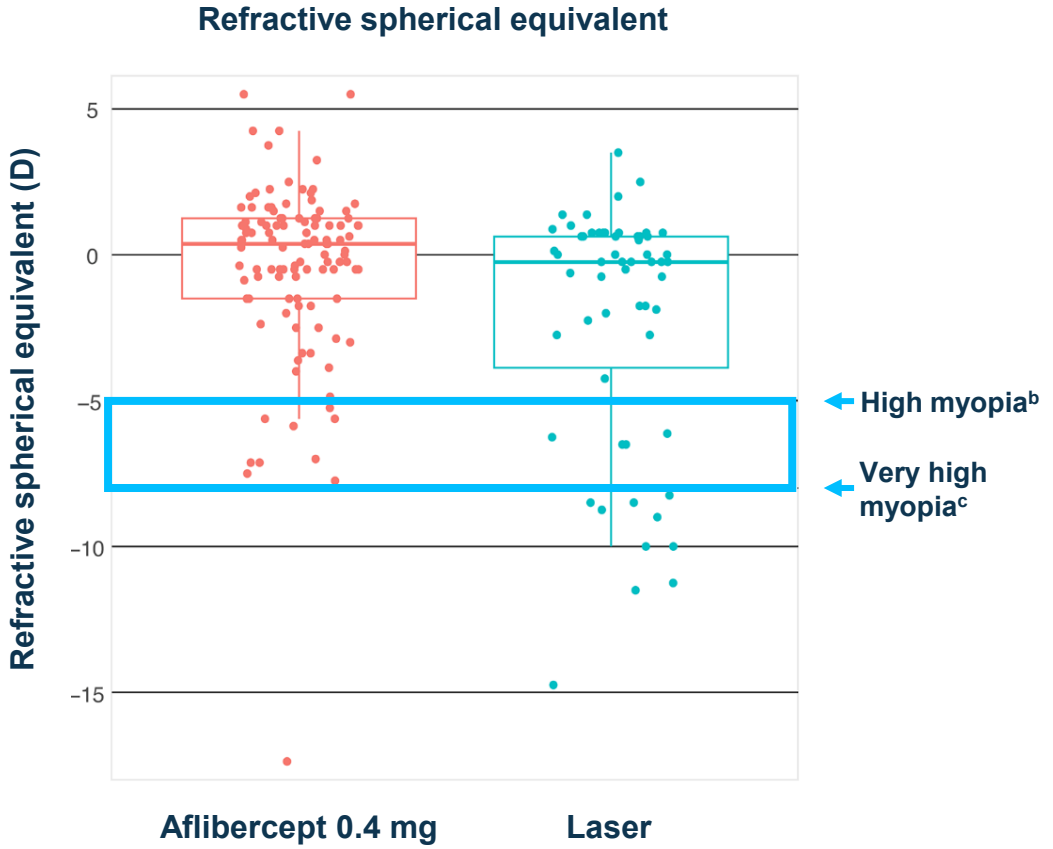
- **No disease reactivation occurred after 50 weeks of chronological age**
- In total, **4 patients were treated** after entry into FIREFLEYE next for ROP complications, all before 1 year of age (including 2 patients with pre-existing bilateral retinal detachment, 1 with reactivated plus disease[b], and 1 with retinal neovascularization not further specified[c])
  - 1 patient showed retinal detachment at age 3 (in the progression of macular fold reported at ages 1 and 2 years)

[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.

Ophthalmic outcomes at 3 years of age

No./Total No. (%)	Aflibercept 0.4 mg	Laser
Ocular findings, eyes		
Nystagmus	4/116 (**3.4**)	2/58 (**3.4**)
Absence of manifest strabismus	98/116 (**84.5**)	50/58 (**86.2**)
Amblyopia	1/116 (**0.9**)	2/58 (**3.4**)
Cataract	1/116 (**0.9**)	**0**
Optic nerve atrophy	2/116 (**1.7**)	**0**
Ability to fix and follow a 5-cm toy	112/116 (**96.6**)	57/58 (**98.3**)
Eyes with complete retinal vascularization[a]		
At 1 year of chronological age	89/128 (**69.5**)	-
At 2 years of chronological age	97/121 (**80.2**)	-
At 3 years of chronological age	89/111 (**80.2**)	-
BCVA (Snellen equivalent score), patients		
≥20/200	44/45 (**97.8**)	23/23 (**100**)
≥20/40	30/45 (**66.7**)	11/23 (**47.8**)

Retinal vascularization after aflibercept treatment appeared to be **complete in 80% of eyes by 2 years of age**



Fix and follow a 5 cm toy

Aflibercept 0.4 mg, **97%**; laser, **98%**

BCVA ≥20/40

Aflibercept 0.4 mg, **67%**; laser, **48%**

Myopia

Mild in both groups and **less pronounced with aflibercept**

Aflibercept 0.4 mg, **−0.4 (3.1) D**; Laser −2.2 (4.2) D

High myopia

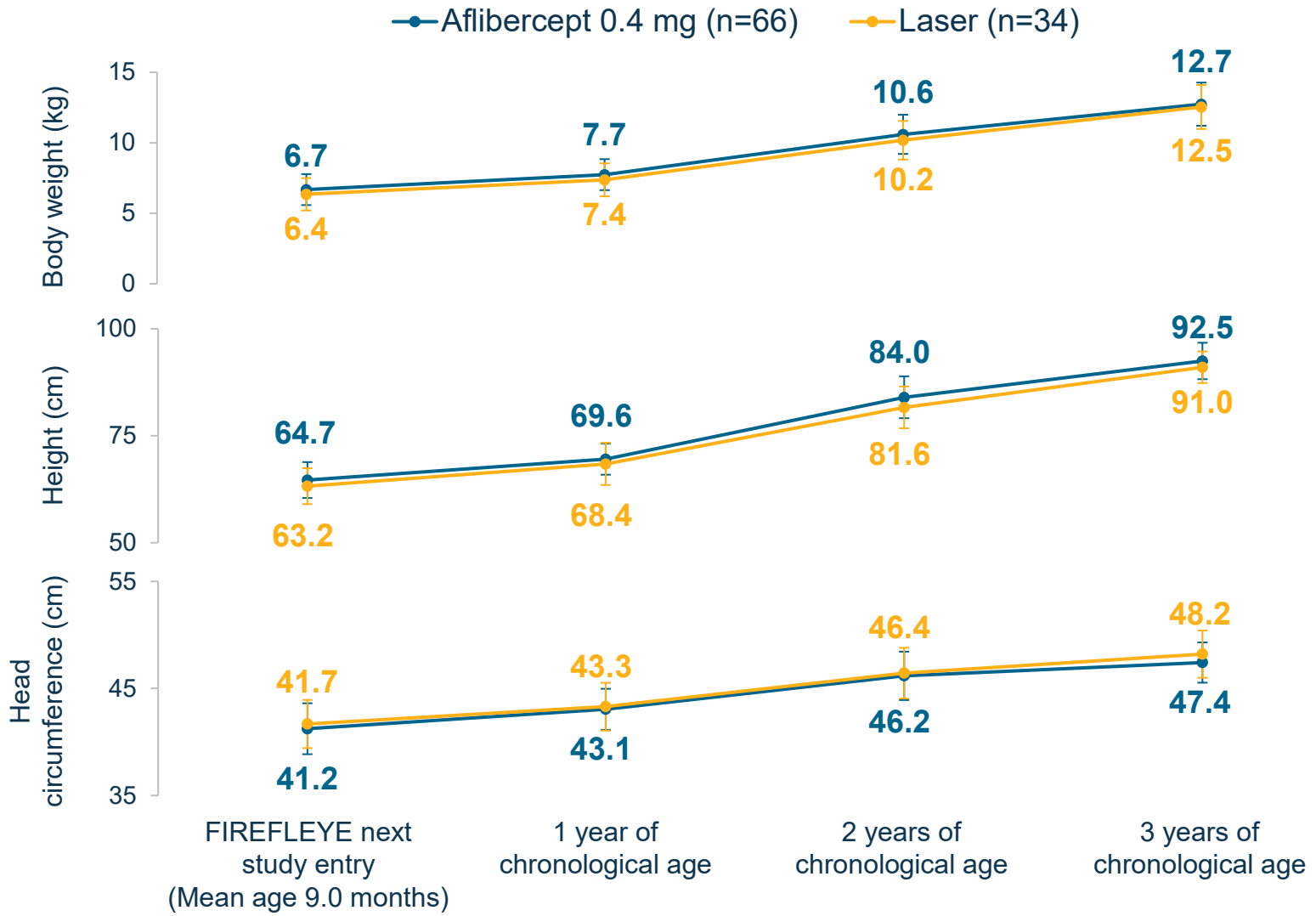
Aflibercept 0.4 mg **10 eyes** (**9%**); Laser **14 eyes** (**24%**)

Very high myopia

Aflibercept 0.4 mg **1 eye** (**1%**); Laser **10 eyes** (**17%**)

Square brackets indicate SD. [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**, diopter.

Growth parameters up to 3 years of age



No clinically relevant differences in growth parameters were observed between both groups through 3 years of chronological age, and **results are in line with what is expected in this prematurely born** pediatric population

Error bars represent SD.

Adverse events (during FIREFLEYE next through 3 years of age)

	Aflibercept 0.4 mg (n=66)	Laser (n=34)
Any AE, n (%)	59 (**89.4**)	29 (**85.3**)
Ocular AEs	33 (50.0)	11 (32.4)
Ocular AEs in eyes formerly treated in FIREFLEYE	32 (48.5)	10 (29.4)
Systemic AEs	56 (84.8)	29 (85.3)
AEs related to aflibercept 0.4 mg	2 (3.0)	1 (2.9)
AEs related to laser treatment	3 (4.5)	6 (17.6)
Ocular AEs in eyes formerly treated in FIREFLEYE (≥10% occurrence in any group), n (%)		
Astigmatism	13 (19.7)	5 (14.7)
Myopia	9 (13.6)	5 (14.7)
Strabismus[a]	9 (13.6)	2 (5.9)
Any SAE, n (%)	21 (**31.8**)	14 (**41.2**)
Ocular SAEs in eyes formerly treated in FIREFLEYE	6 (9.1)	0
Systemic SAEs	19 (28.8)	14 (41.2)
SAEs related to aflibercept 0.4 mg	1 (1.5)	0
Death	0	0
Ocular SAEs, n (%)	6 (9.1)	0
Optic atrophy	2 (3.0)	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)	4 (11.8)
Bronchiolitis	2 (3.0)	2 (5.9)
Bronchospasm	0	2 (5.9)

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

[a]Reported as an adverse event. No imbalance of "clinically 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 versus laser photocoagulation** (final results through 5 years of age expected for 2026)

Through 3 years of chronological age, **efficacy outcomes were well sustained**, and **no ocular or systemic safety concerns**, including outcomes of growth, **were identified:**

Efficacy

- **Disease reactivation** after aflibercept 0.4 mg **was rare**
  - No disease reactivation occurred after 50 weeks of chronological age. One patient showed retinal detachment at age 3 years in the progression of macular fold reported at ages 1 and 2 years of chronological age
- No patient received treatment in the post-acute phase later than 50 weeks of chronological age
- **Retinal vascularization** after aflibercept 0.4 mg **appeared to be complete in 80% of eyes by 2 years** 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 3 years of age
- No ocular or systemic safety concerns through 3 years of age were identified

Overall, aflibercept 0.4 mg injection therapy in very/extremely preterm or very low birthweight patients with acute-phase ROP (as approved[a]) was **effective and generally well tolerated through 3 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 2024]; 2. Bayer AG, 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf [Accessed July 2024]; 3. Regeneron Pharmaceuticals, 2023. Available at: https://www.regeneron.com/downloads/eylea_fpi.pdf [Accessed July 2024]; 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 2024].