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

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Purpose

- Long-term follow-up of infants who were treated for severe acute-phase retinopathy of prematurity (ROP) with intravitreal aflibercept is limited and will contribute toward informed decision-making for the management of ROP
- FIREFLEYE next (NCT04015180), an ongoing multinational Phase 3b study, is assessing long-term ophthalmic, overall clinical, and neurodevelopmental outcomes in patients through 5 years of age following treatment with intravitreal aflibercept (0.4 mg/eye) versus laser therapy (2:1 randomization) for severe acute-phase ROP in the 6-month Phase 3 FIREFLEYE study (NCT04004208)[1]

Conclusions

- FIREFLEYE next is the **first prospective, controlled, Phase 3b** study to evaluate **long-term efficacy and safety** outcomes after the treatment of acute-phase ROP with **aflibercept 0.4 mg** versus laser photocoagulation
- There was no **disease reactivation past 50 weeks of chronological age,** and **retinal vascularization** after aflibercept 0.4 mg was **complete in 80%** of eyes by 2 years of chronological age
- There were **no ROP treatment-specific effects on growth outcomes** through 3 years of age
- **Visual function** was **age-appropriate**, and **myopia** was **less frequent** and **less severe** following intravitreal aflibercept than after laser therapy
- There were **no concerns** regarding **ocular** or **systemic safety**

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Methods

- Efficacy, including binocular best-corrected visual acuity (BCVA), and safety outcomes at 3 years of age were assessed in this preplanned FIREFLEYE next interim analysis
- All patients treated for ROP in the 24-week FIREFLEYE study were offered entry into the follow-up FIREFLEYE next study

Results

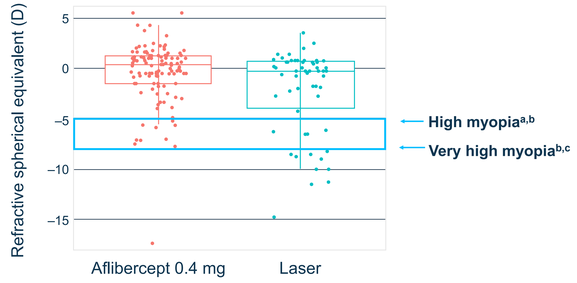
- 100 children were included in the FIREFLEYE next full analysis set (aflibercept, n=66 [128 eyes]; laser, n=34 [64 eyes]); at study entry, 84% of children had no ROP
- By 3 years of age, most children had no ROP and no unfavorable structural outcomes; no disease reactivation occurred after 50 weeks of age (**Table 1**)
- Four children were treated for ROP complications: 2 had pre-existing retinal detachment, 1 had reactivated plus disease (zone 1 both eyes, treated at ~43 weeks of age) and 1 had reactivated neovascularization (treated at ~50 weeks of age)
- One child in the aflibercept group showed retinal detachment at age 3, which was a progression of a macular fold reported at ages 1 year and 2 years

Table 1: Unfavorable structural outcomes in FIREFLEYE next through 3 years

	Aflibercept 0.4 mg (n=66)		Laser (n=34)	
Unfavorable structural outcomes	**At any time until 2 years of age**	**At any time until 3 years of age**	**At any time until 2 years of age**	**At any time until 3 years of age**
Number of children, %				
None	100.0	100.0	100.0	100.0
Retinal detachment	**93.9**	**93.9**	**94.1**	**94.1**
Macular dragging	**4.5**	**6.1**	**2.9**	**2.9**
Macular fold	**1.5**	**1.5**	**2.9**	**2.9**
Retrolental opacity	**1.5**	**1.5**	0	0
Any unfavorable structural outcome	**1.5**	**1.5**	0	0
	6.1	**6.1**	**5.9**	**5.9**
Number of treated eyes, %				
None	100.0	100.0	100.0	100.0
Retinal detachment	**94.5**	**94.5**	**95.3**	**95.3**
Macular dragging	**3.9**	**4.7**	**1.6**	**1.6**
Macular fold	**1.6**	**1.6**	**3.1**	**3.1**
Retrolental opacity	**1.6**	**1.6**	0	0
Any unfavorable structural outcome	**1.6**	**1.6**	0	0
	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**

[a]Post hoc analysis: A child was considered as having ROP recurrence if the inclusion criteria of FIREFLEYE (or worse) were met, and a prior assessment (either in FIREFLEYE or FIREFLEYE next) indicated ROP that did not require treatment based on the inclusion criteria.

Figure 1: Frequency of high myopia and very high myopia with aflibercept 0.4 mg vs laser



[a]Post-hoc analysis. [b]High myopia was defined as −5 D or worse. [c]Very high myopia was defined as −8 D or worse. D, diopter.

Results

- Retinal vascularization after aflibercept treatment appeared to be complete for most eyes by 2 years of age (**Table 2**)
- Binocular BCVA was ≥20/200 for most children and ≥20/40 for more children treated with aflibercept than with laser (**Table 2**)
- Myopia was mild in both groups: mean (standard deviation) aflibercept 0.4 mg, −0.4 (3.1) D; laser, −2.2 (4.2) D; and was less pronounced with aflibercept compared with laser therapy eyes (**Figure 1**)

Table 2: 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), patient		
≥20/200	44/45 (**97.8**)	23/23 (**100**)
≥20/40	30/45 (**66.7**)	11/23 (**47.8**)

[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 that received laser therapy is not reported, as laser scars prevent physiologic vascularization of the peripheral retina. BCVA, best-corrected visual acuity.

- Ocular and systemic AEs were consistent with those expected in children born preterm who developed severe ROP (**Table 3**)
- No clinically relevant differences in growth parameters were observed between the 2 groups through 3 years of age, and results align with what is expected in this prematurely born pediatric population

Table 3: Adverse events (during FIREFLEYE next)

	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)

[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.

Disclosures

Andreas Stahl: Consultant for Allergan, Apellis, Bayer, Novartis, and Roche.

References

1. Stahl A, et al. *JAMA* 2022;328:348–59.

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