

Plain-language commentary: 2-year findings from the FIREFLEYE next study looking at how well aflibercept injected into affected eyes in babies with retinopathy of prematurity works and how safe it is compared with laser treatment

Andreas Stahl , Hidehiko Nakanishi, Domenico Lepore, Wei-Chi Wu, Noriyuki Azuma, Carlos Jacas, Aditya Athanikar, Robert Vitti, Karen Chu, Pablo Iveli, Fei Zhao, Sarah Schlieff, Sergio Leal, Thomas Schmelter, Thomas Miller, Evra Köföncü, and Alistair Fielder; for the FIREFLEYE Next Study Group

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Background

What is retinopathy of prematurity and how is it treated?

Retinopathy of prematurity (ROP) is a condition that can affect the eyes of babies who are born prematurely and is a major cause of childhood blindness worldwide. Blood vessels in the eye that supply oxygen and nutrients usually finish developing during the ninth month of pregnancy. In babies born prematurely, the blood vessels in the eye have not finished developing. This can limit the blood supply to the light-sensitive layer of tissue at the back of the eye called the retina, leading to a rise in levels of a protein called vascular endothelial growth factor (VEGF). VEGF sends messages within the eye for blood vessels to grow, but sometimes this growth happens in an abnormal pattern in the retina, causing ROP.¹ While most cases of ROP are mild in nature, resolve without treatment, and can be managed with observation, more severe forms of ROP require treatment.² The window of opportunity for treatment is very narrow, typically within a few days to a week after preterm birth. Such treatment aims to prevent unfavorable outcomes in the eye, including the most serious complication of ROP called retinal detachment.³ Retinal detachment is

a severe condition of the eye where the retina is pulled away from its usual position which, in most cases, leads to permanent vision impairment.² Furthermore, ROP can cause other eye problems to develop, including cataracts (a clouding of the eye's lens), glaucoma (increased pressure within the eye that can result in damage to the optic nerve), and myopia, also known as nearsightedness (when far away objects look blurry).⁴ These all require treatments and/or the use of corrective devices and lifelong monitoring.

There are two primary ways to treat babies with severe ROP. Laser treatment is an established method, in which laser burns to the retina to create scar tissue thus preventing abnormal blood vessels from forming in the eye.^{5,6} However, laser treatment is not always successful and it can also lead to medical problems or adverse effects, such as high myopia (requiring glasses to see the largest letter on the eye chart), very high myopia (unable to see the largest letter on the eye chart even with eyeglasses), and irreversible peripheral visual field loss.⁷ The other treatment approach is to inject anti-VEGF medicine into the affected eyes to stop VEGF from causing abnormal blood vessels to form.¹ These include agents such as bevacizumab, ranibizumab, and aflibercept, each

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Correspondence to:

Andreas Stahl
Department of
Ophthalmology, University
Medicine Greifswald,
Ferdinand Sauerbruch
Straße, Greifswald 17475,
Germany
andreas.stahl@med.uni-greifswald.de

Hidehiko Nakanishi
Division of Neonatal
Intensive Care Medicine,
Department of Advanced
Medicine, Research and
Development Center for
New Medical Frontiers,
Kitasato University School
of Medicine, Sagami-hara,
Japan

Domenico Lepore
Department of Geriatrics
and Neuroscience,
Catholic University of
the Sacred Heart, A.
Gemelli Foundation
Istituto di Ricovero e Cura
a Carattere Scientifico,
Rome, Italy

Wei-Chi Wu
Department of
Ophthalmology, Linkou
Chang Gung Memorial
Hospital and College of
Medicine, Chang Gung
University, Taoyuan City,
Taiwan

Noriyuki Azuma
Department of
Developmental and
Regenerative Biology,
Medical Research
Institute, Institute of
Science Tokyo, Tokyo,
Japan

Carlos Jacas
Department of Psychiatry,
Hospital Universitari Vall
d'Hebron, Vall d'Hebron
Barcelona Hospital
Campus, Barcelona, Spain

Aditya Athanikar
Robert Vitti
Karen Chu
Regeneron
Pharmaceuticals, Inc.,
Tarrytown, NY, USA

Pablo Iveli
Bayer AG, Wuppertal,
Germany

Fei Zhao
Bayer, Inc., Mississauga,
ON, Canada

Sarah Schlieff
Thomas Schmelter
Evra Köfünçü
Bayer AG, Berlin, Germany

Sergio Leal
Bayer Consumer Care AG,
Basel, Switzerland

Thomas Miller
Bayer Healthcare LLC,
Whippany, NJ, USA

Alistair Fielder
Department of Optometry
and Visual Science, City
St George's, University of
London, London, UK

of which works differently to block VEGF activity.^{8–12} Such anti-VEGF injectable medicines are licensed as an alternative to laser treatment in babies with severe acute-phase ROP.

Why was the FIREFLEYE next study needed?

Aflibercept is an anti-VEGF medication approved for the treatment of ROP in many countries.^{13–15} The FIREFLEYE next study is the first study that has collected long-term information up to 5 years of age on how well an aflibercept injection works and how safe it is compared with laser treatment in preterm infants treated for severe acute-phase ROP.

What is the FIREFLEYE next study?

A previous study called FIREFLEYE evaluated aflibercept for the treatment of severe acute-phase ROP in babies who were born prematurely (those born at 32 weeks of pregnancy or earlier) or underweight (those with a birth weight of 1500 g or less). The goal of the study was to see whether an injection of a 0.4 mg dose of aflibercept into each affected eye could work at least as well as laser therapy at treating ROP.¹⁰ In total, 113 babies from 27 different countries were treated in FIREFLEYE; 75 received aflibercept and 38 received laser treatment at the beginning of the study. The babies were, on average, 10 weeks old at the time of treatment. After receiving the treatment, the babies were followed for 24 weeks to see how well the aflibercept medicine treated the ROP and how safe the medicine was compared with laser treatment.¹⁰

The results of the FIREFLEYE study showed that aflibercept injection worked well within the expected range of effect, although it could not be statistically demonstrated that aflibercept injection was no worse than laser treatment. Similar eye outcomes were observed in babies receiving aflibercept and laser therapy 24 weeks after treatment. A total of 63 out of 75 babies treated with aflibercept and 32 out of 38 babies treated with laser therapy no longer had active ROP and did not develop harmful structures in the retina. Most babies only needed a single aflibercept injection per eye over the 24-week period. No concerns of safety, including any adverse effects on the physical development of the babies, in the two groups were observed. These results were published in the *Journal of the American Medical Association (JAMA)*.¹⁰

FIREFLEYE next is a study that is following 100 of the babies treated in FIREFLEYE until the children are 5 years old to see whether aflibercept and laser therapy continue to protect the children from ROP complications. The study also aims to assess long-term safety outcomes and to keep track of any adverse effects that children may experience, including any impact on growth and neurodevelopment.¹⁶ Adverse events in FIREFLEYE next may happen because of the aflibercept or laser treatment received during FIREFLEYE or for other reasons; for example, the underlying prematurity in these children. Here we discuss the results of the FIREFLEYE next study when the children were 2 years old. These results were recently published in *JAMA Network Open*.¹⁶

Commentary

Results of the FIREFLEYE next study, 2 years of age findings: how well does an aflibercept injection into the eye for the treatment of severe acute-phase ROP work and how safe is it compared with laser treatment through 2 years of age?

The FIREFLEYE next study of children enrolled from the initial FIREFLEYE study showed that at 2 years of age, 97% and 94% of children treated with aflibercept and laser therapy, respectively, no longer had ROP. No harmful structures developed in the retina of the eyes of most of the children: 94% in both the aflibercept and laser groups. Blood vessels in the entire retina developed with no evident abnormalities observed following indirect ophthalmoscopy for 80% of eyes treated with aflibercept. In eyes treated with laser therapy, normal blood vessels cannot form in the peripheral areas of the retina because of the scarring caused by the laser. Nearly all children were able to look at and follow a small toy with their eyes (97% of children in the aflibercept group and 98% of children in the laser group). Fewer children treated with aflibercept had high myopia (8% of eyes in five children) or very high myopia, (1% of eyes in one child) compared with laser treatment. In children treated with laser, high myopia was present in 22% of eyes (nine children) and very high myopia in 13% of eyes (six children).¹⁶

No new safety concerns were seen in either group, including no adverse effects on the children's growth or neurodevelopment.¹⁶

What do these results mean for children who require treatment for severe ROP in the acute disease phase, and for their caregivers, and healthcare providers?

These results mean that aflibercept injection treatment can control ROP and prevent complications of ROP, in particular retinal detachment, in children through two years of age. Babies with severe acute-phase ROP who are treated in a timely manner with aflibercept will usually not need further therapy to treat their ROP.¹⁶ While some children required additional treatment in the FIREFLEYE study with aflibercept and/or laser within 6 months of first treatment, no child required additional treatment for ROP after they were 50 weeks old. In addition, other lifelong vision problems that may be caused by laser treatment can be avoided or mitigated with anti-VEGF injections, most importantly high or very high myopia and retinal scarring.^{17,18} Based on the current data available, caregivers also do not have to be concerned about the treatment causing growth or neurodevelopmental delays in their children.¹⁶

Unlike laser therapy, specialized equipment is not needed to inject aflibercept into patients for the treatment of ROP. In addition, aflibercept injection is faster and simpler to administer than laser therapy, and there is less need for general anesthesia and procedures to help the baby breathe like intubation or mechanical ventilation, thus reducing the risk of subsequent complications.

These results provide caregivers and healthcare providers with helpful information for making choices on how to treat a premature baby with severe acute-phase ROP.

Conclusion

Treating severe acute-phase ROP with an injection of 0.4 mg aflibercept into each affected eye worked well and it did not result in increased safety concerns compared with laser therapy in children through 2 years of age. The FIREFLEYE next study is following the children who were formerly treated in the FIREFLEYE study until they became 5 years old. These results will provide additional useful insight into how aflibercept injection works, including its effect on the eyesight of the children, and how safe it is over a longer period during which children approach school age.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions

Andreas Stahl: Conceptualization; Acquisition, analysis, or interpretation of data; Validation; Writing – original draft; Writing – review & editing.

Hidehiko Nakanishi: Acquisition, analysis, or interpretation of data; Supervision; Writing – original draft; Writing – review & editing.

Domenico Lepore: Conceptualization; Acquisition, analysis, or interpretation of data; Supervision; Methodology; Writing – original draft; Writing – review & editing.

Wei-Chi Wu: Conceptualization; Acquisition, analysis, or interpretation of data; Supervision; Writing – original draft; Writing – review & editing.

Noriyuki Azuma: Conceptualization; Acquisition, analysis, or interpretation of data; Administrative, technical, or material support; Writing – original draft; Writing – review & editing.

Carlos Jacas: Conceptualization; Acquisition, analysis, or interpretation of data; Supervision; Writing – original draft; Writing – review & editing.

Aditya Athanikar: Conceptualization; Acquisition, analysis, or interpretation of data; Writing – original draft; Writing – review & editing.

Robert Vitti: Conceptualization; Acquisition, analysis, or interpretation of data; Administrative, technical, or material support; Supervision; Funding acquisition; Writing – original draft; Writing – review & editing.

Karen Chu: Conceptualization; Acquisition, analysis, or interpretation of data; Administrative, technical, or material support; Supervision; Writing – original draft; Writing – review & editing.

Pablo Iveli: Conceptualization; Acquisition, analysis, or interpretation of data; Administrative, technical, or material support; Supervision; Validation; Writing – original draft; Writing – review & editing.

Fei Zhao: Acquisition, analysis, or interpretation of data; Administrative, technical, or material support; Writing – original draft; Writing – review & editing.

Sarah Schlieff: Acquisition, analysis, or interpretation of data; Writing – original draft; Writing – review & editing.

Sergio Leal: Conceptualization; Funding acquisition; Acquisition, analysis, or interpretation of data; Administrative, technical, or material support; Supervision; Writing – original draft; Writing – review & editing.

Thomas Schmelter: Conceptualization; Acquisition, analysis, or interpretation of data; Formal analysis; Writing – original draft; Writing – review & editing.

Thomas Miller: Conceptualization; Administrative, technical, or material support; Supervision; Writing – original draft; Writing – review & editing.

Evra Köfünçü: Conceptualization; Acquisition, analysis, or interpretation of data; Acquisition, analysis, or interpretation of data; Supervision; Validation; Writing – original draft; Writing – review & editing.

Alistair Fielder: Acquisition, analysis, or interpretation of data; Writing – original draft; Writing – review & editing.

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Competing interests

A.S. reported receiving speaker fees and grants from, serving on the advisory board and contributing to clinical trials for Bayer AG during the conduct of the study and receiving speaker fees from Allergan, Novartis, and Roche; attending the advisory boards for Apellis, Novartis, and Roche; receiving grants from Novartis; contributing to clinical trials for Novartis; and serving on the board of directors for SemaThera, Inc. outside the submitted work. H.N., N.A., and C.J. reported receiving honoraria fees from Bayer AG during the conduct of the study and outside the submitted work. D.L. 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. W.-C.W. reported receiving consultant fees from Bayer AG during the conduct of the study and outside the submitted work and receiving consultant fees from Allergan, Novartis, and Roche outside the submitted work. A.A. reported employment at Regeneron Pharmaceuticals Inc during the conduct of the study. R.V. and K.C. reported former employment at Regeneron Pharmaceuticals Inc during the conduct of the study. P.I. reported former employment at Bayer AG. F.Z. reported former employment at Bayer Inc during the conduct of the study. S.S. and E.K. reported employment at Bayer AG during the conduct of the study. S.L. and T.S. reported employment and stock ownership in Bayer AG. T.M. reported employment with Bayer Healthcare LLC during the conduct of the study. A.F. 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.

Availability of data and materials

Not applicable.

ORCID iD

Andreas Stahl  <https://orcid.org/0000-0002-8013-7597>

References

1. Dogra MR and Vinekar A. Role of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of retinopathy of prematurity: a narrative review in the context of middle-income countries. *Pediatric Health Med Ther* 2023; 14: 59–69.

2. Retinopathy of prematurity, <https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinopathy-prematurity> (2023, accessed 10 July 2024).
3. Fierson WM, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, et al. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2018; 142: e20183061.
4. March de Ribot F, Miller AM, Stevenson E, et al. Retinopathy of prematurity, https://eyewiki.aao.org/Retinopathy_of_Prematurity#:~:text=There%20are%20a%20number%20of,strabismus%2C%20amblyopia%2C%20and%20anisometropia (2024, accessed 10 July 2024).
5. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003; 121: 1684–1694.
6. Good WV and Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233–248.
7. Stuart A. *Walking the ROP treatment tightrope*. EyeNet (American Academy of Ophthalmology), <https://www.aao.org/eyenet/article/walking-rop-treatment-tightrope> (2015).
8. Mintz-Hittner HA, Kennedy KA and Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011; 364: 603–615.
9. Stahl A, Lepore D, Fielder A, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet (London, England)* 2019; 394: 1551–1559.
10. Stahl A, Sukgen EA, Wu WC, et al. Effect of intravitreal aflibercept vs laser photocoagulation on treatment success of retinopathy of prematurity: the FIREFLEYE randomized clinical trial. *JAMA* 2022; 328: 348–359.
11. Public summary of the evaluation of the proposed paediatric investigation plan Ranibizumab for treatment of retinopathy of prematurity, https://www.ema.europa.eu/en/documents/other/public-summary-evaluation-proposed-paediatric-investigation-plan-ranibizumab-treatment-retinopathy-prematurity_en.pdf (2014, accessed 5 August 2024).
12. Novartis receives positive CHMP opinion for Lucentis® treatment in preterm infants with retinopathy of prematurity (ROP), a disease causing visual impairment and blindness, [https://www.novartis.com/news/media-releases/novartis-receives-positive-chmp-opinion-lucentis-treatment-preterm-infants-retinopathy-prematurity-rop-disease-causing-visual-impairment-and-blindness#:~:text=Basel%2C%20July%2026%2C%202019%20%2D,retinopathy%20of%20prematurity%20\(ROP\)](https://www.novartis.com/news/media-releases/novartis-receives-positive-chmp-opinion-lucentis-treatment-preterm-infants-retinopathy-prematurity-rop-disease-causing-visual-impairment-and-blindness#:~:text=Basel%2C%20July%2026%2C%202019%20%2D,retinopathy%20of%20prematurity%20(ROP)) (2019, accessed 5 August 2024).
13. Bayer receives positive CHMP opinion for Eylea™ in the EU for treatment of preterm infants with retinopathy of prematurity, <https://www.bayer.com/media/en-us/bayer-receives-positive-chmp-opinion-for-eylea-in-the-eu-for-treatment-of-preterm-infants-with-retinopathy-of-prematurity/> (2022, accessed 2 July 2024).
14. EYLEA® approved in Japan for treatment of preterm infants with retinopathy of prematurity, <https://www.bayer.com/media/en-us/eylea-approved-in-japan-for-treatment-of-preterm-infants-with-retinopathy-of-prematurity/> (2022, accessed 2 July 2024).
15. EYLEA® (aflibercept) injection approved as the first pharmacologic treatment for preterm infants with retinopathy of prematurity (ROP) by the FDA, <https://investor.regeneron.com/news-releases/news-release-details/eylear-aflibercept-injection-approved-first-pharmacologic> (2023, accessed 2 July 2024).
16. Stahl A, Nakanishi H, Lepore D, et al. Intravitreal aflibercept vs laser therapy for retinopathy of prematurity: two-year efficacy and safety outcomes in the nonrandomized controlled trial FIREFLEYE next. *JAMA Netw Open* 2024; 7: e248383.
17. Shah PK, Ramakrishnan M, Sadat B, et al. Long term refractive and structural outcome following laser treatment for zone 1 aggressive posterior retinopathy of prematurity. *Oman J Ophthalmol* 2014; 7: 116–119.
18. Barnett JM and Hubbard GB. Complications of retinopathy of prematurity treatment. *Curr Opin Ophthalmol* 2021; 32: 475–481.

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