Effect of Intravitreal Aflibercept vs Laser Photocoagulation on Treatment Success of Retinopathy of Prematurity: The FIREFLEYE Randomized Clinical Trial

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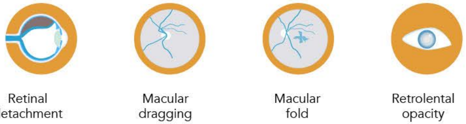
The aim of this study was to compare intravitreal aflibercept versus laser photocoagulation in infants with retinopathy of prematurity (ROP) requiring treatment. The FIREFLEYE (Aflibercept for ROP–IVT Injection versus Laser Therapy) trial evaluated whether a 0.4-mg dose of intravitreal aflibercept was noninferior to laser photocoagulation in preterm infants with severe ROP.

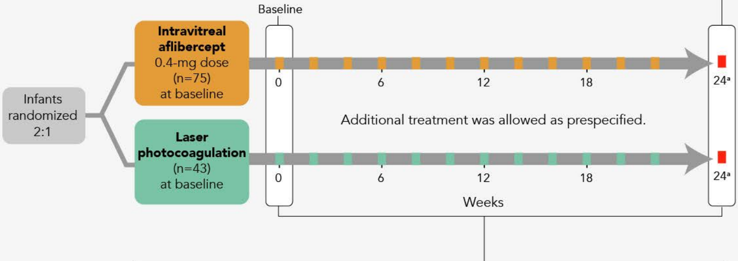
This noninferiority, phase 3, 24-week, randomized clinical trial was conducted in 27 countries throughout Asia, Europe, and South America.

Overall, 118 infants (gestational age ≤32 weeks at birth or birth weight ≤1500 g) with ROP severity (zone I stage 1+ [stage 1 plus increased disease activity], zone I stage 2+, zone I stage 3, zone I stage 3+, zone II stage 2+, or zone II stage 3+) requiring treatment or with aggressive posterior ROP in at least one eye were enrolled between September 25, 2019, and August 28, 2020.

Primary Outcome

Proportion of infants without active ROP and unfavorable structural outcomes such as:





Infants randomized 2:1

Intravitreal aflibercept 0.4-mg dose (n=75) at baseline

Laser photocoagulation (n=43) at baseline

Additional treatment was allowed as prespecified.

Secondary Outcome

The secondary outcomes addressing the primary efficacy objective were:

The requirement for intervention with a second treatment modality from baseline to week 24.

Any recurrence of ROP from baseline to week 24.

Disease severity based on Retinopathy of Prematurity Activity Scale[b] score as proposed by the International Neonatal Consortium.

[a] 24 weeks after starting treatment (assessed by investigators).

[b] Measured on a scale of 0-22; scores from 0-7 are considered mild; 8-12, moderate; and 13-22, severe.

✓ Infants were eligible if they:

- Were born at gestational age of ≤32 weeks or had a birthweight of ≤1500 g
- Weighed ≥800 g at the time of treatment
- Had ROP within the spectrum of severity requiring treatment had ROP within the spectrum of severity requiring treatment (zone I stage 1+, zone I stage 2+, zone I stage 3, zone I stage 3+, zone II stage 2+, zone II stage 3+, or aggressive posterior ROP [according to the International Classification of Retinopathy of Prematurity] in at least one eye).

✗ Infants were not eligible if they had:

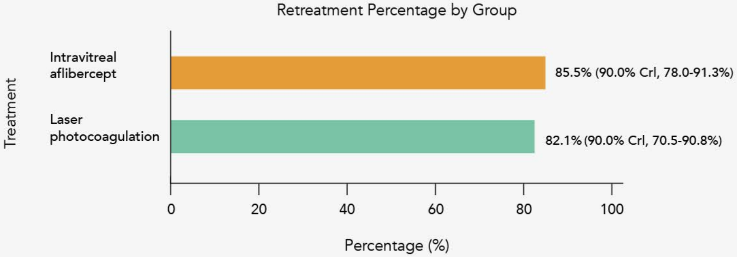
- ROP stages 4 or 5 or ROP involving only zone III
- Active ocular infection within 5 days before investigational treatment
- Neurological comorbidities potentially confounding visual function

If both eyes were treated, both needed to respond for the primary outcome to be met.

Eyes were considered non-responders if rescue treatment was given. The requirement for rescue treatment was considered treatment failure.

Intravitreal aflibercept was deemed noninferior if the lower limit of the 1-sided 95% bayesian credible interval for the treatment difference was greater than −5%.

Intravitreal aflibercept compared with laser photocoagulation did not meet criteria for noninferiority with respect to the primary outcome of the proportion of infants achieving treatment success at week 24.



The between-group difference was 3.4% (1-sided 95% CrI, −8.0% to ∞) in favor of intravitreal aflibercept. However, because the lower limit of the 95% CrI for the treatment difference was −8.0%, and not greater than the prespecified value of −5.0%, noninferiority could not be concluded.

Primary Outcome of Treatment Success Rate Based on Bayesian Analyses Overall and in Prespecified Subgroups

0.4 mg of intravitreal aflibercept

	Treated bilaterally[a]	Treated unilaterally[b]	Estimated success rate, % (90% CrI)[c]
Primary Outcome: proportion of infants without active ROP and unfavourable structural outcomes at 24 wk[e]			
Overall population	59/71 bilateral responders[f]	4/4 unilateral responders	85.5 (78.0-91.3)
Zone I retinopathy of prematurity[h]	11/15 bilateral responders[g]	NA	70.8 (50.7-86.6)
Zone II retinopathy of prematurity[h]	38/42 bilateral responders[i]	4/4 unilateral responders	92.0 (84.1-96.9)
Aggressive posterior retinopathy of prematurity	10/14 bilateral responders[j]	NA	73.3 (52.1-89.1)

Laser photocoagulation

	Treated bilaterally[a]	Treated unilaterally[b]	Estimated success rate, % (90% CrI)[c]
Primary Outcome: proportion of infants without active ROP and unfavourable structural outcomes at 24 wk[e]			
Overall population	28/34 bilateral responders[g]	4/4 unilateral responders	82.1 (70.5-90.8)
Zone I retinopathy of prematurity[h]	4/6 bilateral responders	1/1 unilateral responder	64.4 (36.7-87.1)
Zone II retinopathy of prematurity[h]	20/23 bilateral responders[g]	3/3 unilateral responders	84.9 (71.5-94.0)
Aggressive posterior retinopathy of prematurity	4/5 bilateral responders	NA	72.2 (40.0-93.0)

	Between-group difference, % (1-sided 95% CrI)[d]
Overall population	3.4 (-8.0 to ∞)
Zone I retinopathy of prematurity[h]	6.2 (-23.5 to ∞)
Zone II retinopathy of prematurity[h]	6.9 (-4.8 to ∞)
Aggressive posterior retinopathy of prematurity	1.1 (-28.6 to ∞)

Abbreviations: CrI, credible interval; NA, not applicable.

[a] Both eyes needed to respond to treatment for primary outcome to be met.

[b] The response in the second eye was considered missing information in the analysis model.

[c] Reflects the median of posterior distribution based on the primary (bayesian) analysis model.

[d] The per-protocol-defined noninferiority margin was -5%.

[e] Assessed by investigators. Unfavorable structural outcomes included retinal detachment, macular dragging, macular fold, and retrolental opacity. The eyes were considered to be nonresponsive if rescue treatment was required and administered.

[f] In addition, 4 patients responded unilaterally only and 2 patients did not have data at week 16 or later and were handled by multiple imputations.

[g] In addition, 1 patient responded unilaterally only.

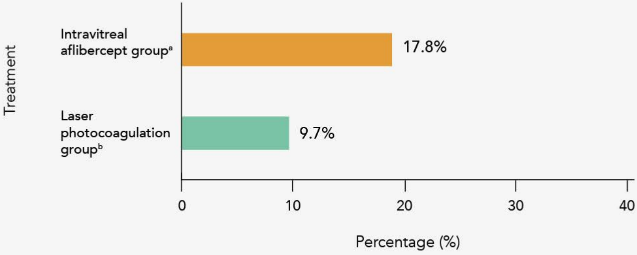
[h] Excludes infants with aggressive posterior retinopathy of prematurity.

[i] In addition, 3 patients responded unilaterally only and 1 patient did not have data at week 16 or later and was handled by multiple imputations.

[j] In addition, 1 patient did not have data at week 16 or later and was handled by multiple imputations.

While some study eyes necessitated retreatment in both study groups, *rescue treatment* was required for a greater proportion of eyes in the laser photocoagulation group.

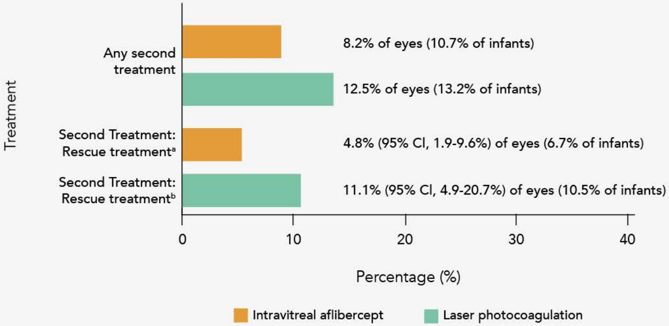
Retreatment Percentage by Group



[a]No infant received more than 2 doses (1 retreatment) per eye.

[b]More than 1 week after baseline session.

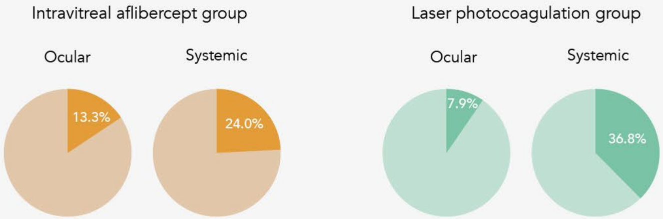
Patients Requiring Second Treatment Modality



[a]used laser photocoagulation as rescue treatment

[b]used intravitreal aflibercept as rescue treatment

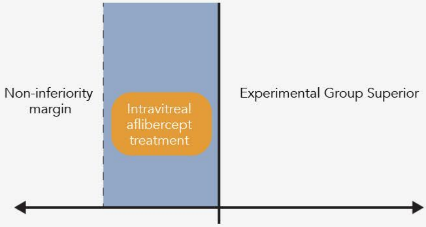
The adverse event profile of a 0.4-mg dose of intravitreal aflibercept in infants with ROP was consistent with the established profile of a 2.0-mg dose of intravitreal aflibercept in adults.



Three deaths, which occurred 4 to 9 weeks after intravitreal aflibercept treatment, were considered unrelated to aflibercept by the investigators.

Response rate to intravitreal aflibercept fell within the expected range, considering randomized clinical trials of other anti-VEGF agents for the treatment of ROP.

In this noninferiority randomized clinical trial of infants with ROP, intravitreal aflibercept compared with laser photocoagulation did not meet the noninferiority margin of 5% with regard to treatment success.


Non-inferiority margin
Intravitreal aflibercept treatment
Experimental Group Superior

The fact that noninferiority of intravitreal aflibercept could not be demonstrated may be attributable to an observed laser photocoagulation response rate that was markedly higher than the treatment response to laser photocoagulation in the RAINBOW and BEAT-ROP trials.

Power calculations using the laser photocoagulation response rate observed in the current trial would have necessitated a larger study population to demonstrate noninferiority given the smaller than expected difference between the laser photocoagulation and intravitreal aflibercept treatments.

It is unlikely that the differences in the study population enrolled and the definition of the primary outcome or its analysis between the current trial, the BEAT-ROP trial, and particularly the RAINBOW trial, fully explain the discrepancies in laser photocoagulation performance across the three trials.

This study has several limitations including small sample size and inability to invoke treatment masking.

The trial had a relatively small sample size, although the size of the intravitreal aflibercept group is consistent with the anti-VEGF treatment groups in the RAINBOW trial. In particular, the study was powered for an effect in the overall population without accounting for potential differences in efficacy between the categories of ROP.

As with other anti-VEGF ROP studies, treatment masking was not possible due to visible laser photocoagulation effects and sham procedures would not have been considered ethical.

Conclusions

Among infants with ROP, intravitreal aflibercept compared with laser photocoagulation did not meet criteria for noninferiority with respect to the primary outcome of the proportion of infants achieving treatment success at week 24. Further data would be required for more definitive conclusions regarding the comparative effects of intravitreal aflibercept and laser photocoagulation in this population.