Amsterdam, 21 May 2026
EMADOC-1700519818-2998842
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Eylea

Aflibercept

Procedure no: EMA/PAM/0000335684

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse Event
AP-ROP	Aggressive Posterior Retinopathy of Prematurity
BCVA	Best-Correct Visual Acuity
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
D	Diopter
EMA	European Medicines Agency
FAS	Full Analysis Set
IVT	IntraViTreal
MedDRA	Medical Dictionary for Regulatory Activities
PAM	Post-Approval Measure
PDCO	PaeDiatric COmmittee
PIP	Pediatric Investigation Plan
PT	Preferred Term
ROP	Retinopathy Of Prematurity
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
WMW	Wilcoxon-Mann-Whitney

1. Introduction

This report addresses the post-authorisation commitments undertaken by the MAH, classified as a Post Approval Measure (PAM), which were discussed during the variation procedure EMEA/H/C/002392/II/0077/G and with regard to the Paediatric Investigation Plan (PIP) advice for aflibercept (EYLEA) (EMEA-000236-PIP05-18). These commitments are detailed in Eylea's Risk Management Plan (RMP), specifically in Section III.2 under "Ongoing and planned additional pharmacovigilance (PV) activities." As part of this pharmacovigilance follow-up, the MAH committed to submit interim study reports from extended FIREFLEYE study on patients with retinopathy of prematurity (ROP) at 2-year of age data (2023), 3-year of age data (2024), 4-year of age data (2025) and a final study report (2026) to the EMA. This is the fourth and last report presenting cumulative long-term efficacy and safety data at 5-year of chronological age (cut-off-date: OCT 2025).

2. Scientific discussion

2.1. Information on the development program

The clinical development program included the following elements:

- Study 20090 (FIREFLEYE, core study) was a randomized, open-label, two-arm, controlled study designed to evaluate the efficacy, safety, and tolerability of intravitreal (IVT) aflibercept 0.4 mg versus laser photocoagulation in patients with retinopathy of prematurity (ROP).

- Study 20275 (FIREFLEYE extension) was an open-label extension study assessing the long-term outcomes of subjects previously treated for ROP in Study 20090. The results of this study were submitted annually as part of the PAM procedures until completion (date of the last visit of the last subject in the study in all centers in all participating countries: 19 SEP 2025).

- An historical/published evidence synthesis study.

2.2. Information on the pharmaceutical formulation used in the studies

In accordance with the PDCO advice (EMEA-000236-PIP05-18) concerning the new indication, a low-volume, high-accuracy syringe for administration of a fixed volume of 10 µl of EYLEA® solution for injection, corresponding to a dose of 0.4 mg, for the treatment of the pediatric population via intravitreal injection, was developed.

2.3. Clinical aspects

Introduction

FIREFLEYE next (20275) is an extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in FIREFLEYE study (20090). FIREFLEYE study was an open-label, randomized, double-arm controlled Phase 3 study, which enrolled male and female preterm infants, treatment-naïve ROP (Zone I Stage 1 plus, 2 plus, 3 non-plus or plus, or Zone II Stage 2 plus or 3 plus or aggressive posterior retinopathy of prematurity (AP-ROP)) in at least one eye.

Patients enrolled in FIREFLEYE next study were not treated and were to be excluded when they had a condition preventing participation in the study, or performance of study procedures. Additionally, any ROP complications were treated at the investigator's discretion according to local standard of care. The study design is shown in Figure 1 and objectives and endpoints in Table 1.

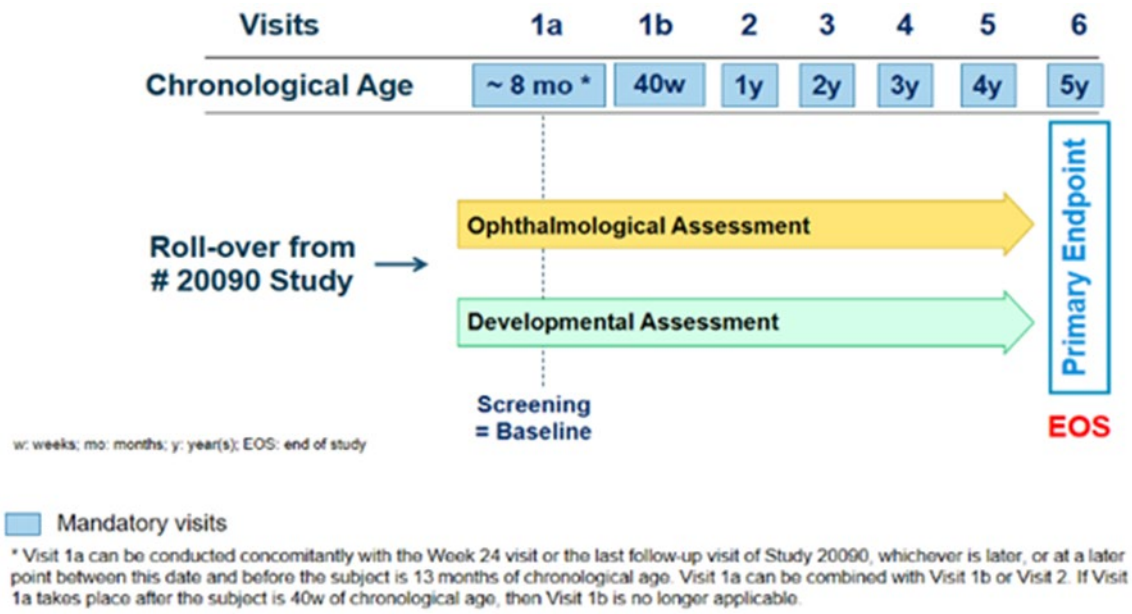


Figure 1. Study design

Objectives	Endpoints
Primary	
To evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for retinopathy of prematurity (ROP)	Primary endpoint: • Binocular best-corrected visual acuity in Snellen equivalent score at 5 years of age Secondary endpoints addressing primary objective: • Proportion of subjects with ocular adverse events (AEs) and serious AEs (SAEs) through 5 years of age • Proportion of subjects with systemic AEs and SAEs through 5 years of age
Secondary	
To describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP	Secondary endpoints addressing secondary objective: • Proportion of subjects developing unfavorable ocular structural outcome (retinal detachment, macular dragging, macular fold, retrolental opacity) at 1, 3, and 5 years of age • Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 1 year of age • Best-corrected visual acuity in each eye at 3 and 5 years of age • Refractive spherical equivalent in each eye at 3 and 5 years of age • Neurodevelopmental outcomes at 2 and 5 years of age using standardized development tests (eg, Bayley Scales of Infant and Toddler Development, Third Edition [BSID-III], the Differential Ability Scales® II [DAS-II®], the Wechsler Preschool and Primary Scale of Intelligence™, Fourth Edition [WPPSI-IV], Vineland Adaptive Behavior Scales, Second Edition [VABS-II]). • Proportion of subjects with recurrence of ROP at 3 and 5 years of age • Proportion of subjects requiring treatment for ROP during this extension study • Proportion of subjects requiring ophthalmological treatment during this extension study

Table 1. Objectives and endpoints

Out of the 100 patients included in Study 20275 (66 patients in aflibercept arm; 34 patients in laser arm), 89 patients completed the study (59 patients in aflibercept arm; 30 patients in laser arm). Additionally, 11 patients in total were discontinued from the study due to lost to follow-up, withdrawal by the parents, or relocation to another city.

Moreover, a total of 60 subjects (38 treated with aflibercept and 22 with laser in Study 20090) had important protocol deviations (59 patients had procedure deviation and 3 patients did not met inclusion/exclusion criteria but entered treatment) during Study 20275.

2.3.1. Efficacy results

Binocular best-corrected visual acuity (BCVA) at 5 years of age was analyzed using the Wilcoxon-Mann-Whitney (WMW) parameter.

The estimation of the primary estimand using the Wilcoxon-Mann-Whitney (WMW) parameter constitutes the main analysis of binocular BCVA at 5 years of age, addressing the primary objective of the study. The WMW parameter estimates the probability that a subject randomly selected from those whose treatment was initiated with aflibercept will have a better binocular BCVA at 5 years of age than a subject randomly selected from those whose treatment was initiated with laser therapy (with adjustment for ties). The more the WMW parameter exceeds 0.5, the better aflibercept is in comparison to laser.

The estimated WMW [95% CI] parameter was 0.624 [0.493, 0.742], exceeding the benchmark of 0.5 for equilibrated effects caused by the different treatment initiations. The estimated probabilities by zone affected by ROP (zone I, zone II, or AP-ROP) at baseline of Study 20090 fit to a homogeneous treatment effect (incl. WMW parameters > 0.5 for all zones).

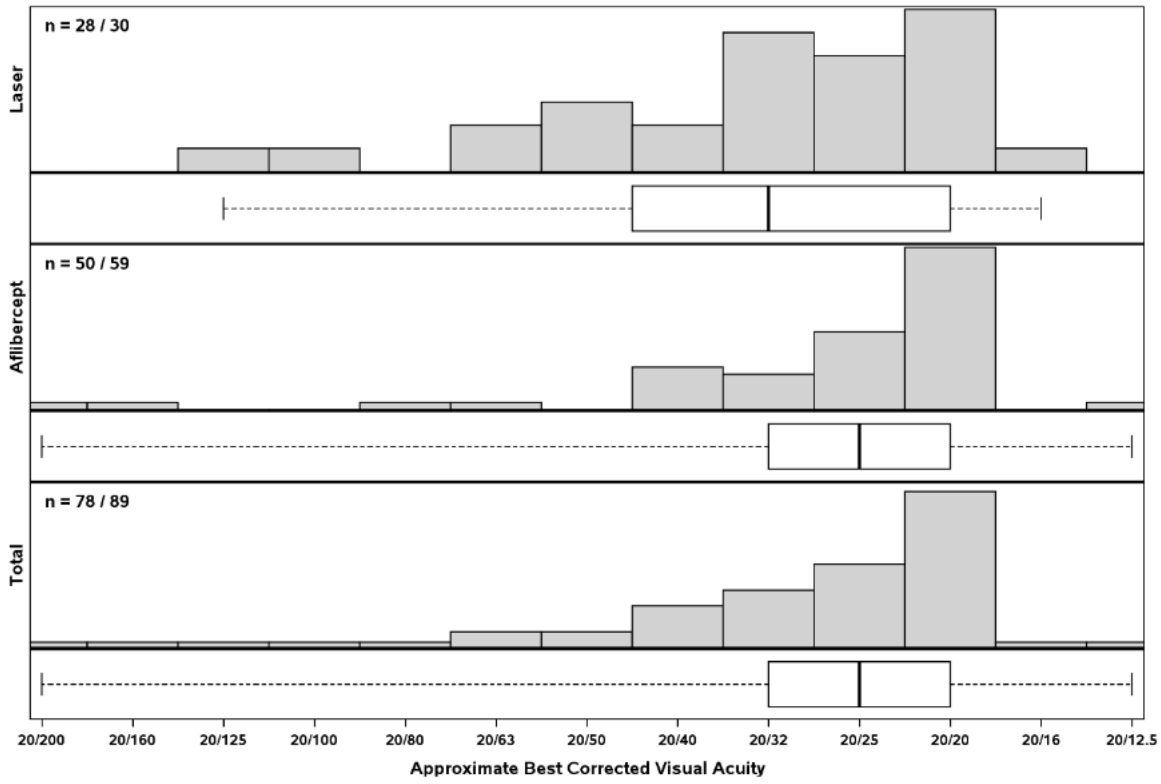
Binocular BCVA at 5 years of age by treatment arm is presented in Figure 5-1.

The median binocular BCVA in Snellen equivalent function at 5 years of age was 20/25 in the aflibercept arm and 20/32 in the laser arm.

Proportion of subjects with binocular BCVA in Snellen equivalent of "20/40 or better" at 5 years of age was 46 (92.0%) in the aflibercept arm and 21 (75.0%) in the laser arm.

Proportion of subjects with binocular BCVA in Snellen equivalent of "20/200 or better" at 5 years of age was 100% in both treatment arms.

Figure 5-1: Binocular best-corrected visual acuity in Snellen equivalent or visual function at 5 years of age (all enrolled subjects)



N = number of subjects; ROP = retinopathy of prematurity

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

For plotting purposes, visual acuity outcomes have been converted to logMAR (logarithm of the Minimum Angle of Resolution) equivalent to represent the distance between outcomes on an additive scale and presented in Snellen equivalent.

Proportion of subjects developing unfavourable structural outcomes through 5 years of chronological age

Unfavorable structural outcomes include retinal detachment, macular dragging, macular fold, and/or retrolental opacity as assessed by the investigator. A subject could have more than one unfavorable structural outcome per eye.

There was no change in the total number of subjects/treated eyes reported with unfavorable structural outcomes until 5 years vs. 1, 2, 3, or 4 years of age (Table 5-1).

Of the 66 (100%) subjects (128 eyes) in the aflibercept arm, 62 (93.9%) subjects did not experience any unfavorable structural outcomes at any time since baseline of Study 20090 until 5 years of age. Seven eyes (5.5%) from 4 subjects (6.1% [Clopper Pearson 95% CI: (1.7, 14.8)]) experienced unfavorable structural outcomes: *retinal detachment* in 6 eyes (4.7%), and *macular dragging*, *macular fold*, and *retrolental opacity* in 2 eyes (1.6%) each.

Of the 34 (100%) subjects (64 eyes) in the laser arm, 32 (94.1%) subjects did not experience any unfavorable structural outcome at any time since baseline of Study 20090 until 5 years of age. Three eyes (4.7%) from 2 subjects (5.9% [Clopper Pearson 95% CI: (0.7, 19.7)]) experienced unfavorable structural outcomes: *retinal detachment* in 1 eye (1.6%) and *macular dragging* in 2 eyes (3.1%).

All subjects who had no unfavorable structural outcomes before entering Study 20275 remained event-free through 5 years of age.

Table 5–1: Number of subjects and number of treated eyes with unfavorable structural outcomes until 1, 2, 3, 4, and 5 years of age based on investigator assessment (all enrolled subjects)

		Aflibercept (N=66)	Laser (N=34)
At any time until 1 yr of age	Number of subjects	66 (100.0)	34 (100.0)
	None	62 (93.9)	32 (94.1)
	Retinal detachment	3 (4.5)	1 (2.9)
	Macular dragging	1 (1.5)	1 (2.9)
	Macular fold	1 (1.5)	0 (0.0)
	Retrolental opacity	1 (1.5)	0 (0.0)
	Any unfavorable structural outcome*	4 (6.1)	2 (5.9)
	Number of eyes	128 (100.0)	64 (100.0)
	None	121 (94.5)	61 (95.3)
	Retinal detachment	5 (3.9)	1 (1.6)
	Macular dragging	2 (1.6)	2 (3.1)
	Macular fold	2 (1.6)	0 (0.0)
	Retrolental opacity	2 (1.6)	0 (0.0)
	Any unfavorable structural outcome*	7 (5.5)	3 (4.7)
At any time until 2 yrs of age	Number of subjects	66 (100.0)	34 (100.0)
	None	62 (93.9)	32 (94.1)
	Retinal detachment	3 (4.5)	1 (2.9)
	Macular dragging	1 (1.5)	1 (2.9)
	Macular fold	1 (1.5)	0 (0.0)
	Retrolental opacity	1 (1.5)	0 (0.0)
	Any unfavorable structural outcome*	4 (6.1)	2 (5.9)
	Number of eyes	128 (100.0)	64 (100.0)
	None	121 (94.5)	61 (95.3)
	Retinal detachment	5 (3.9)	1 (1.6)
	Macular dragging	2 (1.6)	2 (3.1)
	Macular fold	2 (1.6)	0 (0.0)
	Retrolental opacity	2 (1.6)	0 (0.0)
	Any unfavorable structural outcome*	7 (5.5)	3 (4.7)

At any time until 3 yrs of age	Number of subjects	66 (100.0)	34 (100.0)
	None	62 (93.9)	32 (94.1)
	Retinal detachment	4 (6.1)	1 (2.9)
	Macular dragging	1 (1.5)	1 (2.9)
	Macular fold	1 (1.5)	0 (0.0)
	Retrolental opacity	1 (1.5)	0 (0.0)
	Any unfavorable structural outcome*	4 (6.1)	2 (5.9)
	Number of eyes	128 (100.0)	64 (100.0)
	None	121 (94.5)	61 (95.3)
	Retinal detachment	6 (4.7)	1 (1.6)
	Macular dragging	2 (1.6)	2 (3.1)
	Macular fold	2 (1.6)	0 (0.0)
	Retrolental opacity	2 (1.6)	0 (0.0)
	Any unfavorable structural outcome*	7 (5.5)	3 (4.7)
At any time until 4 yrs of age	Number of subjects	66 (100.0)	34 (100.0)
	None	62 (93.9)	32 (94.1)
	Retinal detachment	4 (6.1)	1 (2.9)
	Macular dragging	1 (1.5)	1 (2.9)
	Macular fold	1 (1.5)	0 (0.0)
	Retrolental opacity	1 (1.5)	0 (0.0)
	Any unfavorable structural outcome*	4 (6.1)	2 (5.9)
	Number of eyes	128 (100.0)	64 (100.0)
	None	121 (94.5)	61 (95.3)
	Retinal detachment	6 (4.7)	1 (1.6)
	Macular dragging	2 (1.6)	2 (3.1)
	Macular fold	2 (1.6)	0 (0.0)
	Retrolental opacity	2 (1.6)	0 (0.0)
	Any unfavorable structural outcome*	7 (5.5)	3 (4.7)
At any time until 5 yrs of age	Number of subjects	66 (100.0%)	34 (100.0%)
	None	62 (93.9%)	32 (94.1%)
	Retinal detachment	4 (6.1%)	1 (2.9%)
	Macular dragging	1 (1.5%)	1 (2.9%)
	Macular fold	1 (1.5%)	0 (0.0%)
	Retrolental opacity	1 (1.5%)	0 (0.0%)
	Any unfavorable structural outcome*	4 (6.1%)	2 (5.9%)
	Number of eyes	128 (100.0%)	64 (100.0%)
	None	121 (94.5%)	61 (95.3%)
	Retinal detachment	6 (4.7%)	1 (1.6%)
	Macular dragging	2 (1.6%)	2 (3.1%)
	Macular fold	2 (1.6%)	0 (0.0%)
	Retrolental opacity	2 (1.6%)	0 (0.0%)
	Any unfavorable structural outcome*	7 (5.5%)	3 (4.7%)

N = number of subjects; ROP = retinopathy of prematurity; yr(s) = year(s).
*A subject could have more than one unfavorable structural outcome per eye.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.
Any unfavorable structural outcome reported in Study 20090 and/or Study 20275 was considered in the analysis.
Subjects dropping out of the study prior to reaching a specific visit were still considered in the analysis and included in the denominator.
Subjects dropping out prior to a specific visit who developed (an) unfavorable structural outcome(s) were considered in the analysis based on the respective event.

Proportion of subjects with absence of active ROP and unfavourable structural outcomes through 5 years of chronological age

At 5 years of age, all 55 (100.0%) assessed subjects in the aflibercept arm and 29 (96.7%) assessed subjects in the laser arm had no ROP (Table 8.2.2.2/1). 62 (93.3%) subjects in the aflibercept arm and 32 (94.1%) subjects in the laser arm had no unfavorable structural outcomes (retinal detachment,

macular fold, macular dragging, or retrolental opacity) since the treatment initiation in Study 20090. All subjects who had no unfavorable structural outcomes before entering Study 20275 remained event-free through 5 years of age.

Table 8.2.2.2 / 1: ROP classification in Study 20275 by visit (all enrolled subjects)

Visit		Aflibercept N=66	Laser N=34
Screening/Baseline	Number of subjects	53 (100.0%)	26 (100.0%)
	No ROP	44 (83.0%)	24 (92.3%)
	Zone III Stage 1	2 (3.8%)	0
	Zone II Stage 1	1 (1.9%)	1 (3.8%)
	Zone II Stage 2	2 (3.8%)	0
	Zone I Stage 1	1 (1.9%)	0
	Stage 4a	1 (1.9%)	0
	Stage 4b	1 (1.9%)	1 (3.8%)
	Zone II	1 (1.9%)	0
	Number of eyes	102 (100.0%)	49 (100.0%)
	No ROP	84 (82.4%)	46 (93.9%)
	Zone III Stage 1	4 (3.9%)	0
	Zone II Stage 1	1 (1.0%)	2 (4.1%)
	Zone II Stage 2	4 (3.9%)	0
	Zone I Stage 1	2 (2.0%)	0
	Stage 4a	3 (2.9%)	0
	Stage 4b	1 (1.0%)	1 (2.0%)
	Zone II	3 (2.9%)	0
40 weeks of chronological age	Number of subjects	27 (100.0%)	11 (100.0%)
	No ROP	23 (85.2%)	11 (100.0%)
	Zone III Stage 1	2 (7.4%)	0
	Zone II Stage 2	1 (3.7%)	0
	Stage 5	1 (3.7%)	0
	Number of eyes	51 (100.0%)	20 (100.0%)
	No ROP	43 (84.3%)	20 (100.0%)
	Zone III Stage 1	4 (7.8%)	0
	Zone II Stage 2	2 (3.9%)	0
	Stage 4a	1 (2.0%)	0
	Stage 5	1 (2.0%)	0
1 year of chronological age	Number of subjects	66 (100.0%)	34 (100.0%)
	No ROP	59 (89.4%)	31 (91.2%)
	Zone III Stage 1	2 (3.0%)	0
	Zone II Stage 2	1 (1.5%)	0
	Zone I Stage 1	0	1 (2.9%)
	Stage 4a	1 (1.5%)	0
	Stage 4b	0	1 (2.9%)
	Stage 5	1 (1.5%)	0
	Zone I	0	1 (2.9%)
	Zone II	1 (1.5%)	0
	Zone III	1 (1.5%)	0
	Number of eyes	128 (100.0%)	64 (100.0%)
	No ROP	115 (89.8%)	59 (92.2%)
	Zone III Stage 1	4 (3.1%)	0
	Zone II Stage 1	0	1 (1.6%)
	Zone II Stage 2	2 (1.6%)	0
	Zone I Stage 1	0	1 (1.6%)
	Stage 4a	2 (1.6%)	0
	Stage 4b	0	1 (1.6%)
	Stage 5	1 (0.8%)	0
	Zone I	0	2 (3.1%)
	Zone II	1 (0.8%)	0
	Zone III	3 (2.3%)	0
2 years of chronological age	Number of subjects	63 (100.0%)	32 (100.0%)
	No ROP	61 (96.8%)	30 (93.8%)
	Stage 4a	1 (1.6%)	0
	Stage 4b	0	1 (3.1%)
	Zone I	0	1 (3.1%)
	Zone II	1 (1.6%)	0
	Number of eyes	122 (100.0%)	61 (100.0%)
	No ROP	118 (96.7%)	58 (95.1%)
	Stage 4a	1 (0.8%)	0
	Stage 4b	0	1 (1.6%)
	Zone I	0	2 (3.3%)
	Zone II	1 (0.8%)	0
	Zone III	1 (0.8%)	0
	Missing	1 (0.8%)	0

3 years of chronological age	Number of subjects	58 (100.0%)	30 (100.0%)
	No ROP	57 (98.3%)	29 (96.7%)
	Stage 4b	0	1 (3.3%)
	Zone II	1 (1.7%)	0
	Number of eyes	112 (100.0%)	58 (100.0%)
	No ROP	110 (98.2%)	57 (98.3%)
	Stage 4b	0	1 (1.7%)
	Zone II	1 (0.9%)	0
	Missing	1 (0.9%)	0
4 years of chronological age	Number of subjects	56 (100.0%)	30 (100.0%)
	No ROP	56 (100.0%)	29 (96.7%)
	Stage 4b	0	1 (3.3%)
	Number of eyes	109 (100.0%)	58 (100.0%)
	No ROP	109 (100.0%)	57 (98.3%)
	Stage 4b	0	1 (1.7%)
5 years of chronological age	Number of subjects	55 (100.0%)	30 (100.0%)
	No ROP	55 (100.0%)	29 (96.7%)
	Stage 4b	0	1 (3.3%)
	Number of eyes	107 (100.0%)	58 (100.0%)
	No ROP	107 (100.0%)	57 (98.3%)
	Stage 4b	0	1 (1.7%)

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
In Study 20275, Visit 1a (screening/baseline) could be combined with Visit 1b (40 weeks of chronological age) or Visit 2 (1 year of chronological age). If Visit 1a took place later than at 40 weeks of chronological age, Visit 1b was not applicable.
Subjects with combined visits are presented by their most recent (last) visit.
For the analysis on subject-level, if eyes had different ROP severity, the worse eye was considered.
If stage information is missing, only the affected zone is displayed.

Proportion of subjects with recurrence of ROP through 5 years of chronological age

In Study 20275, disease recurrence was defined as the re-appearance of disease as per ROP inclusion criteria of Study 20090 or worse. The proportions of subjects with recurrence of ROP from baseline treatment through 1, 2, 3, 4, and 5 years of age remained the same: 11 (16.7%) in the aflibercept arm and 1 (2.9%) subject in the laser arm (Table 8.2.2.3/1). No subject experienced any new recurrence of ROP after 1 year of age.

Table 8.2.2.3 / 1: Number of subjects with recurrence of ROP in any treated eye through 1 year, 2, 3, 4, and 5 years of chronological age based on investigator assessment (all enrolled subjects)

		Aflibercept (N=66)		Laser (N=34)	
Time period		n (%)	95% Confidence interval	n (%)	95% Confidence interval
Through 1 year of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Recurrence of ROP	11 (16.7%)	(8.6, 27.9)	1 (2.9%)	(0.1, 15.3)
Through 2 years of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Recurrence of ROP	11 (16.7%)	(8.6, 27.9)	1 (2.9%)	(0.1, 15.3)
Through 3 years of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Recurrence of ROP	11 (16.7%)	(8.6, 27.9)	1 (2.9%)	(0.1, 15.3)
Through 4 years of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Recurrence of ROP	11 (16.7%)	(8.6, 27.9)	1 (2.9%)	(0.1, 15.3)
Through 5 years of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Recurrence of ROP	11 (16.7%)	(8.6, 27.9)	1 (2.9%)	(0.1, 15.3)

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
A subject was considered as having ROP recurrence, if ROP according to the inclusion criteria of Study 20090 (or worse) was reported during the regarded time period for a treated eye and the eye's last reported assessment prior to the time period was ROP not requiring treatment (according to the inclusion criteria of Study 20090).
Subjects dropping out of the study were considered in the analysis of subsequent time periods by inclusion in the denominator (and in the numerator if ROP had recurred).
Exact Clopper Pearson confidence intervals are presented.

Proportion of subjects requiring treatment for ROP during Study 20275

Three (4.5%) subjects in the aflibercept arm required treatment for ROP complications during Study 20275; 2 (3.8%) of these subjects required treatment at screening/baseline for bilateral retinal detachment pre-existing since Study 20090. One subject with bilateral zone I AP-ROP was treated with laser at around 43 weeks of age for reactivated plus disease in both eyes. In addition to those with reported need for treatment, one subject in the aflibercept arm with bilateral zone II Stage 3 plus ROP was treated with laser around 50 weeks of age for recurrent retinal neovascularization not further specified (reported as adverse event only) and incomplete vascularization in both eyes. No subject received treatment in the post-acute phase beyond 50 weeks of age. No subject in the laser arm was reported to require treatment for ROP during Study 20275.

Table 8.2.2.4 / 1: Number of subjects requiring treatment for ROP in Study 20275 based on investigator assessment (all enrolled subjects)

		Aflibercept (N=66)		Laser (N=34)	
Visit		n (%)	95% Confidence interval	n (%)	95% Confidence interval
Screening/Baseline	Number of subjects	53 (100%)		26 (100%)	
	Need for ROP treatment in Study 20275	2 (3.8%)	(0.5, 13.0)	0	(0.0, 13.2)
40 weeks of chronological age	Number of subjects	27 (100%)		11 (100%)	
	Need for ROP treatment in Study 20275	0	(0.0, 12.8)	0	(0.0, 28.5)
1 year of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Need for ROP treatment in Study 20275	0	(0.0, 5.4)	0	(0.0, 10.3)
2 years of chronological age	Number of subjects	63 (100%)		32 (100%)	
	Need for ROP treatment in Study 20275	0	(0.0, 5.7)	0	(0.0, 10.9)
3 years of chronological age	Number of subjects	58 (100%)		30 (100%)	
	Need for ROP treatment in Study 20275	0	(0.0, 6.2)	0	(0.0, 11.6)
4 years of chronological age	Number of subjects	56 (100%)		30 (100%)	
	Need for ROP treatment in Study 20275	0	(0.0, 6.4)	0	(0.0, 11.6)
5 years of chronological age	Number of subjects	55 (100%)		30 (100%)	
	Need for ROP treatment in Study 20275	0	(0.0, 6.5)	0	(0.0, 11.6)
Between screening/baseline and 5 years of chronological age	Number of subjects	66 (100%)		34 (100%)	
	Need for ROP treatment in Study 20275	3 (4.5%)	(0.9, 12.7)	0	(0.0, 10.3)

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
A subject was considered to require treatment for ROP in Study 20275 if the question 'Presence of active ROP requiring treatment' was answered with 'Yes' for at least one eye treated in Study 20090.
Exact Clopper Pearson confidence intervals are presented.
One subject received treatment for the recurrence of retinal neovascularization at around 50 weeks of chronological age. As no presence of ROP was reported, this case is not included in the table.

Proportion of subjects requiring ophthalmological treatment during Study 20275

"Ophthalmological treatment" was defined as any type of ophthalmological treatment and therefore included treatment for ROP and other ophthalmic conditions. Ten (15.2%) of the 66 subjects in the aflibercept arm and 2 (5.9%) of the 34 subjects in the laser arm received (any type of) ophthalmological treatment during Study 20275 (Table 8.2.2.5/1). Of the 10 subjects in the aflibercept arm who received ophthalmological treatment, 4 subjects were treated for the indication of ROP, 3 subjects were treated for the indication of conjunctivitis, and the remainder 3 subjects were treated for the indications of myopia, ocular hyperaemia, and retinoblastoma, respectively. Of the 2 subjects in the laser arm who received treatment, one was treated for conjunctivitis and the other one for chalazion.

Table 8.2.2.5 / 1: Number of subjects requiring ophthalmological treatment in Study 20275 (all enrolled subjects)

	Aflibercept (N=66)		Laser (N=34)	
	n (%)	95% Confidence interval	n (%)	95% Confidence interval
Number of subjects	66 (100%)		34 (100%)	
Need for ophthalmological treatment in Study 20275	10 (15.2%)	(7.5, 26.1)	2 (5.9%)	(0.7, 19.7)

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Exact Clopper Pearson confidence intervals are presented.
"Ophthalmological treatment":
i) Any surgical procedure with anatomical location = 'eye' and laterality in an eye that received study treatment for ROP in Study 20090 and
ii) any concomitant medication in a main indication to treat an ocular adverse event in an eye that received study treatment for ROP in Study 20090
Ophthalmological treatments that are ongoing at or began after the screening/baseline visit and no later than at subject specific cut-off date are included in this table.

Evaluation of visual function and refraction and structural outcomes

Evaluation of visual performance and refraction and structural outcomes through 5 years of age was one of the exploratory endpoints addressing the other pre-specified objective of the study. The exploratory endpoints on visual function are summarized here by the term "visual performance" to distinguish from the visual function assessments defining the primary endpoint.

Best-corrected visual acuity at 3, 4 and 5 years of chronological age

Best-corrected visual acuity in each eye at 3 and 5 years of age was one of the secondary endpoints addressing the secondary objective of the study.

Binocular BCVA was first measured at 3 years of age per protocol. The number and percentage of subjects with **binocular** BCVA in Snellen equivalent score of "20/200 or better" and "20/40 or better" is shown in Table 5–2.

Table 5–2: Proportion of subjects with binocular BCVA in Snellen equivalent score of 20/200 or better and 20/40 or better at 3, 4, and 5 years of age (all enrolled subjects)

Snellen equivalent score	Aflibercept arm (N=66)	Laser arm (N=34)
At 3 years age		
n	45 (100%)	23 (100%)
20/200 or better	44 (97.8%)	23 (100.0%)
20/40 or better	30 (66.7%)	11 (47.8%)
At 4 years age		
n	51 (100%)	22 (100%)
20/200 or better	50 (98.0%)	22 (100.0%)
20/40 or better	38 (74.5%)	17 (77.3%)
At 5 years age		
n	50 (100%)	28 (100%)
20/200 or better	50 (100.0%)	28 (100.0%)
20/40 or better	46 (92.0%)	21 (75.0%)

N = number of subjects; n = number of subjects with binocular assessments at the respective visit.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

The number and percentage of eyes with **monocular** BCVA in Snellen equivalent score of "20/200 or better" and "20/40 or better" is shown in Table 5–3.

Table 5–3: Proportion of treated eyes with monocular BCVA in Snellen equivalent score of 20/200 or better and 20/40 or better at 3, 4, and 5 years of age (all enrolled subjects)

Snellen equivalent score	Aflibercept arm (N=66)	Laser arm (N=34)
At 3 years age		
n	79 (100%)	46 (100%)
20/200 or better	75 (94.9%)	46 (100.0%)
20/40 or better	47 (59.5%)	19 (41.3%)
At 4 years age		
n	99 (100%)	46 (100%)
20/200 or better	96 (97.0%)	46 (100.0%)
20/40 or better	69 (69.7%)	33 (71.7%)
At 5 years age		
n	95 (100%)	58 (100%)
20/200 or better	93 (97.9%)	57 (98.3%)
20/40 or better	82 (86.3%)	36 (62.1%)

N = number of subjects; n = number of eyes with monocular assessments at the respective visit.
The percentages are based on the number of treated eyes with reported data.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

Refractive spherical equivalent in each eye

Refractive spherical equivalent in each eye at 3 and 5 years of age was one of the secondary endpoints addressing the secondary objective of the study (see Section 2). The refractive spherical equivalent was calculated as: sphere + ½ cylinder. At 5 years of age, myopia was less pronounced in the aflibercept arm than in the laser arm, with the mean (SD) refractive spherical equivalent of -0.3036 (2.9434) D in the aflibercept arm and -2.2435 (4.5113) D in the laser arm (Table 5–4).

Spherical equivalent by disease classification at the time of baseline treatment in Study 20090 is presented in Table 8.2.2.7/2. Data on subjects with high or very high myopia in at least one eye treated in Study 20090 by visit is presented in Table 8.2.2.7/4. Data on eyes treated in Study 20090 with high or very high myopia by visit is presented in Table 8.2.2.7/5 of the report body. Mean (SD) axis values by treated eye are shown in Table 8.2.3.3/3 of the report body.

Table 5–4: Refractive spherical equivalent by treated eye (all enrolled subjects)

		Refractive spherical equivalent (diopters)	
Chronological age		**Aflibercept arm (N=66)**	**Laser arm (N=34)**
5 years		n=105	n=58
	Mean (SD)	-0.3036 (2.9434)	-2.2435 (4.5113)
	Range	-16.125 to +6.875	-14.875 to 3.500
4 years		n=106	n=58
	Mean (SD)	-0.2252 (2.9482)	-2.1185 (4.3209)
	Range	-17.875 to +5.500	-14.750 to 3.500
3 years		n=112	n=58
	Mean (SD)	-0.4118 (3.0621)	-2.1918 (4.2252)
	Range	-17.375 to +5.500	-14.750 to +3.500
2 years		n=115	n=60
	Mean (SD)	-0.5685 (2.9635)	-1.8542 (3.9495)
	Range	-16.250 to +5.500	-12.000 to +3.500
1 year		n=121	n=62
	Mean (SD)	-0.1839 (2.7368)	-1.0948 (3.1830)
	Range	-13.000 to +4.000	-10.250 to +4.500

SD = standard deviation; n = number of eyes with assessments at the respective visit.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

Visual performance and refraction and structural outcomes

The number of treated eyes with normal retina attached to periphery are shown below:

Table 5–5: Number of treated eyes reported with normal retina attached to periphery (all enrolled subjects)

Chronological age	Aflibercept arm	Laser arm
5 years	105 (97.2%) of 108 eyes	55 (94.8%) of 58 eyes
4 years	106 (97.2%) of 109 eyes	57 (98.3%) of 58 eyes
3 years	111 (95.7%) of 116 eyes	57 (98.3%) of 58 eyes
2 years	119 (97.5%) of 122 eyes	60 (95.2%) of 63 eyes
1 year	125 (97.7%) of 128 eyes	63 (98.4%) of 64 eyes

The percentages are based on the number of treated eyes with reported data.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

All eyes reported with normal retina attached to periphery at 1 year of age remained with normal retina attached to periphery through 5 years of age except for the one eye of one subject (aflibercept arm), in whom the macular fold reported at 1 and 2 years of age progressed to retinal detachment at 3, 4, and 5 years of age.

The number of treated eyes with abnormalities of the optic nerve and lens are presented below:

Table 5–6: Number of treated eyes with abnormalities of the optic nerve and lens (all enrolled subjects)

Chronological age	Optic nerve hypoplasia		Optic nerve atrophy		Large excavation of optic disc		Cortical cataract of 1+ density	
	Aflibercept arm	Laser arm	Aflibercept arm	Laser arm	Aflibercept arm	Laser arm	Aflibercept arm	Laser arm
5 years	0	0	3/108 (2.8%)	0	2/108 (1.9%)	0	1/108 (0.9%)	0
4 years	0	0	1/109 (0.9%)*	0	2/109 (1.8%)	0	1/109 (0.9%)	0
3 years	0	0	2/116 (1.7%)	0	4/116 (3.4%)	0	1/116 (0.9%)	0
2 years	0	0	2/122 (1.6%)	0	7/122 (5.7%)	0	1/122 (0.8%)	0
1 year	0	0	2/128 (1.6%)	0	5/128 (3.9%)	0	0	0

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

* One subject who had abnormality at 3 years of age, missed the visit at 4 years of age but remained in the study.

Majority of treated eyes were able to fix and follow a 5-cm toy (105 eyes [97.2%] in the aflibercept arm vs. 57 eyes [98.3%] in the laser arm) (Table 5-7). The number of treated eyes with abnormalities in light reaction, central fixation, fixing and following a 5-cm toy, visual evoked potentials, and contrast sensitivity are presented below:

Table 5–7: Number of treated eyes with abnormalities in light reaction, central fixation, fixing and following a 5 cm-toy, visual evoked potentials, and contrast sensitivity (all enrolled subjects)

Chronological age	No light reaction		No central fixation		Unable to fix and follow a 5-cm toy		Abnormal visual evoked potentials*		Abnormal contrast sensitivity*	
	Afliber cept arm	Laser arm	Afliber cept arm	Laser arm	Afliber cept arm	Laser arm	Afliber cept arm	Laser arm	Afliber cept arm	Laser arm
5 years	1/109 (0.9%)	0	3/108 (2.8%)	1/58 (1.7%)	2/108 (1.9%)	1/58 (1.7%)	1/108 (0.9%)	2/58 (3.4%)	3/108 (2.8%)	0
4 years	1/109 (0.9%)	0	4/109 (3.7%)	1/58 (1.7%)	3/109 (2.8%)	1/58 (1.7%)	1/109 (0.9%)	0	2/109 (1.8%)	0
3 years	0	0	4/116 (3.4%)	1/58 (1.7%)	3/116 (2.6%)	1/58 (1.7%)	2/116 (1.7%)	2/58 (3.4%)	0	0
2 years	0	0	5/122 (4.1%)	1/63 (1.6%)	2/122 (1.6%)	1/63 (1.6%)	2/122 (1.6%)	2/63 (3.2%)	0	0
1 year	0	0	5/128 (3.9%)	1/64 (1.6%)	4/128 (3.1%)	1/64 (1.6%)	0	2/64 (3.1%)	0	0

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

* Assessments for visual evoked potentials and contrast sensitivity were either missing (examination was not done) or unknown (examination was done but result reported as unknown) for the majority of the subjects.

Within the timeframe of the study, one subject (aflibercept arm) presented no light reaction of one eye, which had shown no light reaction previously at 40 weeks of age.

Ocular motility tests

Ocular extrinsic motility is presented in Table 5–9. At 5 years of age, the number of subjects with no manifest strabismus was 44/56 (78.6%) in the aflibercept arm and 26/30 (86.7%) in the laser arm.

Table 5–9: Ocular extrinsic motility (all enrolled subjects)

	No manifest strabismus by subject		Nystagmus in primary position of gaze by subject		Ocular palsy by treated eye	
Chronological age	Aflibercept arm	Laser arm	Aflibercept arm	Laser arm	Aflibercept arm	Laser arm
5 years	44/56 (78.6%)	26/30 (86.7%)	1/56 (1.8%)	1/30 (3.3%)	0	0
4 years	46/56 (82.1%)	26/30 (86.7%)	2/56 (3.6%)	1/30 (3.3%)	0	0
3 years	51/60 (85.0%)	26/30 (86.7%)	3/60 (5.0%)	1/30 (3.3%)	1/116 (0.9%) a	0
2 years	49/63 (77.8%)	28/33 (84.8%)	3/63 (4.8%)	2/33 (6.1%)	1/122 (0.8%) b 2/122 (1.6%) c	0
1 year	55/66 (83.3%)	29/34 (85.3%)	1/66 (1.5%)	2/34 (5.9%)	1/128 (0.8%) d	0

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

a Cranial nerve VI (abducens nerve) palsy- Subject (bilateral at 3 years, only left eye was treated

b Cranial nerve IV (trochlear nerve) palsy - Subject (left eye at 2 years)

c Cranial nerve VI (abducens nerve) palsy - Subjects (bilateral at 2 years, only left eye was treated and (left eye at 2 years)

d Cranial nerve VI (abducens nerve) palsy - Subject (left eye at 1 year)

The 2 subjects with cranial nerve palsies displayed above are summarized: one subject presented with abducens nerve palsy at 1 year of age and bilateral abducens nerve palsy at 2 and 3 years of age. No data regarding ocular motor nerve palsy was reported at 4 or 5 years of age. This subject had a history of neurological disorders with posthemorrhagic hydrocephalus and significant delay in statomotive development. One subject presented with trochlear and abducens nerve palsy at 2 years of age, but no longer at 3, 4, or 5 years of age. The reported AEs were consecutively resolved. Preceding AEs included neurological disorders with cerebral arteriospasm, cerebral hypoperfusion and dystonia.

ROP outcomes through 5 years of chronological age according to the International Neonatal Consortium ROP activity scale

The ROP Activity Scale scores were derived for each treated eye based on the investigators' classification of ROP. Scores of 0 to 7 were considered as mild, 8 to 12 as moderate, and 13 to 22 as severe ROP activity. Mean scores of treated eyes and the numbers of eyes with a decrease of ≥2 points compared to the baseline visit of Study 20090 are displayed in Table 5–10 and Table 5–11, respectively.

Table 5–10: ROP Activity Scale scores by treated eye (all enrolled subjects)

	ROP Activity Scale score – Mean (SD)	
Chronological age	**Aflibercept arm**	**Laser arm**
5 years	n=107 0.00 (0.00)	n=58 0.36 (2.76)
4 years	n=109 0.00 (0.00)	n=58 0.36 (2.76)
3 years	n=110 0.00 (0.00)	n=58 0.36 (2.76)
2 years	n=119 0.17 (1.83)	n=59 0.36 (2.73)
1 year	n=124 0.65 (3.29)	n=62 0.55 (2.95)
Baseline of Study 20275	n=99 1.37 (4.36)	n=49 0.55 (3.04)
Baseline of Study 20090	n=128 15.46 (2.22)	n=64 15.00 (2.40)

ROP = retinopathy of prematurity; SD = standard deviation; n = number of eyes with assessments at the respective visit.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

Table 5–11: Number of treated eyes with decreases of ≥2 points compared to the baseline visit of Study 20090 in the ROP Activity Scale score (all enrolled subjects)

	Decrease ≥2 in the ROP Activity Scale score	
Chronological age	**Aflibercept arm**	**Laser arm**
5 years	107 (100.0%)	57 (98.3%)
4 years	109 (100.0%)	57 (98.3%)
3 years	110 (100.0%)	57 (98.3%)
2 years	118 (99.2%)	58 (98.3%)
1 year	121 (97.6%)	61 (98.4%)

ROP = retinopathy of prematurity.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

Subjects with complete vascularization through 5 years of chronological age assessed by indirect ophthalmoscopy

Completion of vascularization was assessed by the investigator by indirect ophthalmoscopy. The rates of complete vascularization by subject and eye in the aflibercept arm increased from 1 year to 2 years of age. Proportion of subjects with complete vascularization (in all treated eyes) in the aflibercept arm increased from 68.2% at 1 year of age to 85.5% at 5 years of age.

The number of treated eyes with complete vascularization according to the investigators' assessments is shown in Table 5–12. Retinal vascularization after the aflibercept treatment appeared to be complete in 80% of the treated eyes by 2 years of age. The interpretability of the rates reported for the laser arm is limited by differences in reporting behavior. While some investigators reported vascularization as not complete considering vascularization in the presence of laser scars as not possible, other investigators reported vascularization as complete if the retinal vessels reached the edge of the treated peripheral retina.

Table 5–12: Number of treated eyes with complete vascularization assessed by indirect ophthalmoscopy (all enrolled subjects)

	Number (%) of treated eyes
Chronological age	**Aflibercept arm**
5 years	91/107 (85.0%)
4 years	87/109 (79.8%)
3 years	89/111 (80.2%)
2 years	97/121 (80.2%)
1 year	89/128 (69.5%)
Screening/baseline	51/102 (50%)

Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There was no study treatment in Study 20275.

2.3.2. Safety results

Safety summary Safety data through 5 years of chronological age were analyzed on all enrolled subjects, which included all 100 subjects enrolled in Study 20275, 66 in the aflibercept arm and 34 in the laser arm. Ocular and non-ocular (systemic) AEs were captured from baseline of Study 20275 until the last subject's last visit (19 SEP 2025). Overall, the proportion of subjects with any AE was higher in the aflibercept arm (93.9%) compared to the laser arm (85.3%). The proportion of subjects with any SAE was higher in the laser arm (aflibercept 37.9% vs. laser 47.1%). No death was reported in either arm (Table 5–13). While the proportion of subjects with ocular AEs (53.0% vs. 47.1%) and ocular SAEs (9.1% vs. 0%) was numerically higher in the aflibercept arm compared to the laser arm, respectively, the events were overall in line with underlying comorbidities known to occur in the follow-up of prematurely born infants with treatment-requiring ROP and no new safety concern has been identified. The most frequent ocular AEs, occurring in >10% of subjects in total, were Astigmatism, Strabismus, and Myopia (Table 5–16). The proportion of subjects with systemic AEs was comparable between the aflibercept arm (89.4%) and the laser arm (85.3%) and compatible with the comorbidity profile of prematurely born children. The most frequent systemic AEs, occurring in >10% of subjects in total, were Bronchitis, Pyrexia, Upper respiratory tract infection, Nasopharyngitis, COVID 19, Respiratory tract infection, Diarrhea, and Otitis media (Table 5–17). Ocular and overall clinical outcomes regarding, e.g., growth, blood pressure, and neuro- and behavioral development did not relevantly differ across the 2 arms and were within the range expected for such a population of prematurely born children. Overall, ocular and systemic safety data through 5 years of age were well in line with the established safety profile of IVT aflibercept, and no new safety concerns for the pediatric population who were treated for ROP as preterm infants were identified.

Adverse events AEs were captured from baseline of Study 20275 until the last subject's last visit (19 SEP 2025). Evaluations of AEs were performed for ocular AEs and non-ocular (systemic) AEs. In the absence of any study treatment in Study 20275, treatment-emergent adverse events are not applicable in this study. Ocular and systemic AEs were presented by:

- Unilaterally and bilaterally treated subjects
- Bilaterally treated subjects
- Unilaterally treated subjects

The informative value is limited by the small number of unilaterally treated subjects. Consequently, the summaries by bilaterally and both unilaterally and bilaterally treated subjects are very similar.

Overview of AEs

The number of unilaterally and bilaterally treated subjects who experienced any AEs from baseline of Study 20275 through 5 years of age is summarized in Table 5–13. Overall, at least one AE was reported in a total of 91 (91.0%) subjects, with a higher proportion of subjects experiencing AEs in the aflibercept arm (93.9%) compared to the laser arm (85.3%). Most of the AEs were mild or moderate in intensity, and severe AEs were reported in 17 (25.8%) subjects in the aflibercept arm and in 6 (17.6%) subjects in the laser arm. SAEs were reported in 41 (41.0%) subjects, with events occurring in a higher proportion of subjects in the laser arm (aflibercept 37.9% vs. laser 47.1%). No AEs with an outcome of death were reported. Ocular and systemic AEs are summarized in sections below.

Table 5–13: Overall summary of number of subjects with any AEs – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Number (%) of subjects with	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Any AE	**62 (93.9%)**	**29 (85.3%)**	**91 (91.0%)**
Any ocular AE	35 (53.0%)	16 (47.1%)	51 (51.0%)
Any ocular AE in treated eye	34 (51.5%)	15 (44.1%)	49 (49.0%)
Any ocular AE in non-treated eye	2 (3.0%)	1 (2.9%)	3 (3.0%)
Any systemic AE	59 (89.4%)	29 (85.3%)	88 (88.0%)
Maximum intensity for any AE			
Mild	19 (28.8%)	6 (17.6%)	25 (25.0%)
Moderate	26 (39.4%)	17 (50.0%)	43 (43.0%)
Severe	17 (25.8%)	6 (17.6%)	23 (23.0%)
Any AE related to aflibercept	2 (3.0%)	1 (2.9%)	3 (3.0%)
Maximum intensity for aflibercept-related AE			
Moderate	0	1 (2.9%)	1 (1.0%)
Severe	2 (3.0%)	0	2 (2.0%)
Any AE related to laser photocoagulation	3 (4.5%)	5 (14.7%)	8 (8.0%)
Maximum intensity for laser photocoagulation-related AE			
Mild	1 (1.5%)	2 (5.9%)	3 (3.0%)
Moderate	0	2 (5.9%)	2 (2.0%)
Severe	2 (3.0%)	1 (2.9%)	3 (3.0%)
Any AE related to injection procedure	0	1 (2.9%)	1 (1.0%)
Any AE related to procedures required by the protocol	0	0	0
Any SAE	**25 (37.9%)**	**16 (47.1%)**	**41 (41.0%)**
Any ocular SAE	6 (9.1%)	0	6 (6.0%)
Any ocular SAE in treated eye	6 (9.1%)	0	6 (6.0%)
Any ocular SAE in non-treated eye	0	0	0
Any systemic SAE	23 (34.8%)	16 (47.1%)	39 (39.0%)
Any SAE related to aflibercept	1 (1.5%)	0	1 (1.0%)
Any SAE related to laser photocoagulation	0	0	0
Any SAE related to injection procedure	0	0	0
Any SAE related to procedures required by the protocol	0	0	0
AE with outcome death	**0**	**0**	**0**

Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
SAEs from Study 20090 ongoing at the time of informed consent for Study 20275 were re-entered for Study 20275.
AEs in treated eye refer to AEs in eyes that received study treatment in Study 20090.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Relationship of AEs to aflibercept, photocoagulation, injection procedure or any other procedure required by the protocol is reported as assessed by the investigator.

Overall summaries of AEs for unilaterally and bilaterally treated subjects were provided.

Ocular AEs

Ocular AEs in treated eyes (i.e., eyes treated in Study 20090) were reported in a total of 49 (49.0%) subjects, as summarized in Table 5–14. The proportion of subjects with ocular AEs in treated eyes was numerically higher in the aflibercept arm (51.5%) compared to the laser arm (44.1%). Ocular AEs in treated eyes were considered mild or moderate in intensity for the majority of subjects who had such events. Severe AEs were reported in 7 (10.6%) subjects in the aflibercept arm and in 3 (8.8%) subjects in the laser arm. Ocular SAEs occurred in 6 (9.1%) subjects in the aflibercept arm, while no ocular SAEs were reported in the laser arm. Regarding related AEs, 2 (3.0%) subjects in the aflibercept arm and 1 (2.9%) subject in the laser arm experienced aflibercept-related ocular AEs, 3 (4.5%) and 5 (14.7%) subjects, respectively, experienced laser-related ocular AEs, and 1 (2.9 %) subject in the laser arm had injection procedure-related ocular AEs. This is possible as there were participants in the laser arm that received aflibercept as rescue treatment as detailed in 4.6.1.

Table 5–14: Overall summary of number of subjects with ocular AEs in eyes treated in Study 20090 – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Number (%) of subjects with	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Any AE	**34 (51.5%)**	**15 (44.1%)**	**49 (49.0%)**
Maximum intensity for any AE			
Mild	20 (30.3%)	8 (23.5%)	28 (28.0%)
Moderate	7 (10.6%)	4 (11.8%)	11 (11.0%)
Severe	7 (10.6%)	3 (8.8%)	10 (10.0%)
Any AE related to aflibercept	2 (3.0%)	1 (2.9%)	3 (3.0%)
Maximum intensity for aflibercept-related AE			
Moderate	0	1 (2.9%)	1 (1.0%)
Severe	2 (3.0%)	0	2 (2.0%)
Any AE related to laser photocoagulation	3 (4.5%)	5 (14.7%)	8 (8.0%)
Maximum intensity for laser photocoagulation-related AE			
Mild	1 (1.5%)	2 (5.9%)	3 (3.0%)
Moderate	0	2 (5.9%)	2 (2.0%)
Severe	2 (3.0%)	1 (2.9%)	3 (3.0%)
Any AE related to injection procedure	0	1 (2.9%)	1 (1.0%)
Any AE related to procedures required by the protocol	0	0	0
Any SAE	**6 (9.1%)**	**0**	**6 (6.0%)**
Any SAE related to aflibercept	1 (1.5%)	0	1 (1.0%)
Any SAE related to laser photocoagulation	0	0	0
Any SAE related to injection procedure	0	0	0
Any SAE related to procedures required by the protocol	0	0	0
AE with outcome death	0	0	0

Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
SAEs from Study 20090 ongoing at the time of informed consent for Study 20275 were re-entered for Study 20275.
AEs in treated eye refer to AEs in eyes that received study treatment in Study 20090.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Relationship of AEs to aflibercept, photocoagulation, injection procedure or any other procedure required by the protocol is reported as assessed by the investigator.
Source: Table 8.3.1.1/1

Ocular AEs in eyes treated in Study 20090 for unilaterally and bilaterally treated subjects are provided in Table 8.3.1.1/2 and Table 8.3.1.1/3, respectively. For bilaterally treated subjects, the results were similar to those described above for unilaterally and bilaterally treated subjects. For unilaterally treated subjects, 1 (25.0%) subject in the aflibercept arm experienced ocular AEs, for which the maximum intensity was severe.

Non-ocular AEs

As summarized in Table 5–15, systemic AEs occurred in 88 (88.0%) subjects. The proportion of subjects experiencing systemic AEs was comparable between the aflibercept arm (89.4%) vs. the laser arm (85.3%). Systemic AEs were considered mild or moderate in intensity for the majority of subjects

who had such events, and severe AEs were reported in 13 (19.7%) subjects in the aflibercept arm and in 5 (14.7%) subjects in the laser arm. Systemic SAEs were reported in 23 (34.8%) subjects in the aflibercept arm and 16 (47.1%) subjects in the laser arm.

Table 5–15: Overall summary of number of subjects with systemic AEs – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Number (%) of subjects with	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Any AE	**59 (89.4%)**	**29 (85.3%)**	**88 (88.0%)**
Maximum intensity for any AE			
Mild	20 (30.3%)	7 (20.6%)	27 (27.0%)
Moderate	26 (39.4%)	17 (50.0%)	43 (43.0%)
Severe	13 (19.7%)	5 (14.7%)	18 (18.0%)
Any AE related to aflibercept	0	0	0
Any AE related to laser photocoagulation	0	0	0
Any AE related to injection procedure	0	0	0
Any AE related to procedures required by the protocol	0	0	0
Any SAE	**23 (34.8%)**	**16 (47.1%)**	**39 (39.0%)**
Any SAE related to aflibercept	0	0	0
Any SAE related to laser photocoagulation	0	0	0
Any SAE related to injection procedure	0	0	0
Any SAE related to procedures required by the protocol	0	0	0
AE with outcome death	**0**	**0**	**0**

Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
SAEs events from Study 20090 ongoing at the time of informed consent for Study 20275 were re-entered for Study 20275.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Relationship of AEs to aflibercept, photocoagulation, injection procedure or any other procedure required by the protocol is reported as assessed by the investigator.
Source: Table 8.3.1.3/1

Systemic AEs for unilaterally and bilaterally treated subjects are provided in Table 8.3.1.3/2 and Table 8.3.1.3/3, respectively. For bilaterally treated subjects, results were similar to those described above for unilaterally and bilaterally treated subjects. For unilaterally treated subjects, 4 (100%) subjects in the aflibercept arm and 1 (25%) subject in the laser arm experienced systemic AEs. In the aflibercept arm, the maximum intensity of the events was moderate in 3 (75%) subjects and severe in 1 (25%) subject. For the 1 (25%) subject in the laser arm, the maximum intensity of the events was moderate. Of the unilaterally treated subjects, 2 (50%) subjects in the aflibercept arm and 1 (25%) subject in the laser arm experienced systemic SAEs.

Analysis of AEs

Ocular AEs in treated eyes

The number of subjects with ocular AEs in treated eyes by SOC and PT is provided in Table 8.3.1.1/4. Overall, 49 (49.0%) subjects experienced ocular AEs, with 34 (51.5%) subjects in the aflibercept arm vs. 15 (44.1%) subjects in the laser arm. The affected primary SOCs were:

- Eye disorders in 45 (45.0%) subjects: aflibercept 32 (48.5%) vs. laser 13 (38.2%)
- Infections and infestations in 7 (7.0%) subjects: aflibercept 3 (4.5%) vs. laser 4 (11.8%)
- Nervous system disorders in 2 (2.0%) subjects: aflibercept 2 (3.0%) vs. no subjects in the laser arm
- Neoplasms benign, malignant and unspecified (incl cysts and polyps) in 1 (1.0%) subject: aflibercept 1 (1.5%) vs. no subjects in the laser arm.

The number of subjects with ocular AEs are presented by PT in Table 5–16. The most frequent ocular AEs in treated eyes, occurring in >10% of subjects in total, were Astigmatism (aflibercept 19.7% vs.

laser 17.6%), Strabismus (aflibercept 16.7% vs. laser 8.8%, and Myopia (aflibercept 13.6% vs. laser 11.8%). Ocular AEs in treated eyes were considered mild or moderate in intensity for the majority of subjects who had such events (Table 8.3.1.1/39). In the aflibercept arm, 7 (10.6%) subjects experienced ocular events of severe intensity, including Retinal detachment in 3 (4.5%) subjects, Optic atrophy and Pathologic myopia in 2 (3.0%) subjects each, and Astigmatism, Retinal neovascularization, Vitreous opacities, and Retinoblastoma in 1 (1.5%) subject each. In the laser arm, events of severe intensity were reported in 3 (8.8%) subjects, including Macular fibrosis, Myopia, and Pathologic myopia in 1 (2.9%) subject each.

Table 5–16: Number of subjects with ocular AEs in eyes treated in Study 20090 by PT – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Number (%) of subjects with at least one ocular AE	**34 (51.5%)**	**15 (44.1%)**	**49 (49.0%)**
Astigmatism	13 (19.7%)	6 (17.6%)	19 (19.0%)
Strabismus	11 (16.7%)	3 (8.8%)	14 (14.0%)
Myopia	9 (13.6%)	4 (11.8%)	13 (13.0%)
Amblyopia	3 (4.5%)	3 (8.8%)	6 (6.0%)
Optic atrophy	5 (7.6%)	1 (2.9%)	6 (6.0%)
Anisometropia	3 (4.5%)	2 (5.9%)	5 (5.0%)
Conjunctivitis	2 (3.0%)	3 (8.8%)	5 (5.0%)
Hypermetropia	2 (3.0%)	1 (2.9%)	3 (3.0%)
Pathologic myopia	2 (3.0%)	1 (2.9%)	3 (3.0%)
Retinal detachment	3 (4.5%)	0	3 (3.0%)
Retinal neovascularisation	3 (4.5%)	0	3 (3.0%)
Conjunctivitis allergic	2 (3.0%)	0	2 (2.0%)
Ocular hyperaemia	2 (3.0%)	0	2 (2.0%)
Refractive amblyopia	2 (3.0%)	0	2 (2.0%)
Adenoviral conjunctivitis	1 (1.5%)	0	1 (1.0%)
Blepharitis	1 (1.5%)	0	1 (1.0%)
Chalazion	0	1 (2.9%)	1 (1.0%)
Conjunctivitis bacterial	0	1 (2.9%)	1 (1.0%)
Dacryostenosis acquired	1 (1.5%)	0	1 (1.0%)
Epiretinal membrane	1 (1.5%)	0	1 (1.0%)
Heterophoria	1 (1.5%)	0	1 (1.0%)
Iris adhesions	1 (1.5%)	0	1 (1.0%)
IVth nerve paralysis	1 (1.5%)	0	1 (1.0%)
Macular fibrosis	0	1 (2.9%)	1 (1.0%)
Nystagmus	1 (1.5%)	0	1 (1.0%)
Refraction disorder	1 (1.5%)	0	1 (1.0%)
Retinal haemorrhage	1 (1.5%)	0	1 (1.0%)
Retinal vascular disorder	1 (1.5%)	0	1 (1.0%)
Retinoblastoma	1 (1.5%)	0	1 (1.0%)
Retinopathy of prematurity	1 (1.5%)	0	1 (1.0%)
VIth nerve paralysis	1 (1.5%)	0	1 (1.0%)
VIth nerve paresis	1 (1.5%)	0	1 (1.0%)
Vitreous opacities	1 (1.5%)	0	1 (1.0%)

A subject is counted only once within each preferred term or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
AEs in treated eye refer to AEs in eyes that received study treatment in Study 20090.
Source: Table 8.3.1.1/4

Ocular AEs in treated eyes for unilaterally and bilaterally treated subjects are provided by SOC and PT in Table 8.3.1.1/5 and Table 8.3.1.1/6, respectively. The respective data are shown by severity (maximum intensity) in Table 8.3.1.1/40 and Table 8.3.1.1/41. For bilaterally treated subjects, the results were very similar to those described above for bilaterally and unilaterally treated subjects. For unilaterally treated subjects, 1 (25.0%) subject in the aflibercept arm experienced ocular AEs in treated eyes reported within the SOCs of Eye disorders and Nervous system disorders. The maximum

intensity was severe for the events reported in the SOC Eye disorders and moderate for the events reported in Nervous system disorders.

Ocular AEs in non-treated eyes

For all 100 subjects who entered Study 20275, a total of 8 eyes (from 4 subjects in each arm) were not treated in Study 20090 (Table 8.3.1.2/1). In the aflibercept arm, 2 (50.0%) subjects experienced ocular AEs in non-treated eyes. The events were reported within the SOC Eye disorders in 1 (25.0%) subject (Astigmatism, Myopia, Optic atrophy, Pathologic myopia, and Strabismus), Infections and infestations in 1 (25.0%) subject (Conjunctivitis), and Nervous system disorders in 1 (25.0%) subject (Nystagmus and VIth nerve paresis). The maximum intensity was severe for the events reported in the SOC Eye disorders, mild for the event reported in Infections and infestations, and moderate for the event reported in Nervous system disorders (Table 8.3.1.2/4). In the laser arm, 1 (25.0%) subject experienced Adenovirus infection and Conjunctivitis (SOC Infections and infestations), both considered mild in intensity (Table 8.3.1.2/4). None of the events were serious (Table 8.3.1.2/2).

Ocular non-serious AEs in treated eyes

The number of subjects with ocular non-serious AEs in treated eyes by SOC and PT are summarized in Table 8.3.1.1/36 (unilaterally and bilaterally treated), Table 8.3.1.1/37 (unilaterally treated), and Table 8.3.1.1/38 (bilaterally treated). For one subject (aflibercept arm), macular fold observed in one eye at 1 and 2 years of age progressed to retinal detachment at 3, 4, and 5 years of age. The AE of retinal detachment was severe in intensity but considered non-serious. The outcome of the event was unknown. According to the investigator, the event was not related to aflibercept or laser photocoagulation.

Systemic AEs

The number of subjects with systemic AEs for subjects treated unilaterally and bilaterally in Study 20090 is provided by SOC and PT in Table 8.3.1.3/4. Overall, 88 (88.0%) subjects experienced systemic AEs, with 59 (89.4%) subjects in the aflibercept arm vs. 29 (85.3%) subjects in the laser arm. The most frequently affected (>20% of subjects in total) primary SOCs were:

• Infections and infestations in 74 (74.0%) subjects: aflibercept 51 (77.3%) vs. laser 23 (67.6%)

• Respiratory, thoracic and mediastinal disorders in 38 (38.0%) subjects: aflibercept 24 (36.4%) vs. laser 14 (41.2%)

• Nervous system disorders in 32 (32.0%) subjects: aflibercept 18 (27.3%) vs. laser 14 (41.2%)

• Gastrointestinal disorders in 29 (29.0%) subjects: aflibercept 18 (27.3%) vs. laser 11 (32.4%)

• General disorders and administration site conditions in 28 (28.0%) subjects: aflibercept 16 (24.2%) vs. laser 12 (35.3%) The 10 most frequently reported PTs in each arm are shown in Table 5–17.

The most frequent systemic AEs by PT, occurring in >10% of subjects in total, were Bronchitis, Pyrexia, Upper respiratory tract infection, Nasopharyngitis, COVID-19, Respiratory tract infection, Diarrhea, and Otitis media.

Table 5–17: Number of subjects with systemic AEs: 10 most frequent PTs in each arm – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Number (%) of subjects with at least one systemic AE	**59 (89.4%)**	**29 (85.3%)**	**88 (88.0%)**
Bronchitis	15 (22.7%)	8 (23.5%)	23 (23.0%)
Pyrexia	15 (22.7%)	8 (23.5%)	23 (23.0%)
Upper respiratory tract infection	15 (22.7%)	7 (20.6%)	22 (22.0%)
Nasopharyngitis	16 (24.2%)	4 (11.8%)	20 (20.0%)
COVID-19	8 (12.1%)	8 (23.5%)	16 (16.0%)
Respiratory tract infection	11 (16.7%)	4 (11.8%)	15 (15.0%)
Diarrhoea	7 (10.6%)	5 (14.7%)	12 (12.0%)
Otitis media	8 (12.1%)	3 (8.8%)	11 (11.0%)
Constipation	8 (12.1%)	2 (5.9%)	10 (10.0%)
Speech disorder developmental	6 (9.1%)	4 (11.8%)	10 (10.0%)
Developmental delay	4 (6.1%)	5 (14.7%)	9 (9.0%)
Cerebral palsy	3 (4.5%)	5 (14.7%)	8 (8.0%)
Rhinitis	7 (10.6%)	1 (2.9%)	8 (8.0%)
Bronchospasm	1 (1.5%)	4 (11.8%)	5 (5.0%)

A subject is counted only once within each PT or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
* In 12 of the 16 aflibercept arm subjects and 3 of the 4 laser arm subjects, nasopharyngitis was reported in the context of common cold (Section 10.2.7.1).
Source: Table 8.3.1.3/4

The number of subjects who experienced systemic AEs by SOC and PT for unilaterally and bilaterally treated subjects are provided in Table 8.3.1.3/5 and Table 8.3.1.3/6, respectively.

Aflibercept related AEs

Aflibercept-related ocular AEs in treated eyes

Aflibercept-related ocular AEs in treated eyes were reported in 2 (3.0%) subjects in the aflibercept arm and in 1 (2.9%) subject in the laser arm (Table 5–18). Of the 2 subjects in the aflibercept arm, 1 subject experienced Retinal detachment and Iris adhesions, and the other subject reported Astigmatism. Iris adhesions were mild in intensity, considered non serious, and were not resolved. The subject with Astigmatism had 2 events, one in each eye, assessed as moderate and severe in intensity, respectively. The severe event was assessed as related to both aflibercept and laser treatment by the investigator. Both events of Astigmatism were non-serious and were not resolved. In the laser arm, Macular fibrosis of moderate intensity was reported for the subject in the laser arm who received aflibercept rescue treatment. The event was considered non-serious and was not resolved (Table 5–18). All 3 subjects were treated bilaterally.

Table 5–18: Number of subjects with aflibercept-related ocular AEs in eyes treated in Study 20090 by primary SOC and PT – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Primary system organ class Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Number (%) of subjects with at least one AE	**2 (3.0%)**	**1 (2.9%)**	**3 (3.0%)**
Eye disorders	2 (3.0%)	1 (2.9%)	3 (3.0%)
Astigmatism	1 (1.5%)	0	1 (1.0%)
Iris adhesions	1 (1.5%)	0	1 (1.0%)
Macular fibrosis	0	1 (2.9%)	1 (1.0%)
Retinal detachment	1 (1.5%)	0	1 (1.0%)

AEs are sorted in alphabetical order by primary SOC and PT.
A subject is counted only once within each PT or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
AEs in treated eye refers AEs in eyes that received study treatment in Study 20090.
Relationship of AEs to aflibercept is reported as assessed by the investigator.
Source: Table 8.3.1.1/12

Aflibercept-related non-ocular (systemic) AEs

There were no aflibercept-related systemic AEs reported in Study 20275 (Tables 8.3.1.3/12 through 8.3.1.3/14).

Injection procedure related AEs

Injection-procedure-related ocular AEs in treated eyes

Injection-procedure-related ocular AEs in treated eyes occurred in 1 (2.9%) subject in the laser arm, for whom Macular fibrosis was reported (Table 5–19). The event was also assessed as aflibercept-related by the investigator (see Section 5.2.2.2.3.1 for more details).

Table 5–19: Number of subjects with injection procedure-related ocular AEs in eyes treated in Study 20090 by primary SOC and PT – unilaterally and bilaterally treated subjects in Study 20090) (all enrolled subjects)

Primary system organ class Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Number (%) of subjects with at least one AE	**0**	**1 (2.9%)**	**1 (1.0%)**
Eye disorders	0	1 (2.9%)	1 (1.0%)
Macular fibrosis	0	1 (2.9%)	1 (1.0%)

AEs are sorted in alphabetical order by primary SOC and PT.
A subject is counted only once within each PT or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
AEs in treated eye refers AEs in eyes that received study treatment in Study 20090.
Relationship of AEs to injection procedure is reported as assessed by the investigator.
Source: Table 8.3.1.1/15

Injection-procedure-related non-ocular (systemic) AEs

There were no injection-procedure-related systemic AEs reported in Study 20275 (Tables 8.3.1.3/15 through 8.3.1.3/17).

Laser related AEs

Laser-related ocular AEs in treated eyes

Laser photocoagulation-related ocular AEs in treated eyes were reported in 3 (4.5%) subjects in the aflibercept arm and in 5 (14.7%) subjects in the laser arm, among which Myopia was the most frequently reported event: 1 (1.5%) subject in the aflibercept arm and 4 (11.8%) in the laser arm (Table 5–20). All 8 subjects were treated bilaterally in Study 20090 (Tables 8.3.1.1/19 and 8.3.1.1/20). Laser-related severe Myopia was reported in 1 subject in each arm and laser-related severe Astigmatism was reported in 1 subject in the aflibercept arm. All other laser-related ocular AEs in treated eyes were considered mild or moderate in intensity. The events were not resolved for the majority of the laser-related ocular AEs in treated eyes.

Laser-related non-ocular (systemic) AEs

There were no laser-related systemic AEs reported in Study 20275 (Tables 8.3.1.3/18 through 8.3.1.3/20).

Table 5–20: Number of subjects with laser photocoagulation-related ocular AEs in eyes treated in Study 20090 by primary SOC and PT – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Primary system organ class Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Number (%) of subjects with at least one AE	**3 (4.5%)**	**5 (14.7%)**	**8 (8.0%)**
Eye disorders	3 (4.5%)	5 (14.7%)	8 (8.0%)
Amblyopia	0	1 (2.9%)	1 (1.0%)
Anisometropia	0	2 (5.9%)	2 (2.0%)
Astigmatism	1 (1.5%)	1 (2.9%)	2 (2.0%)
Myopia	1 (1.5%)	4 (11.8%)	5 (5.0%)
Pathologic myopia	1 (1.5%)	0	1 (1.0%)
Refractive amblyopia	1 (1.5%)	0	1 (1.0%)

AEs are sorted in alphabetical order by primary SOC and PT.
A subject is counted only once within each PT or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
AEs in treated eye refers AEs in eyes that received study treatment in Study 20090.
Relationship of AEs to laser photocoagulation is reported as assessed by the investigator.
Source: Table 8.3.1.1/18

Deaths, serious adverse events, and other significant adverse events

Deaths

No deaths were reported during Study 20275.

Serious adverse events

Ocular SAE in treated eyes Ocular

SAEs in treated eyes occurred in 6 (9.1%) subjects in the aflibercept arm only. All 6 subjects were treated bilaterally in Study 20090. The affected primary SOCs were Eye disorders in 5 (7.6%) subjects and Neoplasms benign, malignant and unspecified (incl. cysts and polyps) in 1 (1.5%) subject (Table 5–21, Tables 8.3.1.1/9 and 8.3.1.1/10). The ocular SAEs in treated eyes were Optic atrophy, Retinal detachment and Retinal neovascularization, each in 2 (3.0%) subjects, and Retinopathy of prematurity, Vitreous opacities, and Retinoblastoma, each in 1 (1.5%) subject. Ocular SAEs were assessed as unrelated to 20090 study treatment by the investigator in all but one subject with Retinal detachment (Tables 8.3.1.1/24 and 8.3.1.1/30). The maximum intensity of the ocular SAEs in treated eyes was mild and moderate in 1 (1.5%) subject each, and severe in 4 (6.1%) subjects (Table 8.3.1.1/45). A summary of the ocular SAEs is provided below. One subject (aflibercept arm)

experienced Retinal detachment of severe intensity in one eye. The outcome was reported as not recovered/not resolved. The investigator considered the event to be related to aflibercept. The subject also experienced Optic atrophy of mild intensity in one eye. The outcome was reported as not recovered/resolved. The investigator considered the event not related to aflibercept. One subject (aflibercept arm) experienced worsening of ROP of moderate intensity in both eyes and was treated with laser photocoagulation. The outcome was reported as recovered/resolved for one eye and recovered/resolved with sequelae for another eye (macular fold). The investigator considered the events not related to aflibercept. One subject (aflibercept arm) experienced Retinal neovascularisation and Vitreous opacities in one eye, both of severe intensity. The outcome was reported as recovered/resolved for the Vitreous opacities and recovered/resolved with sequelae for the Retinal neovascularisation. The investigator considered both events not related to aflibercept. One subject (aflibercept arm) experienced Retinal neovascularization of mild intensity in both eyes and was treated with laser photocoagulation. The outcomes were reported as recovered/resolved for both events. The investigator considered the events not related to aflibercept. One subject (aflibercept arm) was diagnosed with Retinoblastoma in both eyes. The maximum intensity was moderate for the event in the one and severe for the event in another eye. The outcome was reported as not recovered/not resolved for the event in both eyes. Resection surgery (enucleation surgery was performed) was performed in one eye. The investigator considered both events not related to aflibercept. One subject (aflibercept arm) experienced Retinal detachment of severe intensity in both eyes. The outcome was reported as recovering/resolving for the event of one eye and recovered/resolved for the event of another eye (vitrectomy was performed). The subject also experienced Optic atrophy of severe intensity in one eye. The outcome was reported as not recovered/resolved. The investigator considered all the events not related to aflibercept.

Table 5–21: Number of subjects with ocular SAEs in eyes treated in Study 20090 by primary SOC and PT – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Primary system organ class Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%)	Total N=100 (100%)
Number (%) of subjects with at least one SAE	**6 (9.1%)**	**0**	**6 (6.0%)**
Eye disorders	5 (7.6%)	0	5 (5.0%)
Optic atrophy	2 (3.0%)	0	2 (2.0%)
Retinal detachment	2 (3.0%)	0	2 (2.0%)
Retinal neovascularisation	2 (3.0%)	0	2 (2.0%)
Retinopathy of prematurity	1 (1.5%)	0	1 (1.0%)
Vitreous opacities	1 (1.5%)	0	1 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.5%)	0	1 (1.0%)
Retinoblastoma	1 (1.5%)	0	1 (1.0%)

AEs are sorted in alphabetical order by primary SOC and PT.
A subject is counted only once within each PT or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
AEs in treated eye refer AEs in eyes that received study treatment in Study 20090.
Source: Table 8.3.1.1/8

Ocular SAEs in non-treated eyes

There were no subjects with ocular SAEs in non-treated eyes (Table 8.3.1.2/2).

Non-ocular (systemic) SAEs Systemic

SAEs occurred in 23 (34.8%) subjects in the aflibercept arm and in 16 (47.1%) subjects in the laser arm (Table 5–22). The most frequently affected (>5% of subjects in total) primary SOCs were:

• Infections and infestations in 18 (18.0%) subjects: aflibercept 11 (16.7%) vs. laser 7 (20.6%)

• Nervous system disorders in 10 (10.0%) subjects: aflibercept 6 (9.1%) vs. laser 4 (11.8%)

• Congenital, familial and genetic disorders in 9 (9.0%) subjects: aflibercept 5 (7.6%) vs. laser 4 (11.8%)

• Respiratory, thoracic and mediastinal disorders in 7 (7.0%) subjects: aflibercept 3 [4.5%] vs. laser 4 (11.8%).

The most frequently reported systemic SAE was Cerebral palsy, affecting 3 (4.5%) subjects in the aflibercept arm vs. 4 (11.8%) in the laser arm. Overall, the events reported in the aflibercept arm in the SOC Nervous system disorders had plausible explanations in line with Clinical Study Report, the population under study with underlying prematurity such as medical history of intraventricular hemorrhage, or infantile apnea. All systemic SAEs were assessed as unrelated to 20090 study treatment by the investigator (Tables 8.3.1.3/24 and 8.3.1.3/30). Systemic SAEs were considered mild or moderate in intensity for the majority of subjects who had such events (Table 8.3.1.3/45). Systemic SAEs of severe intensity were reported in 10 (15.2%) subjects in the aflibercept arm and in 3 (8.8%) subjects in the laser arm.

Table 5–22: Number of subjects with systemic SAEs by primary SOC and PT – unilaterally and bilaterally treated subjects in Study 20090 (all enrolled subjects)

Primary system organ class Preferred term MedDRA version 28.0	Aflibercept N=66 (100%)	Laser N=34 (100%	Total N=100 (100%)
Number (%) of subjects with at least one AE	**23 (34.8%)**	**16 (47.1%)**	**39 (39.0%)**
Congenital, familial and genetic disorders	5 (7.6%)	4 (11.8%)	9 (9.0%)
Cerebral palsy	3 (4.5%)	4 (11.8%)	7 (7.0%)
Craniosynostosis	1 (1.5%)	0	1 (1.0%)
Cryptorchism	1 (1.5%)	0	1 (1.0%)
Ear and labyrinth disorders	1 (1.5%)	1 (2.9%)	2 (2.0%)
Deafness neurosensory	1 (1.5%)	1 (2.9%)	2 (2.0%)
Gastrointestinal disorders	1 (1.5%)	2 (5.9%)	3 (3.0%)
Abdominal pain upper	0	1 (2.9%)	1 (1.0%)
Ileus	0	1 (2.9%)	1 (1.0%)
Inguinal hernia	1 (1.5%)	1 (2.9%)	2 (2.0%)
General disorders and administration site conditions	0	1 (2.9%)	1 (1.0%)
Pyrexia	0	1 (2.9%)	1 (1.0%)
Hepatobiliary disorders	1 (1.5%)	0	1 (1.0%)
Cholelithiasis	1 (1.5%)	0	1 (1.0%)
Infections and infestations	11 (16.7%)	7 (20.6%)	18 (18.0%)
Bronchiolitis	2 (3.0%)	2 (5.9%)	4 (4.0%)
Bronchitis	2 (3.0%)	1 (2.9%)	3 (3.0%)
COVID-19	0	1 (2.9%)	1 (1.0%)
Gastroenteritis	1 (1.5%)	0	1 (1.0%)
Gastroenteritis bacterial	1 (1.5%)	0	1 (1.0%)
Lower respiratory tract infection	1 (1.5%)	1 (2.9%)	2 (2.0%)
Lower respiratory tract infection viral	1 (1.5%)	0	1 (1.0%)
Otitis media	2 (3.0%)	0	2 (2.0%)
Pneumonia	3 (4.5%)	0	3 (3.0%)
Pneumonia adenoviral	0	1 (2.9%)	1 (1.0%)
Pneumonia bacterial	1 (1.5%)	0	1 (1.0%)
Respiratory syncytial virus bronchiolitis	0	1 (2.9%)	1 (1.0%)
Respiratory tract infection viral	1 (1.5%)	0	1 (1.0%)
Rotavirus infection	0	1 (2.9%)	1 (1.0%)
Tracheobronchitis	0	1 (2.9%)	1 (1.0%)
Viral upper respiratory tract infection	0	1 (2.9%)	1 (1.0%)
Injury, poisoning and procedural complications	1 (1.5%)	0	1 (1.0%)
Subdural haematoma	1 (1.5%)	0	1 (1.0%)

Metabolism and nutrition disorders	1 (1.5%)	0	1 (1.0%)
Malnutrition	1 (1.5%)	0	1 (1.0%)
Musculoskeletal and connective tissue disorders	1 (1.5%)	0	1 (1.0%)
Rhabdomyolysis	1 (1.5%)	0	1 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (2.9%)	1 (1.0%)
Spinal cord lipoma	0	1 (2.9%)	1 (1.0%)
Nervous system disorders	6 (9.1%)	4 (11.8%)	10 (10.0%)
Bell's palsy	0	1 (2.9%)	1 (1.0%)
Cerebellar atrophy	1 (1.5%)	0	1 (1.0%)
Cognitive disorder	1 (1.5%)	1 (2.9%)	2 (2.0%)
Dystonia	0	1 (2.9%)	1 (1.0%)
Focal dyscognitive seizures	1 (1.5%)	0	1 (1.0%)
Gross motor delay	1 (1.5%)	0	1 (1.0%)
Headache	0	1 (2.9%)	1 (1.0%)
Hypotonia	2 (3.0%)	0	2 (2.0%)
Infantile spasms	1 (1.5%)	0	1 (1.0%)
Intellectual disability	1 (1.5%)	1 (2.9%)	2 (2.0%)
Motor developmental delay	1 (1.5%)	0	1 (1.0%)
Psychiatric disorders	1 (1.5%)	0	1 (1.0%)
Autism spectrum disorder	1 (1.5%)	0	1 (1.0%)
Respiratory, thoracic and mediastinal disorders	3 (4.5%)	4 (11.8%)	7 (7.0%)
Adenoidal hypertrophy	1 (1.5%)	0	1 (1.0%)
Aspiration	0	1 (2.9%)	1 (1.0%)
Asthma	0	1 (2.9%)	1 (1.0%)
Atelectasis	0	1 (2.9%)	1 (1.0%)
Bronchopulmonary disease	1 (1.5%)	0	1 (1.0%)
Bronchopulmonary dysplasia	1 (1.5%)	0	1 (1.0%)
Bronchospasm	0	2 (5.9%)	2 (2.0%)

AEs are sorted in alphabetical order by primary SOC and PT.
A subject is counted only once within each PT or any primary SOC.
Table presents AEs since baseline of Study 20275 through 5 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Source: Table 8.3.1.3/8

The number of subjects who experienced serious systemic events for unilaterally and bilaterally treated subjects can be found in Table 8.3.1.3/9 and Table 8.3.1.3/10, respectively. These data are shown by intensity in Table 8.3.1.3/46 and Table 8.3.1.3/47, respectively. Results among bilaterally treated subjects were very similar to those presented in Table 5–22 for unilaterally and bilaterally treated subjects. Among unilaterally treated subjects, Otitis media was reported in 2 (50.0%) subjects, and Bronchitis, Focal dyscognitive seizures and Adenoidal hypertrophy were each reported in 1 (25.0%) subject in the aflibercept arm and Inguinal hernia was reported in 1 (25.0%) subject in the laser arm.

Discontinuations and/or dose modifications due to adverse events

Not applicable.

Surgical procedures after start of Study 20275

Ocular surgical procedures

In the aflibercept arm, 5 (7.6%) subjects underwent a total of 9 ocular surgical procedures after the start of Study 20275 (Tables 8.3.4.1/1 and 8.3.4.1/2). These included laser coagulation therapy (3 subjects), as well as external beam radiation therapy, resection, and other ocular surgical procedure (each performed in 1 subject). No ocular surgical procedures were reported in the laser arm. General anesthesia was administered in 7 of the ocular surgical procedures and general anesthesia with

respiratory assistance was administered in the remaining 2 ocular surgical procedures. Most ocular surgical procedures were performed between the study start and 1 year of age. No procedures were reported after 3 years of age.

Non-Ocular surgeries procedures

After the start of Study 20275, 20 (30.3%) subjects in the aflibercept arm underwent a total of 31 non-ocular surgical procedures and 9 (26.5%) subjects in the laser arm underwent a total of 14 non-ocular surgical procedures (Tables 8.3.4.1/3 and 8.3.4.1/4). The most common surgical procedure was Surgery performed in 10 (15.2%) subjects in the aflibercept arm and in 6 (17.6%) subjects in the laser arm. General anesthesia was administered in 26 of the surgical procedures in the aflibercept arm and 10 of the surgical procedures in the laser arm. General anesthesia with respiratory assistance, local anesthesia, and other type of anesthesia were used in the rest of the procedures. In the aflibercept arm, 4 (6.8%) subjects had non ocular surgical procedures between 4 and 5 years of age.

Ophthalmic examination

Abnormal findings in the posterior segment other than ROP

Abnormal findings in the posterior segment other than ROP are provided in Table 8.3.4.2/1 by visit and arm. At screening/baseline, the proportion of eyes with abnormal findings was low and similar between the 2 arms (aflibercept 6.9% vs. laser 6.1%). From screening/baseline onwards through 2 years of age, the proportion of eyes with abnormal findings remained low but was relatively higher in the aflibercept arm compared to the laser arm (2 years: aflibercept 8.3% vs. laser 4.9%). From 3 years through 5 years of age, the proportion of eyes with abnormal findings was relatively higher in the laser arm, with a decrease over time observed in the aflibercept arm, while the proportion remained unchanged in the laser arm (3 years: aflibercept 3.6% vs. laser 8.6%, 4 years: aflibercept 2.8% vs. laser 8.6%, and 5 years: aflibercept 0.9% vs. laser 8.6%). At 5 years of age, 1 (1.8%) subject in the aflibercept arm had abnormal findings in the posterior segment other than ROP in 1 (0.9%) eye, which was also considered clinically significant by the investigator: optic atrophy. In the laser arm, 3 (10.0%) subjects had abnormal findings in the posterior segment other than ROP in 5 (8.6%) eyes, of which 1 subject had abnormal findings considered clinically significant by the investigator: aphakia and vitreous loss in one eye, and macular fibrosis in both eyes. However, the majority of clinically significant abnormal findings do not reflect posterior segment abnormalities other than ROP but rather sequelae of the underlying ROP.

Abnormal findings in the anterior segment

Abnormal findings in the anterior segment are provided in Table 8.3.4.2/2 by visit and arm. At screening/baseline, abnormal findings were reported in 1 (2.0%) eye in the laser arm only. From screening/baseline onwards through 5 years of age, the proportion of eyes with abnormal findings remained low in both arms. At 5 years of age, 2 (3.6%) subjects in the aflibercept arm had abnormal findings in the anterior segment in 2 (1.9%) eyes, of which 1 (1.8%) subject had clinically significant abnormal findings in 1 (0.9%) eye. In the laser arm, 1 (3.3%) subject had abnormal findings in the anterior segment in 1 (1.7%) eye, which was also considered clinically significant by the investigator.

Physical examinations and vital signs

Weight

Summary statistics for weight and changes from screening/baseline are provided in Table 8.3.4.3/6 by visit and arm. Mean values were similar in both arms at screening/baseline (aflibercept 6.68 ± 1.15 kg vs. laser 6.35 ± 1.15 kg) and remained comparable between the arms through 5 years of age (aflibercept 16.93 ± 3.12 kg vs. laser 17.21 ± 3.25 kg). As expected, weight increased with increasing age.

Body length (height)

Summary statistics for body length (height) and changes from screening/baseline are provided in Table 8.3.4.3/7 by visit and arm. Mean values were similar in both arms at screening/baseline (aflibercept 64.65 ± 4.20 cm vs. laser 63.22 ± 4.20 cm) and remained comparable between the arms through 5 years of age (aflibercept 106.76 ± 4.31 cm vs. laser 107.09 ± 5.42 cm). As expected, height increased with increasing age. Head circumference Summary statistics for head circumference and changes from screening/baseline are provided in Table 8.3.4.3/8 by visit and arm.

Head circumference

Head circumference was monitored until 3 years of age (Visit 4). Mean values were similar in both arms at screening/baseline (aflibercept 41.24 ± 2.38 cm vs. laser 41.68 ± 2.25 cm) and remained comparable between the arms through 3 years of age (aflibercept 47.42 ± 1.88 cm vs. laser 48.21 ± 2.21 cm). As expected, head circumference increased with increasing age.

Temperature

Summary statistics for temperature and changes from screening/baseline are provided in Table 8.3.4.3/1 by visit and arm. Mean values were almost identical in both arms at screening/baseline (aflibercept 36.61 ± 0.33 °C vs. laser 36.60 ± 0.41 °C) and remained stable over time.

Heart rate

Heart rate Summary statistics for heart rate and changes from screening/baseline are provided in Table 8.3.4.3/2 by visit and arm. Mean values were similar in both arms at screening/baseline (aflibercept 125.3 ± 18.8 beats/min vs. laser 127.5± 18.0 beats/min) and remained comparable between the arms through 5 years of age (aflibercept 93.7 ± 13.6 beats/min vs. laser 90.8 ± 15.9 beats/min). As expected, heart rate decreased with increasing age.

Respiratory rate

Respiratory rate Summary statistics for respiratory rate and changes from screening/baseline are provided in Table 8.3.4.3/3 by visit and arm. Mean values were similar in both arms at screening/baseline (aflibercept 39.3 ± 10.1 breaths/min vs. laser 38.9 ± 10.1 breaths/min) and remained comparable between the arms through 5 years of age (aflibercept 24.3 ± 3.8 breaths/min vs. laser arm 25.9 ± 3.3 breaths/min). As expected, respiratory rate decreased with increasing age.

Systolic blood pressure

Systolic blood pressure Summary statistics for systolic blood pressure and changes from screening/baseline are provided in Table 8.3.4.3/4 by visit and arm. Mean values were generally comparable between the arms from screening/baseline (aflibercept 90.1 ± 11.2 mmHg vs. laser 86.6 ± 13.6 mmHg) through 5 years of age (aflibercept 96.8 ± 9.4 mmHg vs. laser 97.2 ± 13.7 mmHg).

Minor changes in mean systolic blood pressure were observed over time in both arms but were not considered clinically relevant.

Diastolic blood pressure

Diastolic blood pressure Summary statistics for diastolic blood pressure and changes from screening/baseline are provided in Table 8.3.4.3/5 by visit and arm. Mean values were generally comparable between the arms from screening/baseline (aflibercept 53.6 ± 10.2 mmHg vs. laser 49.1 ± 14.1 mmHg) through 5 years of age (aflibercept 60.9 ± 8.1 mmHg vs. laser 61.1 ± 12.9 mmHg). Minor changes in mean diastolic blood pressure were observed over time in both arms but were not considered clinically relevant

Hearing tests

Hearing tests were conducted at screening/baseline and at 5 years of age. The preferred hearing test for screening/baseline was a brainstem auditory evoked response (BAER), also referred to as an auditory brainstem response (ABR), using electrodes placed on the child's head and ears to generate a response. At 5 years, the choice of the tool was to consider the child's age, degree of cooperation, and available resources. The number of subjects with abnormal findings, as judged by the investigator, is provided in Table 8.3.4.4/1 by visit and hearing test type. Subjects could have multiple tests per visit. Overall, the proportion of subjects with any abnormal finding, irrespective of the hearing test type, was comparable between the arms both at screening/baseline and at 5 years of age (Table 5–23).

Table 5–23: Number of subjects and ears with any abnormal findings in hearing test by visit (all enrolled subjects)

	Aflibercept N=66	Laser N=34	Total N=100
Screening/baseline			
Number of tested subjects	66 (100.0%)	32 (100.0%)	98 (100.0%)
Abnormal findings in any ear	8 (12.1%)	5 (15.6%)	13 (13.3%)
Number of tested ears	132 (100.0%)	64 (100.0%)	196 (100.0%)
Abnormal findings	14 (10.6%)	8 (12.5%)	22 (11.2%)
5 years of chronological age			
Number of tested subjects	46 (100.0%)	23 (100.0%)	69 (100.0%)
Abnormal findings in any ear	7 (15.2%)	4 (17.4%)	11 (15.9%)
Number of tested ears	92 (100.0%)	46 (100.0%)	138 (100.0%)
Abnormal findings	12 (13.0%)	7 (15.2%)	19 (13.8%)

Abnormal result in any performed hearing test is summarized, i.e., irrespective of the test type (Otoacoustic Emissions, Auditory Brainstem Response, Audiometry, or Other).
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Source: Table 8.3.4.4/1

Neurodevelopmental test outcomes at 5 years of chronological age using standardized tests

Neurodevelopmental tests were administered throughout the study as follows:

• Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) was optional at Visits 1 and 2 and mandatory at 2 years of age (Visit 3). Descriptive and categorical summary data are provided in Sections 8.3.5.1 and 8.3.5.2, respectively, and the results were summarized in the 2-year report (PH-42724). At 2 years of age, no relevant differences between the treatment arms were seen for any of the BSID-III scores.

• Vineland Adaptive Behavior Scales, Second Edition (VABS-II) was optional at Visits 4 and 5 and mandatory at 2 and 5 years of age (Visits 3 and 6).

• Either Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI IV) or Differential Ability Scales, Second Edition (DAS-II) were optional at Visits 4 and 5 and one of the two was mandatory at 5 years of age (Visit 6). As no investigator administered DAS-II, this test is not applicable for this report (Table 8.3.5.7/1).

WPPSI-IV test at 5 years of chronological age

The administration of the WPPSI-IV test at 5 years of age was mandatory. The test framework and the calculation of age-corrected standard scores (scaled scores and composites scores) from investigator-reported raw scores are detailed in the SAP (Section 10.1.9). Descriptive summaries of age-corrected scaled scores by subtests (receptive vocabulary, information, picture naming, block design, object assembly, picture memory, matrix reasoning, bug search, similarities, picture concepts, cancellation and zoo locations) by visit and arm are provided in Tables 8.3.5.3/1 to 8.3.5.3/12, respectively. Subgroup analyses based on body weight at birth, gestational age at birth, APGAR score 5 min after birth, and O2 supplementation at Study 20090 entry are provided in Tables 8.3.5.3/13 to 8.3.5.3/60. Descriptive summaries for the age-corrected composite scores (Verbal Comprehension Index, Visual Spatial Index, Fluid Reasoning Index, Processing Speed Index, Working Memory Index, Full Scale Intelligence Quotient) by visit and arm are provided in Tables 8.3.5.3/61 to 8.3.5.3/66, respectively, and subgroup analyses are provided in Tables 8.3.5.3/67 to 8.3.5.3/90. Qualitative descriptions of the composite scores by visit and arm are provided in Table 8.3.5.4/1 and subgroups analyses are provided from Tables 8.3.5.4/2 to 8.3.5.4/5. Depending on the subtest, WPPSI-IV (sub-)test scores at 5 years of age were analyzed for 40 to 48 subjects of the 66 subjects in the aflibercept arm and for 27 to 30 of the 34 subjects in the laser arm. The data were not available for subjects who discontinued the study (7 subjects in the aflibercept arm and 4 in the laser arm). In the aflibercept arm, other reasons for missing scores or exclusion from the analysis included tests performed outside of the specified time window (4 subjects) and other operational reasons (1 subject), as well as mental/developmental/neurological disorders (3 subjects), AEs (1 subject), and lack of cooperation (1 subject). No relevant differences between the arms were seen for any of the scores (mean Full Scale IQ: aflibercept 83.25 ± 23.61 vs. laser 81.50 ± 20.21) overall and across the subgroups (Table 5–25).

Table 5–25: Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) composite scores at 5 years of chronological age (all enrolled subjects)

	Aflibercept N=66 (100%)		Laser N=34 (100%)	
	n	Mean (SD)	n	Mean (SD)
Verbal Comprehension Index	46	79.98 (20.22)	29	80.52 (16.80)
Visual Spatial Index	48	92.54 (26.82)	30	91.03 (24.30)
Fluid Reasoning Index	41	94.00 (16.57)	29	87.48 (19.79)
Processing Speed Index	40	92.25 (17.81)	27	80.96 (17.45)
Working Memory Index	43	98.51 (21.65)	29	94.45 (19.15)
Full Scale IQ	48	83.25 (23.61)	30	81.50 (20.21)

The test was optional at 3 years and at 4 years of chronological age and mandatory at 5 years of chronological age.
Raw scores reported by investigators were converted to age-adjusted scaled scores as per test manual.
Scores determined as per WPSSI-IV Technical and Interpretive Manual. Composite scores are scaled to a metric with a mean of 100, and a standard deviation of 15.
Fluid Reasoning Index and Processing Speed Index are applicable to children of ≥4 years of chronological age.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
Source: Table 8.3.5.3/61 to Table 8.3.5.3/66

VABS-II test at 5 years of chronological age

The administration of the VABS-II test at 5 years of age was mandatory. This parent/caregiver interview assessed the domains of Communication, Daily Living Skills, Socialization, and Motor Skills, with subdomains of receptive, expressive and written communication, of personal, domestic and

community daily living skills, of interpersonal relationships, play and leisure time and coping skills socialization, and of fine motor and gross motor skills. The test framework and the calculation of V-scale scores by subdomains, standard domain scores and the standard adaptive behavior composite score are detailed in the SAP (Section 10.1.9). Descriptive summaries of standard scores for each domain and adaptive behavior composite scores by visit and arm are provided in Tables 8.3.5.5/1 to 8.3.5.5/5. Subgroup analyses based on body weight at birth, gestational age at birth, APGAR score 5 min after birth, and oxygen (O2) supplementation at Study 20090 entry are provided in Tables 8.3.5.5/6 to 8.3.5.5/25. As VABS-II was not available in all subjects' native languages, an additional subgroup analysis for the communication domain was performed for subjects without non-adaptable items vs. with non-adaptable items as a sensitivity analysis. The standard scores for communication domain and adaptive behavior composite scores by subjects with non adaptable items is provided in Table 8.3.5.5/26. Descriptive summaries of V-scale scores for the subdomains by visit and arm are provided in Tables 8.3.5.5/27 to 8.3.5.5/37 and subgroup analyses are provided in Tables 8.3.5.5/38 to 8.3.5.5/81. Categorical summary for the domain scores and adaptive behavior composite scores by visit and arm are provided in Table 8.3.5.6/1 and subgroup analyses are provided in Tables 8.3.5.6/2 to 8.3.5.6/5. VABS-II test scores at 5 years of age were analyzed for 52 of the 66 subjects in the aflibercept arm and for 29 of the 34 subjects in the laser arm. The data were missing or excluded from the analysis for some subjects, mainly due to discontinuation of the study prior to Visit 6 (7 subjects in the aflibercept arm and 4 in the laser arm), tests being performed outside of the specified time window (4 subjects in the aflibercept arm and 1 in the laser arm), and other operational reasons (1 subject in the aflibercept arm). Additionally, the tests were not performed for subjects in the aflibercept arm due to AEs (1 subject) and lack of cooperation (1 subject). Mean domain scores and the mean adaptive behavior composite score (aflibercept 73.67 ± 22.39 vs. laser 72.72 ± 17.50) were comparable between the aflibercept arm and the laser arm overall and across the subgroups (Table 5–24). In both arms, the majority of subjects were categorized as with moderately low or low adaptive levels for all the domain scores and the adaptive behavior composite score (Table 8.3.5.6/1).

Table 5–24: Vineland Adaptive Behaviour Scales, Second Edition (VABS-II) domain and adaptive behavior composite standard scores at 5 years of chronological age (all enrolled subjects)

	Aflibercept N=66 (100%)		Laser N=34 (100%)	
	n	Mean (SD)	n	Mean (SD)
Communication [a]	52	75.23 (24.79)	29	73.41 (15.94)
Daily Living Skills	52	76.98 (18.28)	29	78.52 (14.09)
Socialization	52	76.00 (21.17)	29	74.38 (19.79)
Motor Skills	52	74.88 (26.33)	29	74.00 (23.84)
Adaptive Behavior Composite Score	52	73.67 (22.39)	29	72.72 (17.50)

The test was mandatory at 2 and 5 years of chronological age, and optional at 3 and 4 years of chronological age.
Raw scores reported by investigators were converted to v-scaled scores adjusted for age as per test manual.
Domain scores are the sum of the respective v-scale scores obtained for subdomains of the domains communication, daily living skills, socialization and motor skills. The adaptive behavior composite score is the sum of all four domain scores.
Subjects received study treatment (aflibercept, laser) for ROP in Study 20090. There is no study treatment in Study 20275.
a: Expressive communication raw scores were adjusted before converting to v-scale scores in case of items non-adaptable to the subject's native language.
Source: Table 8.3.5.5/1 to 8.3.5.5/5

Pharmacokinetics

Exposure to free and bound aflibercept and any effects on blood pressure and urine protein were analyzed in Study 20090. In Study 20275, no pharmacokinetic samples were taken.

2.3.3. Discussion on clinical aspects

This is the fourth and final annual interim study report for the extended study FIREFLYE NEXT (20275) as part of the Post-Authorization Measure (PAM) following the positive opinion for the extension of indication for patient with ROP under procedure EMEA/H/C/002392/II/0077/G. In this report, the MAH presented efficacy and safety data up to 5 years of chronological age (cut-off date: 10 OCT 2025) for 100 patients (66 and 34 patients previously treated by aflibercept and laser respectively in Study 20090).

The primary objective of this follow-up study is to assess long-term (5 years of chronological age) efficacy and safety outcomes of patients previously treated for ROP. The primary efficacy outcome was the analysis of BCVA using the WMW parameter. At 5 years of age, the WMW [95% CI] parameter was 0.624 [0.493, 0.742], exceeding the benchmark of 0.5 for equilibrated effects caused by the different treatment initiations. At 5 years of age, the median binocular BCVA in Snellen equivalent was 20/25 in aflibercept arm and 20/32 in the laser arm. The proportion of subjects with binocular BCVA of "20/40 or better" at 5 years of age was 46 (92.0%) in aflibercept arm and 21 (75.0%) in laser arm, while 100% of subjects in both arms achieved "20/200 or better". This indicates a sustained improvement in visual acuity during the patient's growth and confirms the durability of the treatment effect.

Secondary efficacy outcomes included the absence of unfavourable structural outcomes, absence of active ROP, recurrence of ROP, any need for retreatment and other outcomes included among others completion of vascularization. Functional outcomes of particular interest comprised refraction and visual function, measured age-appropriately (the ability to fix and follow a 5-cm toy, followed by BCVA assessment starting at 3 years of chronological age).

Unfavorable structural outcomes included retinal detachment, macular dragging, macular fold, and/or retrolental opacity as assessed by the investigator. A subject could present more than one unfavorable structural outcome per eye. Overall, similar results were observed since the baseline: 62 (93.9%) and 32 (94.1%) patients in the aflibercept and laser arm respectively showed no development of unfavourable effect. The number of patients without ROP at 5 years of chronological age (56 (100%) in the aflibercept arm and 29 (96.7%) in the laser arm) remained consistent with previous data from 3 and 4 years of age. The proportions of patients with recurrence through the 5 years of chronological age remained unchanged, with 11 patients (16.7%) in the aflibercept arm and 1 (2.9%) in the laser arm. Additionally, no subjects required treatment for ROP after 40 weeks of chronological age. Moreover, 10 patients in the aflibercept arm (15.2%) and 2 in the laser arm (5.9%) received any ophthalmological treatment for conditions such as ROP, conjunctivitis, myopia, ocular hyperaemia, retinoblastoma, and chalazion.

Globally, over the 5 years of follow-up, the majority of patients demonstrated normal visual function, including normal retinal attachment to the periphery, absence of optic nerve and lens abnormalities, reported light reaction and ability to fix and follow a 5-cm toy. At 5 years of age, 46 patients (92.0%) in the aflibercept arm and 21 patients (75.0%) in the laser arm achieved a binocular BCVA of "20/40" in Snellen equivalent, favoring the aflibercept arm.

Myopia was numerically less pronounced in the aflibercept arm, with a mean (SD) refractive spherical equivalent of -0.3036 (2.9434) D in the aflibercept arm compared to -2.2435 (4.5113) D in the laser arm. As well, the majority of eyes were considered without manifest strabismus in both arms (78.6% in aflibercept arm; 86.7% in laser arm) and one patient in each arm presented nystagmus. The severity of the disease decreased in both groups. At 5 years of chronological age, 91 (85%) eyes in the

aflibercept arm and 40 (69%) eyes in the laser arm had shown complete vascularization, confirming that retinal vascularization continues beyond 1 year of age following aflibercept treatment.

Overall, efficacy outcomes following treatment by IVT aflibercept 0.4 mg per eye in ROP subjects are well sustained through the 5 years of chronological age.

Up to 5 years of chronological age, a slightly higher proportions of any AEs were reported in the aflibercept arm (93.9% in aflibercept arm vs 85.3% in laser arm) mainly due to a higher incidence of ocular AE in the treated eye (51.5% in aflibercept arm vs 44.1% in laser arm). Frequency of non-ocular AEs were comparable between treatment arms (89.4% in aflibercept arm vs 85.3% in laser arm). Most of the AEs were mild to moderate in intensity and severe AEs were more reported in the aflibercept arm (25.8% vs % 17.6% in laser arm). Serious AEs were more reported in the laser arm (47.1% vs 37.9% in aflibercept arm) which were mainly non-ocular AEs (47.1% in laser arm vs 34.8% in aflibercept arm). No deaths occurred in study 20275.

Most reported ocular AE in the treated eye consisted of the PT Astigmatism (aflibercept 19.7% vs laser 17.6%), Myopia (aflibercept 13.6% vs laser 11.8%), and Strabismus (higher in aflibercept 16.7% vs laser 8.8%). For Strabismus, while the proportion was higher in aflibercept arm, none were severe or related to photocoagulation, intravitreal injection, or protocol-required procedures and there was no imbalance for manifest strabismus. While Ocular AEs were mainly mild to moderate in intensity, severe Ocular AEs in the treated eye were more reported in the aflibercept arm (10.6% vs 8.8% in laser arm). These events in aflibercept arm consisted of severe Retinal detachment reported in 3 subjects, severe Myopia and Optic atrophy each reported in 2 subjects, and severe Astigmatism, Retinal neovascularization, Vitreous opacities and Retinoblastoma each reported in 1 subject. In the laser arm, one subject presented severe Myopia. Ocular AEs in the study eye reported as related to aflibercept, were low and similar between arms (3.0% in aflibercept arm; three events of retinal detachment (two serious) and one non-serious event of iris adhesions (mild, not recovered) in one patient and two non-serious events of astigmatism (one moderate assessed as not related and one severe assessed as related to both aflibercept and laser in one patient in each eye, both were not recovered) vs 2.9% in laser arm; one non-serious event of macular fibrosis in one patient with unknown outcome). Ocular AEs reported as injection procedure related, in the treated eye, occurred in one patient in the laser arm (2.9%, one event of macular fibrosis also assessed as aflibercept related). No Ocular AEs were assessed as related to procedure required by protocol. Ocular SAEs occurred in aflibercept arm only (9.1%; 6 patients) and were severe in intensity in four patients (6.1%) and not recovered/not resolved in three patients, recovered with sequelae in two patients and recovered/resolved in one patient. Two serious events of Retinal detachment were assessed as related to aflibercept in one patient and none to laser or injection procedure and procedure required by the protocol. No ocular SAEs or severe ocular AE in treated eye were reported during year 5 of chronological age.

Non-Ocular AEs consisted mainly of the PT Upper respiratory tract infection (22.7% in aflibercept vs 20.6% in laser), Pyrexia (higher in laser arm), Bronchitis (higher in laser arm), Nasopharyngitis (24.2% in aflibercept and 11.8% in laser) with most case reported in context of common cold, COVID-19 (higher in laser arm) and Respiratory tract infection (16.7% in aflibercept vs 11.8% in laser). Non-Ocular AEs were mainly mild to moderate and severe non-ocular AEs were slightly more reported in the aflibercept arm (19.7%% vs 14.7%). No events were assessed as related to aflibercept, laser, injection procedure or procedure required by the protocol. Non-Ocular SAE were more reported in laser arm (47.1%) than aflibercept arm (34.8%). Non-ocular SAE were in line with the study population underlying prematurity (such as medical history of intraventricular haemorrhage, or infantile apnoea), mainly mild to moderate in intensity and none were assessed as related to study treatment. A total of

7,6% of the patients underwent ocular surgical procedures and comparable proportions of patient in both treatment arms (30.3% in aflibercept arm and 26.5% in laser arm) underwent non-ocular surgeries procedures. No ocular procedures were reported after 3 years of age and in the aflibercept arm, 4 (6.8%) subjects had non ocular surgical procedures between 4 and 5 years of age.

At 5 years of chronological age, abnormal findings in the posterior segments by eyes were reported in higher proportion in laser arm with a decreased observed in aflibercept arm (aflibercept 0.9 % vs laser 8.6%) and were clinically significant in 1 patient (optic atrophy) for aflibercept and in 1 patient (aphakia and vitreous loss in one eye, and macular fibrosis in both eyes) in laser arm. Abnormal findings in the anterior segment by eyes were low and comparable between arms (2 subjects, aflibercept 3.6% vs 1 subject, laser 3.3%) and clinically significant in one subject in each arm. Through 5 years of chronological age, mean values were comparable between both arms for physical parameters which included weight, body length/height, head circumference, temperature, heart rate, respiratory rate and blood pressure (systolic SBP and diastolic DBP). At 5 years of age, hearing test were performed and proportion of subjects with any abnormal finding, irrespective of the hearing test type, was comparable between the arms (15.2% in aflibercept arm vs 17.4% in laser arm). Neurodevelopmental tests (WPPSI-IV and VABS-II) were performed (mandatory) at 5 years of chronological visit and were available in 78.8% (aflibercept arm) and 85.3% (laser arm) of the patients for VABS-II and 79.4% to 88.2% (laser arm) and 60.6% to 72.7% (aflibercept arm) of the patients for WPPSI-IV. No relevant differences between the two treatment arms were seen for the WPPSI-IV test (mean full scale IQ for aflibercept 83.25 and for laser arm 81.50) and for the VASB-II test (mean adaptive behavior composite score for aflibercept 73.67 and for laser arm 72.72). Overall, no concerns are raised regarding ocular and systemic safety, growth, neurodevelopment and overall development up to 5 years of chronological age.

3. CHMP overall conclusion and recommendation

Overall, the efficacy profile confirms the durability of the treatment effect up to 5 years of chronological age and the safety profile is reassuring. Therefore, the B/R remains unchanged.

☒ **Fulfilled:** No regulatory action required.