20 September 2012
EMA/44020/2023
Committee for Medicinal Products for Human Use (CHMP)

Group of variations including an extension of indication assessment report

Eylea

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/002392/0000

Note

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

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 8 November 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
B.IV.1.a.3	Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the AS	Type II	I, IIIA and IIIB
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

B.IV.1.a.3 (Change of a measuring or administration device, type II) Addition of a stand-alone paediatric dosing device (PDD) for the administration of 10 µL of aflibercept solution 40 mg/mL (corresponding to a dose of 0.4 mg of aflibercept) in prefilled syringe for intravitreous injection (PFS) which will be cross-labelled to the EU-PI.

C.I.6 (Extension of indication) Extension of indication to include the paediatric indication retinopathy of prematurity (ROP) for Eylea; as a consequence, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Separate Package Leaflet is proposed for the guardians of preterm babies. Version 32.1 of the RMP has also been submitted.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0115/2019 on the agreement of a paediatric investigation plan (PIP) and on the granting of a product-specific waiver.

At the time of submission of the application, the PIP P/0115/2019 was completed. The PDCO issued an opinion on compliance for the PIP P/0115/2019.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products, because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
B.IV.1.a.3	Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the AS	Type II	I, IIIA and IIIB
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B.IV.1.a.3 (Change of a measuring or administration device, type II) Addition of a stand-alone paediatric dosing device (PDD) for the administration of 10 µL of aflibercept solution 40 mg/mL (corresponding to a dose of 0.4 mg of aflibercept) in prefilled syringe for intravitreous injection (PFS) which will be cross-labelled to the EU-PI.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0115/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Eylea EMEA/H/C/002392/II/0077/G'

4. Scientific discussion

4.1. Introduction

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

EYLEA (aflibercept) is registered via Centralised Procedure (EMA/H/C/002392) and is indicated in adults for the treatment of:

1. neovascular (wet) age-related macular degeneration (AMD),
2. visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO),
3. visual impairment due to diabetic macular oedema (DME),
4. visual impairment due to choroidal neovascularisation (myopic CNV).

4.1.1. Problem statement

The pathophysiology of ROP is characterised by abnormal neovascularisation (prevalence 1-5 / 10 000; Opharnet). The disruption of angiogenesis in preterm infants with ROP typically occurs in 2 postnatal phases (Hellström et al 2013). In Phase 1 (~22 to 30 weeks postmenstrual age), high oxygen saturation in the immature retina (relative hyperoxia), coupled with low concentrations of growth factors and

nutrients normally present *in utero* during the third trimester of pregnancy, lead to suppression of new vessel growth. As a result, the metabolically active but poorly vascularised retina becomes hypoxic. In Phase 2 (~31 to 44 weeks postmenstrual age), the hypoxic environment in the retina stimulates release of various angiogenic factors, such as vascular endothelial growth factor (VEGF), that lead to proliferation of new blood vessels. In preterm infants with disrupted angiogenesis, the abnormal neovascularisation and the leaky new blood vessels formed in this environment result in intraocular fibrosis, leading to retinal distortion, detachment, and visual disability.

According to the International Classification of Retinopathy of Prematurity (IC-ROP 2005), the main features for the classification of ROP are:

- The location of retinal involvement (Zone I: central circle, Zone II: mid-peripheral ring, or Zone III: peripheral ring),

- The extent of circumferential disease (measured in number of clock hours),

- The stage of severity (stage 1 through 5, depending on the morphological appearance of the disease)

- And presence of plus disease (characterized by venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least 2 quadrants and indicating more aggressive course at any stage).

A subtype called aggressive posterior ROP (AP-ROP) is an uncommon severe form of ROP, characterized by posterior location, prominence of plus disease, with extremely intense vascular activation and, if untreated, shows rapid progression (over a few days) to advanced stages. AP-ROP is typically seen in Zone I but may occur in posterior Zone II.

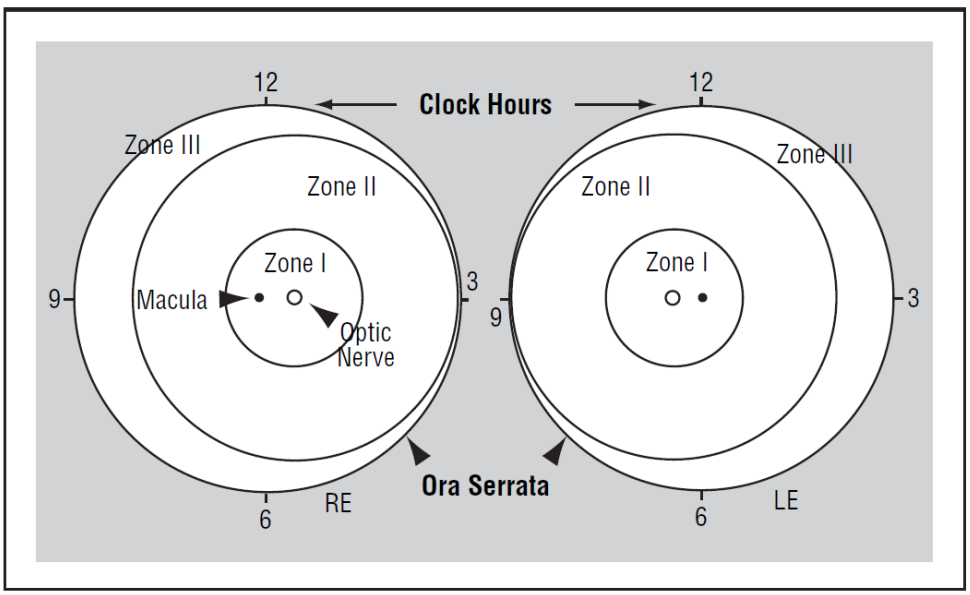


Figure 1 - Schema of right eye (RE) and left eye (LE) showing zone borders and clock hour sectors used to describe the location of vascularization and extent of retinopathy. Solid circles represent borders of zones I through III, and dotted circles represent borders of posterior zone II (2 disc diameters beyond zone I).

A regulator of angiogenesis, VEGF, plays a key role in the progression of ROP and is involved in both phases of ROP pathophysiology. The levels of VEGF differ in the two phases of abnormal neovascularisation and are associated with different outcomes. Suppression of VEGF by non-physiologically high tissue oxygenation in Phase 1 of ROP inhibits normal vessel growth, whereas upregulation of VEGF induced by relative hypoxia in Phase 2 of ROP leads to pathological

neovascularisation (Chen and Smith 2007). Excessive levels of VEGF lead to abnormal vascular proliferation and ultimately, if left untreated, to retinal detachment, which may result in blindness.

Based on the finding that VEGF also plays a critical role in the pathophysiology of ROP, several studies have led to publications on the successful treatment of infants with ROP with anti-VEGF agents (e.g. Mintz-Hittner et al 2011, Stahl et al 2018). Following data obtained from RAINBOW study, the marketing indication of ROP was obtained for Lucentis® in 2019 both in the EU and in Japan. No prospective, randomized-controlled data was available on aflibercept in patients with ROP requiring treatment, prior to the conduct of the submitted pivotal study (20090 and 20275 study).

At this time, there is an approved medicinal treatment for ROP with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease (Lucentis®) and the standard of care being laser ablation therapy, which is invasive is associated with severe long-term sequelae such as permanent loss of visual field and high myopia. Vitreoretinal surgery is currently perform for more advanced stages of ROP with retinal detachment.

4.1.2. The development programme/compliance with CHMP guidance/scientific advice

1. No new preclinical studies have been submitted as agreed with PDCO, only reference to the literature is submitted.
2. Biopharmaceutical development.

For the proposed 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 following the European Medicines Agency (EMA) Paediatric Investigation Plan (PIP) decision.

1. Clinical development programme (see Section 5.4).

Study 20090 (FIREFLEYE, Core study) Open-label, Randomized, Two-Arm, Controlled Study to Assess the Efficacy, Safety, and Tolerability of Intravitreal (IVT) Aflibercept 0.4 mg Compared to Laser Photocoagulation in Patients With Retinopathy of Prematurity (ROP).

Study 20275 (FIREFLEYE extension) is a currently ongoing Extension Study evaluationg the Long-term Outcomes of Subjects Who Received Treatment for Retinopathy of Prematurity in Study 20090. The Last subject last visit for the Extension Study is planned for Jul 2025.

Both studies are part of the European Medicines Agency (EMA) Paediatric Investigation Plan (PIP) for aflibercept (EYLEA) (EMEA-000236-PIP05-18).

Historical/published evidence synthesis study
In the completed evidence synthesis study, no new data was collected, however, clinical data collected in Study 20090 was complemented by historical evidence for laser efficacy from the published randomized clinical trials BEAT-ROP and RAINBOW (Mintz-Hittner et al. 2011, Stahl et al. 2019), using a Bayesian statistical model.

4.2. Quality aspects

The Aflibercept solution 40 mg/mL in prefilled syringe for intravitreous injection (PFS) is indicated for adult patients (e.g. Wet Age-related Macular Degeneration - AMD, Diabetic Macular Edema - DME) to

administer 50 µL. The paediatric device is to be used for paediatric patients with the indication of Retinopathy of Prematurity (ROP) in addition to the current indications in adult patients (e.g. AMD, DME).

A paediatric dosing device (PDD) has been developed for the administration of 10 µL of Aflibercept solution 40 mg/mL in prefilled syringe for intravitreous injection (PFS). The dosing device is assembled with a female luer connection to the syringe and a needle for injection is assembled to its male luer connection. The assembly is primed by depressing the syringe plunger rod to eliminate air bubbles from the assembly and to fill the device and the needle with finished product. The device has a short time contact with the finished product during administration.

The impact on quality has been evaluated by compatibility studies and extractable and leachable studies. Potential impact on the dose delivery has been evaluated by dose accuracy studies.

4.2.1. Compatibility studies

For the study, the inner chamber of the paediatric dosing device was filled with aflibercept solution 40 mg/mL and the solution was analysed after a contact time of 6 hours (t6) at 25 °C (corresponding to a maximum expected contact time in practice). As a control, aflibercept solution 40 mg/mL in prefilled syringe was analysed at starting point (t0) and after 6 hours (t6) at 25°C without any contact to the device. The potential impact of shear forces implemented by the device was mimicked by passing the valve of the dosing device while it was filled with finished product.

An initially performed device material screening study had shown no influence of the tested device materials on aflibercept solution 40 mg/mL. No noticeable observations regarding the tested materials in interaction with aflibercept solution 40 mg/mL could be observed with regards to physicochemical characteristics, adsorption or aggregation. Therefore, a triplicate of sample preparation for the physicochemical compatibility study was not considered necessary and one sample preparation is considered adequate.

The analytical methods were assessed with regards to criticality for product quality and their predictability for compatibility and were selected accordingly for this study. Physical and chemical compatibility, including adsorption, precipitation of the finished product solution, and stability, are covered by determination of protein content, SE-UPLC and pH measurement.

The test samples of aflibercept solution 40 mg/mL in contact with the paediatric dosing device fulfilled the specification and acceptance criteria with no significant differences to the control samples. The paediatric dosing device does not influence the physicochemical characteristics of aflibercept solution 40 mg/mL and does not induce adsorption or aggregation. Based on the results of this study and considering the material screening study, the dosing device is suitable for the administration of aflibercept solution 40 mg/mL from compatibility perspective.

4.2.2. Extractables

The paediatric dosing device was studied with regard of extractable compounds according to the EN ISO 10993-18 ‘Biological evaluation of medical devices’ performing exaggerated extraction.

The PDD is packed into a blister and provided sterile, and it is packed together with the instructions for use into a carton box.

To also ensure safety of primary packaging, devices were studied. The test materials were extracted. The total incubation time is equivalent with the estimated worst-case contact time of the finished

product with the PDD. After each incubation samples from 8 paediatric dosing devices were pooled to collect sufficient volume of the extracts for the analyses.

Testing methods, samples and AET concentrations were provided.

Multiple extractable compounds were detected but those extractable compounds were not detected in Aflibercept solution 40 mg/mL extract.

In Aflibercept solution 40 mg/mL sample extract one detected compound was also detected in the matrix blank. Two other compounds were not detected in the matrix blank but were related to the active substance and fragmentation products of that.

Summary and conclusion

The majority of detected extractable compounds were released from the paediatric dosing device component polymers during heating. Similar sampling procedure with Aflibercept solution 40 mg/mL had negligible effects on dosing chamber materials. None of the reported polymer fragments were detected in Aflibercept solution 40 mg/mL extracts.

No clear differences between the packed and unpacked device extractable profiles were observed in regard of effects of primary package or printing on the primary package materials.

It can be concluded from the extractables study data that, from the toxicological point of view, there is no objection to use the PDD for Aflibercept solution 40 mg/mL for intravitreous injection in premature infants with ROP. None of the identified organic extractables found above the AET is known to cause unacceptable toxicities at the calculated estimated daily intake values or the theoretical maximum dose, after intravitreous administration of Aflibercept solution 40 mg/mL, considering amounts determined in the extractables study. Extractable compounds represent potential leachable compounds, but as shown with Aflibercept solution 40 mg/mL simulation samples, there were not detected any compounds without relation to Aflibercept solution 40 mg/mL. Thus, risks to human health are judged negligible (de minimis).

There is sufficient evidence to conclude that the sterile, single-use and short-term PDD, which is specifically designed to be placed between the syringe and injection needle and filled with Aflibercept solution 40 mg/mL, is of suitable quality for treating premature infants with ROP.

4.2.3. Dose accuracy

No available alternative low-volume syringe or device was identified that is considered appropriate for the administration of the 10 µL of Aflibercept solution 40 mg/mL for intravitreous injection. Therefore, the Company has developed a dedicated paediatric dosing device for Aflibercept solution 40 mg/mL for intravitreous injection with the intended trade name PICLEO. This paediatric dosing device is designed to provide a single dose of 0.4 mg aflibercept (in 10 µL solution for injection) in use with Aflibercept solution 40 mg/mL for intravitreous injection already available and registered. The paediatric dosing device is provided sterile in a sealed tray to maintain sterility until opening.

The paediatric dosing device was assembled with the PFS and the 30G ½” injection needle and the assembly was manually primed according to the instructions for use (IFU) of the dosing device. The dose was manually injected into a sealed vial, following the IFU, and by measuring the weight balance on a micro-balance scale, each delivered dose was recorded. Care was taken to follow the procedure for optimal reproducibility of the results.

The delivered dose volume in [µL] was calculated. The delivered dose volume in [µL] was used for further statistical evaluation.

Several different operators performed the test where each operator performed the test with 20 several assemblies. A total range of the dispensed volume was determined for the paediatric dosing device used in combination with the PFS. The mean dispensed volume was determined with no detectable variability between operators.

The distribution is very narrow.

The summary of the results from dose accuracy test with Aflibercept solution 40 mg/mL in prefilled syringe for intravitreous injection and paediatric dosing device PICLEO was provided.

The test results demonstrate that targeted dose of 0.4 mg aflibercept (in 10 µL solution for injection) can be administered with use of the paediatric dosing device with adequate accuracy and consistency. The dose volume range of the developed paediatric dosing device is well within the distribution range of a 1 mL disposable syringe. Therefore, the requirement to develop or identify an available application device to ensure accuracy for administration of 10 µL is considered fulfilled as demonstrated by the presented data in this section.

The paediatric dosing device, used in line with instructions for use, will ensure accurate application of the dose with improved accuracy compared to a 1 mL disposable syringe.

4.2.4. Regional information

The paediatric dosing device (PDD) will be a CE-marked medical device which is a stand-alone device and will be provided as a separate sales pack with cross-labelling to the EU-PI of the Eylea. The medical device (paediatric dosing device) PICLEO will be cross-labelled to Sections 4.2, 4.4 and 6.6 of the Eylea Summary of Product Characteristics (SmPC) and in the Eylea Package Leaflet (PL).

The dosing chamber and the valve adapter with valve are in contact with the finished product during administration.

Classification

EU Device classification (2017/745/MDR)	class Is (rule 2), transient, non-invasive, sterile

The EU Declaration of conformity (DoC) as well as the CE certificate for the PDD was requested but the CHMP was finally of the opinion that the grouped variation can conclude positively even in the absence of the EU certificate and DoC for the PDD, since the NBOp for the PFS was provided and because the level of information submitted in Module 3 as regards the PDD (data on compatibility, extractable, dose accuracy; information on usability studies) is considered sufficient.

Human Factor study

Together with its development partner for the paediatric dosing device, Bayer has conducted a comprehensive usability engineering program according to IEC 62366-1, to establish that the paediatric dosing device can be used safely and effectively by the intended users, for the intended uses, and in the intended use environments – that is, without use errors that could lead to serious harm for which further mitigation would be practicable.

Within this Human Factors (HF) / Usability Engineering (UE) program, a total of four (4) formative usability evaluations were executed involving physicians who perform intravitreal injections to treat prematurely born patients with retinopathy of prematurity (ROP). Based on the observations and

feedback from the formative evaluations, the user interface of the dosing device was optimised, and the use risk analysis was updated.

No additional formative usability evaluations were deemed to be required before the summative usability evaluation for the paediatric dosing device, as all observed use problems were addressed by design and in the instructions for use.

Formative usability studies were performed. The summative usability study was requested and was provided in response to the Request for Supplementary Information.

Any observed use errors or use difficulties will be analysed for their root cause, the severity of harm that could result from the observation and, if needed, the practicality of modification of the user interface to further mitigate use-related risks.

4.2.5. Discussion and Conclusion on quality aspects

The impact of the paediatric dosing device (PDD) on product on quality has been evaluated by compatibility studies and extractable and leachable studies. Potential impact on the dose delivery has been evaluated by dose accuracy studies.

Compatibility studies demonstrate that the test samples of aflibercept solution 40 mg/mL in contact with the paediatric dosing device fulfilled the specification and acceptance criteria with no significant differences to the control samples.

As regards the extractable/leachable study, no safety concern was identified.

The dose accuracy study concluded that the total range of the dispensed volume was determined for the paediatric dosing device used in combination with the PFS. The total range of the dispensed volume is deemed acceptable.

Aflibercept is an aqueous buffered solution, containing sodium phosphate, sodium chloride, sucrose and polysorbate 20. The solution is iso-osmotic and suitable for IVT injection. All excipients are of compendial grade. None of the excipients is known to have safety implications for paediatric use concerning the intended use and quantities.

Therefore, the formulation of the pre-filled syringe is appropriate for use in preterm infants with ROP.

As regards regional information, the paediatric dosing device will be a CE-marked medical device which is a stand-alone device and will be provided as a separate sales pack with cross-labelling to the EU-PI of Eylea.

The transmitted certificate is a certificate issued according to the standard EN ISO 13485: 2016 related to the quality management system for medical devices.

The EU Declaration of conformity (DoC) as well as the CE certificate for the PDD was requested but the CHMP was finally of the opinion that the grouped variation can conclude positively even in the absence of the EU certificate and DoC for the PDD, since the NBOp for the PFS was provided and because the level of information submitted in Module 3 as regards the PDD (data on compatibility, extractable, dose accuracy; information on usability studies) is considered sufficient.

An other concern was raised as regards the potential measuring function of the PDD. The MAH has clarified that the PDD is not classified as device with a measuring function.

Formative usability studies were performed. The summative usability study was requested and was provided in response to the Request for Supplementary Information.

The IFU (Instructions for Use) of the PDD were not initially submitted as part of this type II variation, but later on the MAH provided a preliminary IFU of the PDD. Nonetheless, in order to assess the safety and efficacy of the pre-filled syringe used in combination with the PDD for treatment of preterm infants, the finalised IFU of the PDD were requested. The Instructions for Use were provided in response to the RfSI. It is outlined in the IFU that the PDD is for single use which shall be used only with the Eylea PFS. The finalised IFU is considered acceptable.

4.3. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

4.3.1. Introduction

The initial pharmacology program comprised in vitro studies to characterize the binding characteristics and activity of Aflibercept (VEGF Trap), as well as in vivo studies to characterize its efficacy in preventing pathological neovascularization and vascular permeability in relevant animal models of ocular vascular disease Aflibercept was found to bind with picomolar affinity to mouse, rat, rabbit and human VEGF-A, and to the related angiogenic molecules, human placental growth factor-1 (PlGF-1) and mouse and human PlGF-2, but not to human VEGF-C and VEGF-D. In a mouse model of oxygen-induced ischemic retinopathy (OIR), which induces a neovascular response similar to effects seen in retinopathy of prematurity, proliferative diabetic retinopathy, and other ischemic retinopathies, a single IVT dose of Aflibercept (0.5 or 0.24 µg) prevented the development of pathological retinal neovascularization. It was agreed that IVT administration of Aflibercept effectively inhibited pathological neovascularization and/or abnormal vascular leak in all animal models tested.

4.3.2. Pharmacology

Retinopathy of Prematurity (ROP) is characterized by abnormal development of the retinal vascularization in preterm infants with a young gestational age (GA) (≤ 32 weeks) only and has been associated with disturbances in the levels of vascular endothelial growth factor (VEGF). Thus, anti-VEGF products such as Aflibercept, are capable of treating ROP based on clinical positive feedbacks [Stahl 2018, Salman 2015].

For the indication Retinopathy of Prematurity (ROP), no additional primary or secondary pharmacology or safety pharmacology studies were conducted on aflibercept as agreed with PDCO. Since no additional studies were required, the applicant has submitted publications on animal models of ROP and the existing safety pharmacology studies, already conducted, have been re-assessed with regard to safety margins in the preterm infant.

4.3.2.1. Primary pharmacodynamic studies

The development of the retinal vasculature and the progression of ROP has been learned through the use of animal models of oxygen-induced retinopathy (OIR), which approximate the human condition. Animal models of OIR have provided a wealth of information regarding the cellular and molecular pathogenesis of ROP. Two rodent models, mouse and rat, are commonly used to study the pathophysiology of ROP and to test the preclinical efficacy of drug candidates for ROP. The two models differ in their mode of induction (chronic hyperoxia in mice versus alternating hyperoxia/hypoxia in rats) .and in the manifestation of their vascular phenotypes. In mice, vaso-obliteration occurs primarily in the central retina. In contrast, vaso-obliteration is more peripheral in the rat oxygen-induced retinopathy model and in human ROP. In addition, canine oxygen-induced retinopathy (OIR) was also developed in an effort to experimentally determine the effects of hyperoxia on the development of the retinal

vasculature. The canine OIR model has many characteristics in common with human retinopathy of prematurity. Exposure of 1-day-old dogs to hyperoxia for 4 days causes a vaso-obliteration throughout the retina. The end-stage pathology of the canine model is similar to stage IV human retinopathy of prematurity. Therefore, canine OIR is an excellent forum to evaluate the response to drugs targeting VEGF and its receptors.

Effects of aflibercept on normal retinal vascular development

Effects of aflibercept on pathologic ocular neovascularization in adult animals

In agreement with the important role played by VEGF in pathologic neovascularization, aflibercept has been shown to be effective in reducing neovascularization and vascular leak after systemic or IVT administration in several models of pathological ocular neovascularization in adult animals (see below).

Table 6–1: Effect of aflibercept in reducing neovascularization and vascular leak after systemic or IVT administration in several models of pathological ocular neovascularization in adult animals

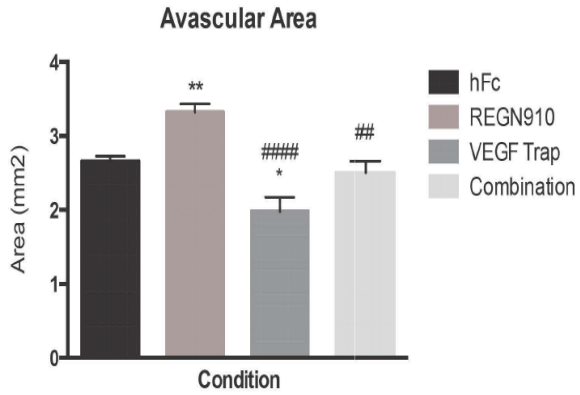
Model	Species	Treatment	Effect	Source
Corneal suture injury	mouse	1 x 12.5 mg/kg IP	• reduced corneal neovascular area • reduced inflammatory cell infiltrate	Cursiefen 2004 (8)
Laser-induced CNV	mouse	5 x 25 mg/kg SC	• reduced choroidal neovascular area	Saishin 2003 (9)
		1 x 4.92 mcg IVT	• reduced choroidal neovascular area	
	cynomolgus monkey	6 x 3 or 10 mg/kg IV	• reduced number/absence of severe CNV lesions	Report VGFT-TX-03027
		3 x 50, 250 or 500 mcg IVT	• reduced number/absence of severe CNV lesions	
		1 x 500 mcg IVT	• regression of established CNV lesions	
CNV induced by subretinal matrigel	rat	2 x 12.5 mg/kg SC	• reduced choroidal neovascular area	Cao 2010 (10)
		3 x 12.5 mg/kg SC	• regression of established choroidal neovascular area • reduced CNV-associated progressive leukocyte infiltration and fibrosis	
Diabetes-induced BRB leakiness	rat	1 x 3 mcg IVT	• normalization of retinal vascular permeability	Report VGT-NC-007
VEGF-induced BRB leakiness	mouse	1x 25 mg/kg SC	• reduced BRB leakiness after IVT administration of VEGF	Saishin 2003 (9)
		2x 25 mg/kg SC	• reduced BRB leakiness in tg mice expressing VEGF under control of the rhodopsin promoter	

BRB = blood-retinal barrier; CNV = choroidal neovascularization; SC = subcutaneous; IP = intraperitoneally; IVT = intravitreal; tg = transgenic; VEGF = vascular endothelial growth factor.

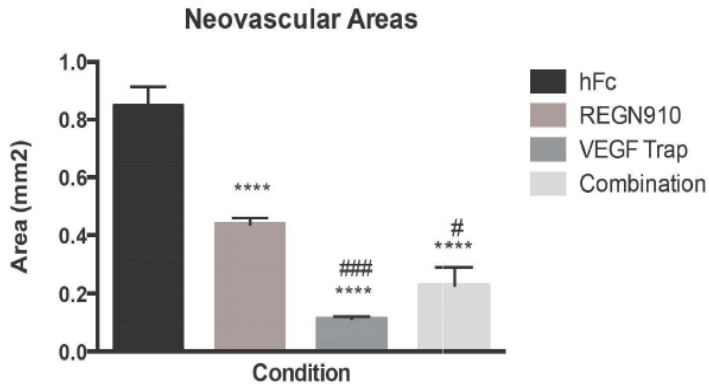
Effects of aflibercept in the mouse OIR model

In study, C57Bl/6 mouse pups were placed in a hyperoxic chamber(75% oxygen atmosphere) with their dams on post-natal day (P) 6, and returned to room air on P11, at which time pups received a single subcutaneous (SC) injection of a control protein (hFc, 25 mg/kg), REGN910 (anti-Ang2 antibody; 25 mg/kg), VEGF Trap (25 mg/kg) or both REGN910 and VEGF Trap, and the effects of treatment on the extent of pathological neovascularization as well as blood vessel regrowth in the retina were assessed.

Effects of treatment with REGN910, VEGF Trap or both REGN910 and VEGF Trap on retinal revascularization



Effects of treatment with REGN910, VEGF Trap or both REGN910and VEGF Trap on retinal neovascularization



Aflibercept treatment significantly reduced the area of pathologic retinal neovascularization at P16 by more than 80% and also reduced the central retinal avascular area by approximately 25%, indicating an improvement in normal retinal vascularization

Qualitatively similar effects were seen at P19 in animals treated with this dose of aflibercept every other day from P13 (12-24 h after returning animals to normoxia) to P17 [Wang 2002]. Mouse pups exposed to 75% oxygen from P7 to P12 followed by return to normoxia were treated intravitreally with aflibercept (0.5 mcg at P14 with retinas harvested at P17, or 0.24 mcg at P15 with retinas harvested at P19) or an inactive control protein. In both studies, aflibercept caused a marked significant reduction of pathologic retinal neovascularization.

Aflibercept-treated animals showed a larger retinal avascular area in the higher dose study at P17, whereas the animals treated with the lower dose of aflibercept assessed at P19 showed a significant reduction in avascular area by about 80% compared to control animals (Module 4.2.1.1 report VGT-NC-013). Additional data from the mouse OIR model indicate that systemic pretreatment (intraperitoneal, 25 mg/kg) with aflibercept before exposure to hyperoxia can ameliorate the loss of normal retinal vasculature in this phase, thereby reducing the avascular zone [Wang et al., 2002 , cited in Cheung E].

A further publication [Tokunaga 2014] in this model (hyperoxia from P7 to P12, unilateral IVT application of saline or 2.5 or 10 mcg aflibercept on P14, fellow eye as uninjected control) showed broadly similar effects of aflibercept on retinal vasculature: significant reduction in pathologic neovascularization, transient increase in retinal avascular area at P15 and P17, which had recovered by P21 (i.e. as might be expected, the effect of aflibercept on normal retinal development was a delay and not a permanent reduction).

This study also looked at nonvascular consequences of OIR, electroretinogram and retinal structure, and the authors describe potential negative effects of aflibercept treatment on these parameters:

1. Dose-dependent disruption of the outer plexiform layer of the retina.

This parameter appears to show very high variability, with marked disruption seen also in the non-injected control eyes (group averages for the non-injected eyes ranged from 5.9% to 29% compared to 22.1% in saline-injected eyes, 27.9% for aflibercept low dose and 36.5% for aflibercept high dose).

2. Thinning of the retina.

Aflibercept low dose had a more marked apparent effect, retinal thickness was 122 µm (compared to 172 µm in the fellow eye), retinal thickness in the high dose group was 140 µm (compared to 166 µm in the fellow eye). No data are given for the saline treated group.

3. Electroretinogram/electroretinography

All OIR groups at P21 and P42 showed reduced B-wave amplitude compared to normal adult animals. No significant differences were observed between uninjected OIR control group and aflibercept-treated eyes at P21. At P42 reduced B-wave amplitude in the low dose aflibercept group compared to OIR alone was detected.

Proper interpretation of these nonvascular anatomic and functional outcomes is made difficult by the fact that these data were obtained in only a small subset of the animals (N=2-4 per group), data are not given in all cases for the injection control group (saline treated), and it is not clear from the publication whether litter bias was adequately excluded. In addition, the IVT doses used in this study (2.5 and 10 µg) were much higher than in another study outlined above which already showed inhibition of pathological neovascularization at doses of 0.24 and 0.5 µg, with only the higher dose showing reduction in normal retinal vascular development at the assessment time point employed.

<u>Effects of aflibercept in the dog OIR model</u>

The canine OIR model appears to be perhaps the most relevant model for human ROP, as development of the dog superficial retinal vasculature show anatomic mechanistic similarities to human retinal vascular development and the pathology of OIR in the dog shares many of the characteristics of human ROP [McLeod & Lutty 2016].

Exposure of P1 dogs to 100% oxygen for 4 days results in arrest of retinal vasculogenesis and vasoobliteration of portions of the developing retinal vasculature. When animals are then returned to room air, the resulting hypoxia induces progressive and persistent pathological IVT neovascularization, which may be accompanied by IVT haemorrhage and tractional retinal folds, while the normal retinal revascularization remains incomplete.

Intravitreal administration of aflibercept (5, 25 or 250 µg/eye; the fellow eye received the same dose of inactive control protein) on P8, 3 days after animals were returned to room air, resulted in an almost complete inhibition of pathological IVT neovascularization at P21 at all doses tested compared to the control fellow eyes. Physiological revascularization of the retina was dose-dependently reduced by aflibercept at 25 and 250 µg/eye, the 5 µg/eye dose did not inhibit retinal revascularization. In same-age pups raised in room air and not exposed to hyperoxia, normal retinal vascular development was also reduced by aflibercept at 25 or 250 µg/eye, here also 5 µg/eye had no effect on normal retinal vascular development. The effects of aflibercept at a dose of 5 µg/eye administered at P22 on established pathological IVT neovascularization were also studied. In this setting, a marked reduction in the pathological IVT neovascular area at P45 was seen with no effect on retinal revascularization [Lutty 2011].

This study indicates that in the dog OIR model, efficacy is seen already at a low dose of aflibercept. However, no data are available for the effects of aflibercept on pathologic ocular neovascularization in adult dogs and therefore direct translation of the doses used in this study to the human situation (e.g. by comparison with dog and human adult doses) is not possible.

Conclusion

In conclusion, aflibercept shows efficacy in inhibiting pathological ocular neovascularization across multiple preclinical models in adult and neonatal animals after systemic or IVT administration. Aflibercept shows robust efficacy in preventing or reversing the pathological neovascularization in mouse and dog models of OIR, which are regarded as standard preclinical models for ROP. Despite the uncertainties related to the quantitative translation of the preclinical doses to humans, the data obtained using IVT administration of aflibercept in the mouse and dog OIR models are supportive of the clinical dose of 0.4 mg per eye. The findings from the OIR studies with respect to normal retinal vascular development, which is arrested by hyperoxia, are divergent, with some studies reporting delayed vascularization and others improved / accelerated physiological vascularization (depending on dose and time of observation), but in most cases where a delay is reported, it appears to be transient.

Overall, elements in favour of the use of aflibercept in ROP are agreed.

4.3.2.2. Safety pharmacology programme

In a series of safety pharmacology studies with systemic administration, no effects on respiratory or central nervous system function, or on the potential for thrombus formation were identified. Single, SC injections of aflibercept in rats and mice resulted in transient, dose-dependent increases in systolic and diastolic blood pressure. Repeated dose studies in rabbits (IV infusion every 7 days, 4 doses in total) revealed dose-related delays in wound healing and decreases in mechanical wound strength. For all safety pharmacological endpoints multiples of exposure (MoEs, safety margins) regarding the peak free aflibercept concentrations were calculated for a preterm infant of 0.8 kg body weight (BW) dosed with 0.4 mg aflibercept/eye (both eyes treated). The preterm infant of 0.8 kg BW was selected as a baby with the minimal body weight at baseline included in the FIREFLEYE study, representing the worst case with regard to aflibercept exposure. In addition, exposure multiples with regard to mean free aflibercept Cmax from the FIREFLEYE study were calculated (see Table 6–2).

Table 6–2: Estimated multiples of exposure (MoEs) for free aflibercept for a premature infant of 0.8 kg BW and MoEs in premature infants from the FIREFLEYE study [in brackets in 3rd column] after bilateral IVT treatment with 0.4 mg aflibercept/eye with regard to endpoints from secondary and safety pharmacology studies with systemic dosing of aflibercept

Study / Endpoint / Finding	Dose	Estimated MoEs based on free Cmax
NOEL for respiratory & central nervous system function tested in a toxicological monkey study# (Module 2.6.3, Pharmacology Tabulated Summary, Section 3, VGFT-MX-08018)	30 mg/kg BW IV (once weekly#)	≥715 [≥1033]
NOEL for the potential of thrombosis formation in the rabbit (Module 2.6.3, Pharmacology Tabulated Summary, Section 4, VGFT-TX-05009)	30 mg/kg BW IV (once weekly, 3 treatment occasions)	1652 [2387]
Blood pressure in telemetered mice and rats	Single dose	
NOEL rat	0.15 mg/kg BW SC	1.6 [2.3]
LOAEL rat (↑ by 4/3 mmHg syst./diast.)	0.5 mg/kg BW SC	3.5 [5.1]
LOAEL mouse* (↑ by 14/12 mmHg syst./diast.)	2.5 mg/kg BW SC	18 [26]
(Module 2.6.3, Pharmacology Tabulated Summary, Section 4, VGFT-TX-06012)		
Incisional / excisional wound healing in the rabbit		
LOAEL (delays in wound healing)* (Module 2.6.3, Pharmacology Tabulated Summary, Section 4, VGFT-TX-06010 and VGFT-TX-06011)	0.3 mg/kg BW IV (once weekly, 4 treatment occasions)	≥9.5 [≥13.7]

[] = MoEs in premature infants from the FIREFLEYE study (calculated using the arithmetic mean of free Cmax) after bilateral IVT treatment with 0.4 mg aflibercept/eye; BW = body weight; IV = intravenous; LOAEL = lowest observed adverse effect level; MoEs = multiples of exposure; NOAEL = no observed adverse effect level; NOEL = no observable effect level; SC = subcutaneous. *: No NOAEL identified; #: 9-month monkey study: once weekly up to week 15, then every 2 weeks.

For the NOEL for respiratory and central nervous system functions as well as venous and arterial thrombus formation, MoEs of at least 715x were achieved. Smaller safety margins were observed regarding the effects on systolic and diastolic blood pressure (MoE = 1.6x at the NOEL, first effects at MoE of 3.5x) and wound healing (MoE ≥9.5x). Taken together, most of these effects are not considered to be relevant to IVT administration of up to 3 injections with a maximum of 0.4 mg aflibercept/eye (both eyes treated) in premature infants with ROP, however, a potential risk for a transient increase of BP cannot entirely be excluded.

4.3.3. Pharmacokinetics

No additional preclinical (PK) studies were conducted on the use of aflibercept in ROP patients. PK studies using intravitreal (IVT) administration in juvenile animals are not considered appropriate to generate further meaningful information, as the target population (premature infants with ROP) has a different developmental status and there is no appropriate model available. Given the lack of information on clearance mechanisms from the eye in premature infants across species, the translational value of a PK analysis in neonatal animals is unknown.

4.3.4. Toxicology

As agreed with PDCO no additional non-clinical studies were conducted on aflibercept for the indication ROP (PDCO decision P/0115/2019).

The safety of aflibercept has been assessed in a comprehensive nonclinical safety program following IVT and systemic administration up to very high multiples of human exposure (exceeding 1000 fold with regard to free aflibercept in studies with systemic dosing) and includes studies in adolescent monkeys. The animal species chosen were selected based on similarly high binding affinities of aflibercept with VEGF from that species, based on amino acid sequence homology compared to human VEGF. Species chosen were highly homologous (mouse, rat and rabbit) or even identical (monkey). The cynomolgus

monkey as the primary relevant species was used for all IVT and systemic toxicological studies up to and including chronic exposure.

Adverse findings and target organs of toxicity identified were generally considered to be consistent with VEGF inhibition and due to exaggerated pharmacological effects observed from estimated Multiples of Exposure (MoEs) in the range of approximately 12 to 25-fold for a 0.8 kg BW ROP patient. The pattern of findings, i.e. their type, incidence and severity, was related to dose / exposure and treatment duration. Following systemic treatment, sexually immature monkeys tended to be more sensitive compared to adults particularly with regards to developing adverse findings on the nasal cavities/sinuses.

There is no suitable toxicological juvenile animal model for IVT dosing in preterm human infants available: At birth, the developmental stage of the retina of mice, rats and rabbits is considered largely to correspond to that of a preterm human infant but the eyes remain closed until eyelid opening occurs around day 10 to 14 in these species. At eyelid opening, the developmental stage of the eyes is generally equivalent to a term human newborn and no longer corresponds to a prematurely born infant (Abdo et al. 2017, Van Cruchten et al. 2017). IVT treatment of the eyes prior to eye opening is technically not feasible. Therefore, the only feasible option was to consider systemic dosing of juvenile mice. However, based on the consistent safety profile of aflibercept in the available safety studies to date, it is not expected that such a study would significantly alter the risk-benefit profile. This is supported by off-label use data in preterm infants, published results from the RAINBOW trial (Stahl et al. 2019) as well as the results of the Phase 3 Study 20090 (FIREFLEYE), which revealed no safety issues so far.

For all toxicological endpoints multiples of exposure (MoEs) regarding Cmax and, where available, AUC of free aflibercept were calculated for a preterm infant of 0.8 kg body weight (BW) dosed with 0.4 mg aflibercept/eye (both eyes treated). The preterm infant of 0.8 kg BW was selected as a baby with the minimal body weight at baseline included in the FIREFLEYE study, representing the worst case with regard to aflibercept exposure. AUC for the preterm infant was calculated based on clearance, scaled with body weight (CL=D/AUC) according to the equation:

$$AUC\_preterm = AUC\_adult \times \frac{BW\_adult}{BW\_preterm} \times \frac{DOSE\_preterm}{DOSE\_adult}$$

With DOSE_adult = 2 mg; AUC_adult = 2,856 µg·h/mL; BW_preterm infant: 0.8 kg, BW_adult: 66.5 kg

The Cmax was calculated similarly according to this formula and considered as reasonable for the eye but a rough estimation of systemic Cmax; therefore AUC-based MoEs appear to be more reliable.

In addition, exposure multiples with regard to mean Cmax of free aflibercept from the FIREFLEYE study were calculated, which lay in the range of the estimated MoEs.

The respective animal species were selected based on similarly high binding affinities of aflibercept with VEGF, consistent with amino acid sequences compared to human VEGF that are either highly homologous (mouse, rat and rabbit) or even identical (monkey). A strong anti-aflibercept antibody response in rats and mice upon repeat dosing led to mortality and excluded the use of rodents for longer toxicological studies. Rabbits developed antibodies only to a limited extent, while monkeys did not show a significant formation. Furthermore, the monkey eye is structurally and physiologically most similar to the human eye, and due to its size allows to safely inject an aflibercept IVT dose equivalent to or higher than that used in human patients. Thus, the cynomolgus monkey as the primary relevant species was used for all IVT and systemic toxicological studies of up to chronic duration, and the rabbit for the embryo-fetal development studies.

In addition, and for completeness of reporting: Cmax measured in the FIREFLEYE study reached 0.481 µg/mL. Cmax and AUC0-28days values calculated by the applicant reached 0.642 µg/mL and 94.962 µg.h/mL, respectively.

4.3.4.1. Repeat dose toxicity

1. Toxicity studies evaluating intravitreal (IVT) administration

Toxicological studies in monkeys with repeated IVT dosing of both eyes with aflibercept for up to 13 weeks (bilateral dosing with up to 2 mg/eye every 4 weeks or with 4 mg/eye every 6 weeks, 3-4 treatments in total) cover the maximal number of injection time points in preterm infants (including baseline treatment and potential retreatments if needed after a minimum interval of 28 days). However, since the 4- and 13-week studies did not include histopathology of the nasal turbinates as the primary target organ after IVT dosing, and the studies were mostly conducted using research formulations, the 8-month IVT monkey study with aflibercept in the commercial formulation is used as the key study for the risk assessment for aflibercept in premature infants with ROP.

Repeated IVT dosing of aflibercept up to 13 weeks produced mild, transient ocular inflammation that was generally reversible between doses or after the recovery period. In no instance was this inflammation associated with angiographic or electroretinographic changes, nor were any abnormalities detected upon ocular imaging or microscopic evaluation. There were no signs of systemic toxicity or histopathological findings up to the high dose of 4 mg/eye. However, it has to be noted, that the nasal turbinates as a target organ were not investigated in these studies. For a preterm infant of 0.8 kg BW bilaterally treated with 0.4 mg aflibercept per eye, systemic exposure measured in these animals was equivalent to estimated multiples of exposure (MoEs) of at least 16 with regard to Cmax and 27 with regard to $AUC_{(0\text{-}28\ days)}$, respectively, for free aflibercept.

In the 8-month pivotal IVT study in monkeys (no. VGFT TX-05011), aflibercept doses ranging from 0.5 to 4 mg/eye were administered bilaterally every 4 weeks for 9 doses in total. Ocular findings were similar to those seen in the 13-week studies consisting primarily of signs of mild and transient ocular inflammation. Systemic toxicity was evident but confined to chronic inflammation of the nasal turbinates with erosions and ulcerations of the respiratory epithelium from 2 mg/eye (equivalent to estimated MoEs of at least 9.2 and 10 regarding Cmax and $AUC_{(0\text{-}28\ days)}$, respectively). This finding had not completely resolved after recovery. The no observed adverse effect level (NOAEL) of 0.5 mg/eye in this study was equivalent to estimated MoEs of at least 1.9 and 1.5 regarding Cmax and $AUC_{(0\text{-}28\ days)}$ for free aflibercept.

The estimated multiples of exposure were confirmed by the recent results of the FIREFLEYE study: Cmax of free aflibercept in preterm infants after treatment with 0.4 mg/eye (treated bilaterally in 95% of the cases) was 23-fold lower than Cmax at the NOAEL in the 13-week study (no. VGFT TX 04025). In the chronic monkey study, at the LOAEL of 2 mg/eye the systemic exposure for free aflibercept was approximately 10-fold higher based on Cmax when compared to corresponding values observed in preterm infants after an intravitreal dose of 0.4 mg/eye. At the No Observed Adverse Effect Level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was about 2-fold higher when compared to corresponding values observed in preterm infants based on Cmax.

2. Toxicity studies evaluating systemic intravenous (IV) or subcutaneous (SC) administration

In monkeys, the toxicity of aflibercept was assessed in multiple repeat dose toxicity studies at doses of 1.5 to 30 mg/kg administered SC 2 to 3 times weekly for 4 to 13 weeks (no. VGFT-TX-03004 and VGFT-TX-02037) or at doses of 0.5 to 30 mg/kg administered IV weekly or bi-weekly for 4 to 26 weeks (no. VGFT-TX-02029, VGFT-TX-03048, VGFT-TX-05010, and VGFTTX-05009).

Although preterm infants with ROP will be dosed with aflibercept by the IVT route, also the toxicological studies with systemic administration were reviewed to identify target organs appearing at low multiples of exposure and after short treatment durations. This was done in order to monitor the respective target organs in the FIREFLEYE study. With the dosing schedule in preterm infants with ROP (single IVT

treatment of one or both eyes with one possible repetition not earlier than 28 days after the previous dose) the studies considered most relevant for safety assessment are the 4- and 13-week studies.

Toxicological findings from systemic intravenous (IV) and/or subcutaneous (SC) studies of up to 6 month duration in adult and sexually immature monkeys suggest exaggerated pharmacological effects that are generally consistent with VEGF inhibition. In these studies, free aflibercept exposures were significantly higher as compared with IVT administration. No NOAELs were identified in any of the systemic toxicology studies and immature monkeys tended to be more sensitive compared to adults particularly with regards to developing adverse findings on the nasal cavities/sinuses. This finding was the only systemic observation following IVT treatment of adult monkeys over 8 months, and therefore is considered toxicologically relevant. An overview on the target organs and estimated MoEs at the lowest doses at which respective findings were observed in the 4- and 13-week studies as well as in the 6-month study is given in the table at the end of this section.

Major target organs in adult monkeys in studies of up to 4 weeks of treatment include the kidneys, growth plates of the bones, adrenal glands (observed from estimated MoEs of $\geq$ 101 for Cmax), and, at higher doses, also the ovaries (at estimated MoEs ≥ 426 for Cmax). At the low dose, the kidney and bone findings were mostly minimal to slight and occurred in only a few animals; the reduced vacuolization of adrenal zona fasciculata cells was more pronounced, but is considered to reflect functional changes and not to be adverse *per se*.

After 13 weeks of dosing, all target organs observed in adult monkeys previously in studies of up to 4 weeks duration were identified at estimated MoEs from ≥ 11 regarding Cmax. In sexually immature monkeys, target organs identified at similar MoEs (≥ 13 to 17 fold for Cmax) were the nasal cavities/sinuses (degeneration/regeneration of epithelia) and the ovaries with MoEs of 18 or 19, respectively, based on $AUC_{(0\text{-}28\ days)}$. Again, findings at these exposure levels were only minimal to slight (in 2 cases moderate) and only present in a proportion of the animals.

Dosing over 13 weeks revealed additional target organs of toxicity in both adult and/or sexually immature monkeys, but only at much higher estimated MoEs of at least 94 fold for Cmax and/or 174 fold for $AUC_{(0\text{-}28\ days)}$. These include: the vertebrae (proliferation / degeneration of adjacent microvasculature, after recovery myofiber atrophy of axial musculature), the brain (macrophage infiltration in the choroid plexus, vascular degeneration / fibrosis) and the intestines (vasculitis). Further target organs were identified at even higher estimated MoEs from ≥ 746 and 1284 for Cmax and $AUC_{(0\text{-}28\ days)}$, respectively, and include the heart and urinary bladder (both: vasculitis), as well as the digestive tract (gall bladder, gastrointestinal tract and pancreas: vascular proliferation / degeneration and inflammatory changes).

Chronic treatment of adult monkeys up to 6 months affected further target organ systems such as male and female reproductive functions and organs (sperm motility and abnormalities, vagina and uterus: epithelial and endometrial / myometrial atrophy) at estimated MoEs of $\geq$ 147 in terms of Cmax and 226 in terms of $AUC_{(0\text{-}28\ days)}$, and the liver (portal inflammation and/or periportal necrosis) at estimated MoEs $\geq$ 715 in terms of Cmax and 1152 in terms of $AUC_{(0\text{-}28\ days)}$.

MoEs calculated based on the mean Cmax from the FIREFLEYE study were in the range of the predicted exposure margins and are presented in brackets in Table 9–2 below.

Taken collectively, the pattern of adverse organ findings in the systemic toxicity studies falls into two categories: those considered potentially relevant to human safety, i.e. occurring at MoEs in the range of approximately 25 – 50 fold, and those considered unlikely to be of toxicological significance for human risk assessment, i.e. occurring at MoEs of around 100 and much greater, i.e. from 1000 and above. In sexually immature monkeys, only two organ systems were identified in the low range of MoEs after 13 weeks of IV treatment, i.e. the ovaries and the nasal cavities/sinuses. It was noted that in adults, the MoEs for Cmax following SC dosing generally were lower compared to IV treatment consistent with the

respective route of administration. However, no AUCs could be calculated for SC dosing, limiting the further PK interpretation to some extent.

With the exception of exostosis in the 6-month study, all findings showed partial or complete reversibility.

Table 9–2: Estimated multiples of exposure (MoEs) for free aflibercept for a premature infant of 0.8 kg BW and MoEs in premature infants from the FIREFLEYE study [in brackets in the 3rd – 5th column] after bilateral IVT treatment with 0.4 mg aflibercept/eye with regard to endpoints from toxicological studies of different duration with systemic dosing of aflibercept in adult as well as sexually and skeletally immature monkeys (2-2.5 years of age)

Toxicological finding	Monkeys : adult (A) or sexually immature (I)	Estimated MoEs for a premature infant of 0.8 kg BW [MoEs from FIREFLEYE in brackets] based on Cmax / $AUC_{(0\text{-}28\ days)}$* of free aflibercept 4 weeks	13 weeks	6 months
Nasal cavities/sinuses: degeneration/ regeneration of the epithelium and/or necrosis, suppurative exsudate, hemorrhage, after 6 months: also atrophy or loss of septum or turbinate	A	NE	NE	≥ 147 / 226 LDlv [≥ 213] LDlv
	I	nd	**≥ 13 / 18** LDlv [≥ 18] LDlv	nd
Kidney (not immune-complex related in contrast to rats): ↑ of mesengial matrix of glomeruli, after 6 months: tubular cast, glomerulopathy	A	≥ 101 /nd LDsc [≥ 146] LDsc ≥ 181 /nd LDlv [≥ 263] LDlv	**≥ 11 / nd** LDsc [≥ 16] LDsc ≥ 184 / 295 LDlv [≥ 266] LDlv	≥ 147 / 226 LDlv [≥ 213] LDlv
	I	nd	≥ 94 / 174 MDlvf [≥ 136] MDlvf	nd
Bone: long bones, vertebrae & sternum: interference with growth plate maturation, exostoses at long bones only after 6 months	A	≥ 101 /nd LDsc [≥ 146] LDsc ≥ 181 /nd LDlv [≥ 263] LDlv	**≥ 11 / nd** LDsc [≥ 16] LDsc ≥ 184 / 295 LDlv [≥ 266] LDlv	≥ 147 / 226 LDlv [≥ 213] LDlv
	I	nd	≥ 94 / 174 MDlvf [≥ 136] MDlvf	nd
Vertebrae: osteocartilaginous exostoses, kyphosis / scoliosis & subsequent paravertebral muscle atrophy	A	NE	≥ 623 / 1020 MDlvf [≥ 903] MDlvf	≥ 147 / 226 LDlv [≥ 213] LDlv
	I	nd	≥ 94 / 174 MDlvf [≥ 136] MDlvf	nd
Adrenals: ↓ vacuolisation with eosinophilia of cortex	A	≥ 101 /nd LDsc [≥ 146] LDsc ≥ 181 /nd LDlv [≥ 263] LDlv	**≥ 11 / nd** LDsc [≥ 16] LDsc ≥ 184 / 295 LDlv [≥ 266] LDlv	≥ 147 / 226 LDlv [≥ 213] LDlv
	I	nd	≥ 94 / 174 MDlvf [≥ 136] MDlvf	nd
Ovaries: ↓ of maturing follicles, granulosa and theca cells, absence of corpora lutea	A	≥ 426/nd MDscf [≥ 617] MDscf ≥1762/nd MDlvf [≥2553] MDlvf	**≥ 12 / nd** LDscf [≥ 17] LDscf ≥ 493 / 736 LDlvf [≥ 339] LDlvf	≥ 147 / 226 LDlv [≥ 213] LDlv
	I	nd	**≥ 17 / 19** LDlvf [≥ 25] LDlvf	nd
Intestines: vasculitis **Heart**: vasculitis (n = 1/8 m) **Urinary bladder**: vasculitis (n = 1/8 m)	A	NE	≥ 184 / 295 LDlv [≥ 266] LDlv ≥ 746 / 1284 MDlvm [≥1081] MDlvm ≥2135 / 2152 HDlvm [≥3093] HDlvm	NE
	I	nd	NE	nd

Choroid plexus (brain): infiltration of macrophages in choroid plexus	A	NE	NE	≥ 147 / 226^{LDIv} [≥ 213] ^{LDIv}
	I	nd	≥ 136 / 232^{MDIvm} [≥ 197] ^{MDIvm}	nd
Brain: chronic vascular degeneration / fibrosis	A	NE	NE	≥715 / 1152^{HDIvm} [≥1036] ^{HDIvm}
	I	nd	≥ 136 / 232^{MDIvm} [≥ 197] ^{MDIvm}	nd
Uterus: endometrial and myometrial atrophy	A	NE	NE	≥ 181 / 236^{LDIvf} [≥ 262] ^{LDIvf}
	I	nd	NE	nd
Testes: ↓ sperm motility & ↑ sperm abnormalities#	A	nd	nd	≥ 147 / 226^{LDIv} [≥ 213] ^{LDIv}
	I	nd	nd	nd
Vagina: epithelial atrophy	A	NE	NE	≥502 / 772^{MDIvf} [≥ 727] ^{MDIvf}
	I	nd	NE	nd
Gastrointestinal System (stomach, duodenum/rectum) & gallbladder: vascular proliferation/degeneration and/or inflammation, duodenum: ulceration or villous/mucosal atrophy, slight hemorrhage	A	NE	≥ 746 / 1284^{MDIvm} [≥ 1081] ^{MDIvm}	≥435^{MDIvm}/772^{MDIvf} [≥ 630] ^{MDIvm}
	I	nd	≥1292^{HDIvm}/1684^{HDIvf} [≥3093] ^{HDIvm}	nd
Liver: portal inflammation and/or periportal necrosis	A	NE	NE	≥715 / 1152^{HDIvm} [≥1036] ^{HDIvm}
	I	nd	NE	nd
Pancreas: vascular proliferation / degeneration	A	NE	≥ 1963/3368^{HDIvf} [≥ 2844] ^{HDIvf}	≥715 / 1152^{HDIvm} [≥1036] ^{HDIvm}
	I	nd	NE	nd

[] = MoEs in premature infants from the FIREFLEYE study (calculated using the arithmetic mean of free Cmax) after bilateral IVT treatment with 0.4 mg aflibercept/eye; BW = body weight; f = female; HD = high dose; IV = intravenous; LD = low dose; m = male; MD = mid dose; MoEs = multiples of exposure; nd = no data; NE = no effect; SC = subcutaneous.
# = investigation of sperm.

The nasal cavity/ sinuses were identified as the sole systemic target organ after IVT administration. Findings were noted at 10-fold higher Cmax level than in ROP patients, with a Cmax-based safety margin of 1.6-1.7 (rounded to 2 in proposed SPC 5.3 wording). Similar findings were reported at all dose levels in the 13-week and 6-month intravenous studies wherein immature animals (13-week study, animals aged 2-2.5 years at initiation of treatment) seemed more sensitive (17-20-fold clinical exposure based on Cmax or AUC).

Other effects were in general consistent with the pharmacological activity of aflibercept, and occurred mostly at high exposure multiples (≥100). To be noted, kidney, bone growth plate, adrenal and ovary findings were seen from the low dose level in the 13-week SC study (11- to 16-fold the clinical Cmax) and reported to be of minimal to slight severity. The NOAELs determined for these organs (except ovaries) in the 13-week IV study in immature monkeys was 0.5 mg/kg which corresponds to Cmax- and AUC-based safety margins of 17-23 and 18-19, respectively (Cmax determined in FIREFLEYE study).

As regards ovary findings, they consisted in absent corpora lutea, and decreased maturating follicles and/or granulosa and/or theca cells; they do not appear of relevance to ROP patients. Similarly, the reported sperm findings in the 6-month IV study do not appear relevant for ROP patients.

Proteinuria, nasal bleeding, and growth were monitored in the FIREFLEYE clinical trial to account for the nasal cavity/ sinuses, kidney and bone growth plate findings in toxicological studies and continuous kidney and skeleton development in ROP patients. A follow-up period of 5 years is also planned in the

FIREFLEYE NEXT extension study. This is considered as adequate in view of the toxicological profile of aflibercept in repeat-dose toxicity studies. Up to now, no AE was reported on these parameters.

Effects on the brain (chronic vascular degeneration/fibrosis, infiltration of macrophages in choroid plexus) were noted in the 13-week IV study in immature monkeys and in the 6-month IV study at the mid and high dose levels inducing ≥136-fold clinical exposure. At the low dose levels, exposure multiples were ≥17-fold (based on Cmax measured in ROP patients in FIREFLEYE study). This leads to potential uncertainties about impact of anti-VEGF treatment on neurodevelopment. Neurodevelopmental outcomes will be assessed as part of the 5-year follow-up study.

4.3.4.2. Reproduction toxicity

An effect of aflibercept on intrauterine development was demonstrated in embryo-fetal development (EFD) studies in pregnant rabbits with IV (3 to 60 mg/kg) as well as SC (0.1 to 1 mg/kg) administration either during organogenesis or from day of gestation 1 up to the end of organogenesis, respectively (studies no. VGFT-TX-06002 and VGFT-TX-11034). Maternal NOAELs were 3 mg/kg IV and 1 mg/kg SC; a developmental NOAEL was not identified. Continuous exposure was demonstrated in spite of intermittent treatment on gestation days (GDs) 6, 9, 12, 15 and 18 in the IV and 1, 7 and 13 in the SC study. Adverse developmental effects were evident mainly as visceral malformations and variations of the cardiovascular system, consistent with the anti-angiogenic properties of aflibercept. Further malformations and variations of other organ systems and/or the skeleton were also seen across groups. However, there was no evidence of specific adverse effects on the development of the eyes. A single foetus at 60 mg/kg IV (maternal exposure equivalent to estimated MoEs of 3833 or 706 regarding Cmax or AUC(0-3 days) of free aflibercept, respectively, in comparison with the premature infant) was found to exhibit unilateral microphthalmia, for which a relation to treatment cannot be totally discounted. Notably, the development of the eye occurs early in development and microphthalmia is the clinical presentation of a fundamentally disturbed developmental process resulting in major and multiple malformations of the eye structures. Therefore, this isolated finding at very high MoEs is not considered relevant to the risk assessment of aflibercept in a clinical situation, where a developed eye of a prematurely born child is dosed directly to treat the clinical condition of ROP.

The malformations and variations described above develop early in organogenesis whilst in preterm infants with ROP, the major organogenesis is already completed (the period of major organogenesis in humans is completed after the first trimester of pregnancy). Therefore, similar effects are not expected to occur after IVT treatment of these patients with aflibercept.

Effects on male and female fertility were assessed as part of the 6-month study in monkeys with IV administration of aflibercept ranging from 3 to 30 mg/kg BW (no. VGFT-TX-05009). Absent or irregular menses associated with alterations in female reproductive hormone levels, and changes in sperm morphology and motility were observed at all dose levels, but were reversible after recovery. For the preterm infant these reversible effects on fertility are not considered to be relevant, since premature infants are not yet fertile and are treated on only one or two treatment occasions with aflibercept IVT.

Table 9–3: Estimated multiples of exposure (MoEs) for free aflibercept for a premature infant of 0.8 kg BW and MoEs in premature infants from the FIREFLEYE study [in brackets in the 3rd column] after bilateral IVT treatment with 0.4 mg aflibercept/eye with regard to endpoints from toxicological studies on embryo-fetal development and fertility of aflibercept

Study / Endpoint / Finding	Dose	Estimated MoEs based on Cmax of free aflibercept	Estimated MoEs based on AUC of free aflibercept
EFD study rabbit, IV (GD 6, 9, 12, 15 and 18):			$AUC_{(GD\ 6\text{-}21)}$*
maternal NOAEL / developmental LOAEL	3 mg/kg BW IV	87 [127]	102
EFD study rabbit, SC (GD 1, 7 and 13):			$AUC_{(GD\ 1\text{-}20)}$#
maternal NOAEL	1 mg/kg BW SC	6 [9]	6
developmental LOAEL	0.1 mg/kg BW SC	0.4 [0.6]	0.4
Male and female fertility: 6-month IV toxicity study in monkey (5 months recovery):			$AUC_{(0\text{-}28\ days)}$
LOAEL for male and female fertility	3 mg/kg BW IV (once weekly up to week 15, then every 2 weeks)	≥ 147 [≥ 213]	≥ 226

[] = MoEs in premature infants from the FIREFLEYE study (calculated using the arithmetic mean of free Cmax) after bilateral IVT treatment with 0.4 mg aflibercept/eye; BW = body weight; EFD = embryo-fetal development; GD = gestational day; IV = intravenous; LOAEL = lowest observed adverse effect level; MoEs = multiples of exposure; NOAEL = no observed adverse effect level; SC = subcutaneous; * = $AUC_{(GD6\text{-}21)}$ was calculated from $AUC_{(0\text{-}7\ days)}$ after the 5th dose multiplied with the number of doses (5); # = $AUC_{(GD1\text{-}20)}$ was calculated from $AUC_{(0\text{-}7\ days)}$ after the 3rd dose multiplied with the number of doses (3).

Results of the EFD study mainly point to treatment-related effects occurring during major organogenesis, so that most are not expected to occur in ROP patients. Therefore, the applicant's proposal to add in SPC 5.3 that the systemic exposure in rabbits at the LOAEL (0.1 mg/kg, sc) is 0.6-fold that in ROP patients but that effects reported in rabbit foetuses are not expected to occur in this patients after IVT administrations since major organogenesis is already complete in this population is not supported.

As regards effects on the male and female fertility/ sexual organs, they are considered of limited relevance in ROP patients (see also previous section).

4.3.5. Ecotoxicity/environmental risk assessment

The European 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use' (EMEA/CHMP/SWP/4447/00, London, June 2006) stipulates the requirement for an ERA for medicinal products licensed in the EU after 20061. In accordance with the EMA guideline1 for proteins an ERA statement is sufficient, which details why no ERA studies are provided and why there is no significant risk to the environment.

Aflibercept (BAY 86-5321) is a recombinant protein consisting of human vascular endothelial growth factor receptor (VEGFR) extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). It contains portions of the extra- cellular domains of two different VEGF receptors, VEGFR-1 and VEGFR-2. The two domains bind the vascular endothelial growth factor (VEGF) with different potency.

The recombinant protein is expressed in Chinese Hamster Ovary (CHO) K1 cells.

Recovery and purification of the protein is accomplished via a combination of filtration and chromatographic techniques. Aflibercept is then formulated for intravitreal (IVT) administration.

Aflibercept has a market approval in the EU for a variety of ophthalmological diseases in adult patients, i.e., for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular edema secondary to retinal vein occlusion (branch or central RVO), visual impairment

due to diabetic macular edema (DME), and visual impairment due to myopic choroidal neovascularization (myopic CNV) in adults.

The new targeted pediatric indication is on treatment of retinopathy of prematurity in preterm infants. This new treatment may potentially increase the emission of aflibercept into the environment.

However, aflibercept is a protein which can generally be expected to be readily and completely degraded in the environment. Neither bioaccumulation nor toxicity is to be expected from proteins when released into environmental compartments. Thus, based on common knowledge there is no indication that aflibercept could be a risk to the environment and consequently no ERA studies are required. Therefore, in accordance with the EMA guideline1 no ERA has to be provided for the protein- based medicinal product EYLEA.

The applicant provided a suitable justification for not performing an Environmental Risk Assessment (ERA) in line with the guidance from the "Guideline on the Environmental Risk Assessment of the medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2).

4.3.6. Discussion on non-clinical aspects

Aflibercept is a recombinant fusion protein that binds human VEGF-A and PlGF-2 with high affinity, blocking the interaction of these ligands with their cognate receptors. During the initial pharmacological development program, it was demonstrated that local (IVT) and systemic (IV and SC) administrations of Aflibercept were capable of inhibiting neovascularization and/or pathological vascular leak in disease-relevant animal models in mice, rats and monkeys.

For the indication Retinopathy of Prematurity (ROP), no additional primary or secondary pharmacology or safety pharmacology studies were conducted on aflibercept as agreed with PDCO. Since no additional studies were required, the applicant has submitted publications on animal models of ROP and the existing safety pharmacology studies, already conducted, have been re-assessed with regard to safety margins in the preterm infant. Thus, a review of Aflibercept's effectiveness in the treatment of ocular neovascular disorders, has been presented by the applicant in various preclinical studies following IV, SC or IVT routes of administration. The development of the retinal vasculature and the progression of ROP has been learned through the use of animal models of oxygen-induced retinopathy (OIR), which approximate the human condition. The applicant has justified the usefulness of Aflibercept with data generated in mouse and canine OIR models in neonatal animals via various routes of administration.

High significant MoEs (> 700 fold) were observed for respiratory effects, CNS effects, thrombosis after IV administration. These effects are not considered relevant based on exposures after IVT administration are by far lower than those after IV route. However weak MoEs have been observed regarding blood pressure (MoE = 1.6x at the NOEL, first effects at MoE of 3.5x) after SC administration and therefore transient effects on blood pressure cannot be totally ruled out in clinics.

No additional preclinical studies were conducted regarding the extension of use of aflibercept in ROP patients. It is agreed that IVT administration in juvenile animals are not considered feasible in order to give translational information in regards of the target population.

The applicant provided a suitable justification for not performing an Environmental Risk Assessment (ERA) and no ERA was requested for the initial MA in adults regarding a broad panel of ophthalmological diseases.

A comprehensive program of toxicological studies conducted either via intravitreal or systemic (subcutaneous, intravenous) routes of administration was undertaken to support the development of aflibercept in adult patients. The pharmaco-toxicological profile of aflibercept was well characterized in

these studies, and the main findings were consistent with VEGF inhibition. Toxicological studies performed in Cynomolgus monkeys, including a 13-week study in immature animals, were reviewed and margins of exposure were calculated considering measured Cmax, and predicted Cmax and AUC values in ROP patients. Target organs of particular relevance for paediatric patients were identified, notably the kidney, and bone growth plate. Except for the finding in the nasal cavity/sinuses, adverse effects occurred in general at high exposure multiples with acceptable safety margins. Based on the toxicological profile and ongoing development of some target organs in paediatric patients (kidney, skeleton), nasal bleeding, proteinuria and growth and development were monitored in the FIREFLEYE clinical trial, with a planned 5-year follow-up in the extension study. This includes neurodevelopmental outcomes due to concerns about impact of anti-VEGF treatment on this aspect. Overall, potential effects of concerns with generally acceptable exposure ratios were identified from the available toxicological data, and clinical safety monitoring was subsequently put in place. Additional toxicological data are not considered of potential added value.

Results of the EFD study mainly point to treatment-related effects occurring during major organogenesis, so that most are not expected to occur in ROP patients. Therefore, the applicant's proposal to add in SPC 5.3 that the systemic exposure in rabbits at the LOAEL (0.1 mg/kg, sc) is 0.6-fold that in ROP patients but that effects reported in rabbit foetuses are not expected to occur in this patients after IVT administrations since major organogenesis is already complete in this population is not supported. In addition, it is suggested to remove from SPC 5.3 the exposure ratios at the LOAEL for effects on respiratory epithelium, to provide a clearer wording for the prescriber and considering that exposure ratios at the NOAEL for these effects are mentioned.

4.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view the extended indication of aflibercept in ROP can be granted.

4.4. Clinical aspects

4.4.1. Pharmacokinetics

Absorption

The Phase 3 study FIREFLEYE (Study 20090) was conducted in ROP patients receiving IVT injection of 0.4 mg aflibercept. FIREFLEYE was a randomized, 2-arm, open-label study of the efficacy, safety, and tolerability of aflibercept compared to laser photocoagulation in patients with ROP. The extension study FIREFLEYE NEXT evaluates the long term outcomes of patients who received treatment for ROP in FIREFLEYE. Aflibercept (Eylea 40 mg/mL solution for injection) was investigated at a single dose of 0.4 mg (in an injection volume of 0.01 mL) per injection and eye. The 0.4 mg dose corresponds to 20% of the Eylea dose (2 mg) approved for use in adults.

After IVT administration of 0.4 mg aflibercept (mostly bilaterally on the same day), mean concentrations of free (pharmacologically active) aflibercept declined until week 4 after dosing (mean concentration of 133 ng/mL at week 4), and further declined thereafter to values below or close to the lower limit of quantification by 8 weeks after start of treatment. Over time, with decreasing concentrations of free aflibercept (binding to VEGF by aflibercept'smode of action), levels of bound aflibercept increased up to week 4, and declined thereafter.

Table 2–1: Mean concentration-time data of free and adjusted bound aflibercept [ng/mL] in plasma (PKS)

Time	N total	N ≥ LLOQ [a]	Arith. Mean ± SD (ng/mL)	Range (ng/mL)
	Free aflibercept			
Week 0/Day 1	75	66	481 ± 885	<LLOQ – 4570
Week 2	66	60	219 ± 359	<LLOQ – 2750
Week 4	68	54	133 ± 205	<LLOQ – 923
Week 8	3	1	N.C.	<LLOQ – 16.1
Week 12	7	1	N.C.	<LLOQ – 194 [b]
Week 24	14	0	N.C.	<LLOQ
	Adjusted bound aflibercept			
Week 0/Day 1	75	66	149 ± 166	<LLOQ – 968
Week 2	65	60	1154 ± 677	<LLOQ – 2646
Week 4	67	61	1336 ± 990	<LLOQ – 5887
Week 8	3	1	N.C.	<LLOQ – 1090
Week 12	7	5	281 ± 297	<LLOQ – 803
Week 24	14	9	N.C.	<LLOQ – 457

Abbreviations: LLOQ=lower limit of quantitation; N=number of observations; N.C. =not calculated, PKS= Pharmacokinetics analysis set, SD= standard deviation.

a: Values below LLOQ were substituted by 0 for arithmetic statistics. LLOQ of free aflibercept = 15.6 ng/mL; LLOQ of adjusted bound aflibercept = 22.4 ng/mL

b: The patient showing high concentrations of free aflibercept in plasma at week 12 (RNR 300010001) results from a bilateral re-dosing in week 11 (see Module 5.3.5.1 (ROP), PH-41617, Listing 16.2.5 / 1 and 16.2.5 / 4).

Abbreviations: LLOQ=lower limit of quantification, N=number of subjects, N.C.=not calculable, SD=standard deviation.

Source: Module 5.3.5.1 (ROP), PH-41617, Table 14.4 / 1

Exploratory comparisons between sub-populations included in the study were primarily based on plasma concentrations of free aflibercept until Week 4, as most of the samples thereafter being <LLOQ. For the interpretation of data, it should generally be considered that the numbers of subjects across subgroups varied considerably.

Mean free aflibercept concentrations all declined from Week 0/Day1 onwards independent of the baseline BW. Mean adjusted bound aflibercept concentrations increased from Week 0/Day1 until Week 4 and declined thereafter, independent of baseline BW. Between the different BW groups at a single time point, mean free and adjusted bound aflibercept concentrations were highest in the lowest BW group and lowest in the highest BW group.

No apparent differences in exposure to free aflibercept between GA groups were observed. When comparing the mean values in the different groups, the numbers per group as well as the high variability of data should be considered. Across all time points, no relevant difference between males and females was observed. Differences in mean concentrations were most likely a result of extreme values in the respective group (male or female) rather than a real difference in groups. Likewise, the comparison between regions did not reveal any relevant and consistent differences among Japanese and Non-Japanese subjects. Concentration ranges of Japanese subjects were fully contained within ranges of Non- Japanese subjects. Comparison of mean plasma concentrations of free aflibercept across different race groups did not show large differences and were mainly influenced by a few extreme values.

There seemed to be a trend towards lower plasma concentrations of adjusted bound aflibercept in the GA groups 24 - <27 weeks compared to the younger and older age groups. However, when comparing the mean values in the different groups, the numbers per group as well as the high variability of data should be considered. Therefore, this difference appeared to be small and clinically not relevant. Across all time points, no relevant difference between males and females was observed. Differences in mean

concentrations were most likely a result of extreme values in the respective group (male or female) rather than a real difference in groups. There was a trend towards slightly higher mean plasma concentrations of adjusted bound aflibercept in the Japanese group compared to the Non-Japanese group. However, the number of Japanese subjects was considerably lower than in the Non-Japanese group and concentration ranges of Japanese subjects were fully contained within ranges of Non-Japanese subjects. Comparison of mean plasma concentrations of adjusted bound aflibercept across different race groups did not show large differences and were mainly influenced by few extreme values. The Black and African American as well as the Multiple race group contained only few subjects with single plasma concentrations.

For both free and adjusted bound aflibercept, oxygen supplementation at baseline as well as histories of previous conditions (history of sepsis, history of necrotizing enterocolitis, history of intraventricular hemorrhages) did not reveal any systematic differences between these groups. The largest differences were seen at Week 0/Day 1, mainly due to single extreme values. In general, plasma concentrations of free aflibercept were highly variable and the numbers per group with concentrations >LLOQ varied.

There seemed to be a trend toward lower plasma concentrations of adjusted bound aflibercept in the subjects with history of intraventricular hemorrhages. Subject numbers in this group were lower than in the group of no history of intraventricular hemorrhages and concentration ranges were fully contained in the other group. Therefore, the difference appeared to be small and not clinically relevant.

In conclusion, mean free aflibercept concentrations all declined from Week 0/Day1 onwards independent of the baseline BW. Mean adjusted bound aflibercept concentrations increased from Week 0/Day1 until Week 4 and declined thereafter. Exploratory sub-population analysis revealed no clinically relevant differences in free or adjusted bound aflibercept concentrations in plasma with respect to baseline BW, gender, race, GA, oxygen supplementation at baseline, history of sepsis, necrotizing enterocolitis and intraventricular hemorrhage.

Distribution and elimination

It may be hypothesized that the increased expression in preterms plays a key role in the distribution and elimination processes of both free and bound aflibercept, leading to a prolonged elimination half-life of free aflibercept compared to adults. As the FcRn expression depends on the GA (gestational age), this may also add to the overall variability in the distribution and elimination processes of both free and bound aflibercept.

Special populations

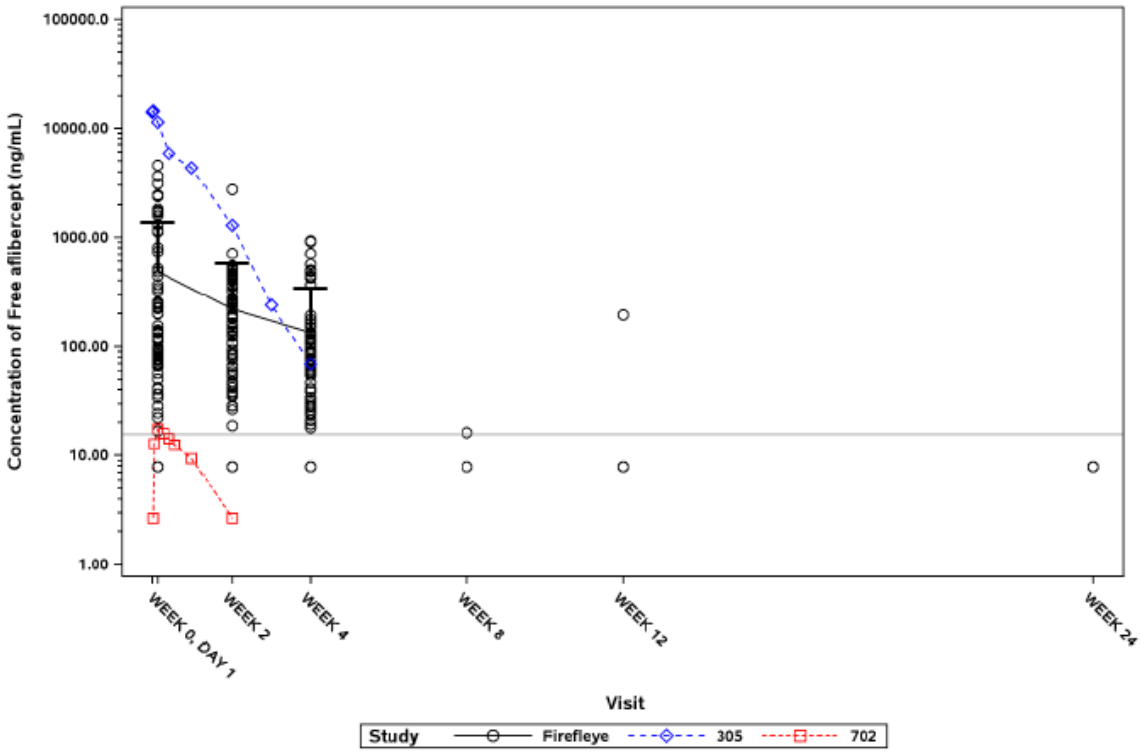
Exploratory sub-population analyses revealed no relevant effects on free or bound aflibercept concentrations with respect to baseline body weight, gestational age, gender, region (Japan, outside Japan), race, oxygen supplementation at baseline, history of sepsis, history of necrotizing enterocolitis, and history of intraventricular hemorrhage.

Comparison between adult and paediatric populations is detailed below.

3. Free aflibercept

Mean plasma concentrations of free aflibercept in patients with ROP were higher compared to adult patients with AMD following monthly IVT administrations (2 mg), but stayed below mean concentrations measured after administration of the maximum tolerated IV dose in adult AMD patients (1 mg/kg IV, see Module 5.3.3.2, Report VGFT-OD-0305, Section 5.1.1) until around week 4 where they exceeded adult concentrations due to slower elimination. (see Figure 1, Tableau 1). Mean free aflibercept concentrations in ROP patients declined after IVT administration until week 4. Thereafter, plasma concentrations of free aflibercept were <LLOQ in most of the patients. At week 8, there was

only one out of three patients with a measurable concentration close to the LLOQ. At week 12, one out of seven patients showed high concentrations of free aflibercept in plasma resulting from a bilateral re-dosing in week 11. At week 24, all 14 patients had no measurable concentrations.

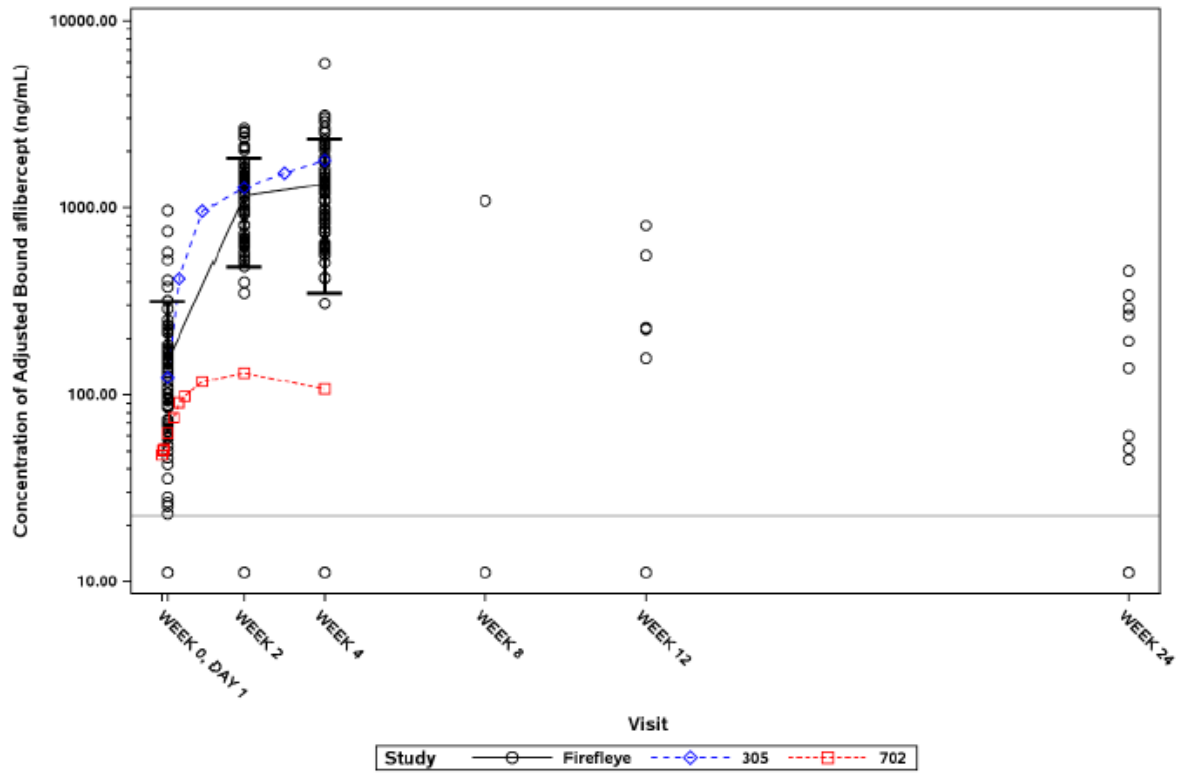


Abbreviations: ROP=retinopathy of prematurity, IV=intravenous, IVT=intravitreal. SD=standard deviation.
Adult reference data: Upper dashed line: Mean concentrations of free aflibercept after 1 mg/kg IV administration in adult patients (n=7) (Module 5.3.3.2, VGFT-OD-0305, Section 6, and Table 7.2); Lower dashed line: Mean concentrations of free aflibercept after repeated IVT administration of 2 mg in adult patients (n=6) (VGFT-OD-0702, see Module 5.3.3.2, VGFT-OD-0702.PK, Section 3 and Table 3.4.1.2.); Solid line: Mean concentrations of free aflibercept in pediatric ROP patients. The lower error bars are not shown as the SD exceeded the arithmetic mean (Module 5.3.5.1 (ROP), PH-41617, Table 14.4 / 1 and Table 2–1).
LLOQ for free aflibercept: 15.6 ng/mL. Values below LLOQ are presented as ½ LLOQ.
Source: Module 5.3.5.3 (ROP), PH-42122, Figure 1.1.1 / 1.

Figure 1: Individual and mean plasma concentration of free aflibercept in paediatric patients with ROP vs arithmetic mean concentrations in adults after IV and IVT

4. Adjusted bound aflibercept

Mean plasma concentrations of adjusted bound aflibercept in patients with ROP after single administration were higher compared to plasma concentrations in adult patients with AMD following multiple IVT administrations, but were close to plasma concentrations of adjusted bound aflibercept measured after single administration of the maximum tolerated IV dose of 1 mg/kg in adult patients with AMD (see Figure 2). Mean adjusted bound concentrations increased up to week 2 and stayed at that level until week 4. Thereafter, plasma concentrations declined up to week 12 and were <LLOQ at week 24.



Abbreviations: ROP=retinopathy of prematurity, IV=intravenous, IVT=intravitreal SD=standard deviation.
Adult reference data: Upper dashed line: Mean concentrations of adjusted bound aflibercept after 1 mg/kg IV administration in adult patients (n=7) (Module 5.3.3.2, VGFT-OD-0305, Section 6 and Table 7.3); Lower dashed line: Mean concentrations of adjusted bound aflibercept after multiple IVT administrations of 2 mg in adult patients (n=6) (VGFT-OD-0702, see Module 5.3.3.2, VGFT-OD-0702.PK, Section 3 and Table 3.4.1.3); Solid line: Mean concentrations of adjusted bound aflibercept in pediatric ROP patients. The lower error bar is only shown if the SD did not exceed the arithmetic mean (Module 5.3.5.1 (ROP), PH-41617, Table 14.4 / 1 and Table 2–1).
LLOQ for adjusted bound aflibercept: 22.4 ng/mL. Values below LLOQ are presented as ½ LLOQ.
Source: Module 5.3.5.3 (ROP), PH-42122, Figure 1.1.1 / 2.

Figure 2: Individual and mean plasma concentration of adjusted bound aflibercept in paediatric patients with ROP vs arithmetic mean concentrations in adults after IV and IVT

5. Conclusion

Taken together, mean values of free and adjusted bound Cmax in FIREFLEYE were higher than those seen in adults after 2 mg aflibercept (approximately 25-fold higher for free, approximately 7-fold higher for adjusted bound aflibercept) (see Tableau 1). Considering only the mean difference of body weight between preterm patients and adult patients (which differed by a factor of approximately 40), and the 0.4-fold lower total dose applied in preterms, the differences are within the expected range.

Tableau 1: Exposure in preterm patients vs adult exposure data

Parameter	Adult (n=6)	Preterm (n= 75)
IVT Dose	2 mg	2 x 0.4 mg
Body Weight	Mean (range)	Mean (range)
	77.0 (69 - 87) kg	2.03 kg (0.800 - 3.80 kg)
Max. mean plasma concentration (ng/mL)	Mean (range)	Mean (range)
Free aflibercept	19.3 (LLOQ – 54.0)	481 (LLOQ –4570)
Adj. bound aflibercept	186 (100 – 286)	1336 (LLOQ - 5887)

Abbreviations: IVT= intravitreal; LLOQ=lower limit of quantitation.
Source: Module 5.3.5.4, VGFT-OD-0702, Table 14.1.2/2; Module 5.3.3.2, VGFT-OD-0702.PK, Table 3.4.2.2 and Table 3.4.2.4; Module 5.3.5.1 (ROP), PH-41617, Table 14.1.4 / 1 and Table 14.4 / 1.

Exposure for free as well as adjusted bound aflibercept after IVT in preterm patients was more important than in adults, and was very variable. However, it was still mostly below IV adult exposure. This may be explained by variation of FcRn expression, the variability being also linked with gestational age. The increase of exposure, as well as the variability, is to be expected and paediatric exposure after IVT has been adequately explored.

4.5. Clinical efficacy

4.5.1. Main study

The MAH submitted the results of the FIREFLY study (Study 20090), an open-label, randomized, two–arm, controlled trial to assess the efficacy, safety, and tolerability of intravitreal aflibercept compared to laser photocoagulation in patients with retinopathy of prematurity. This study is part of clinical development programme and was carried out according to the Paediatric Investigation Plan of EYLEA.

FIREFLEYE study followed the several points discussed and agreed in the PIP, such as: indication, population, criteria of participation in the study, endpoints, number of patients and duration of the treatment. Regarding the study design, discussions were held on the number of arms and dose proposed. Following exchanges, the PDCO agreed with 2 arms (aflibercept 0.4 mg and laser). Furthermore, the MAH agreed with the PDCO on the participation of all eligible patients in an extension study (not part of the PIP), FIREFLEYE next (Study 20275), until they are 5 years of age to assess ocular effects, clinical and neurodevelopmental outcomes at 5 years of chronological age.

Overall, the presented evidence supporting the clinical efficacy of aflibercept 0.4 mg for the treatment of ROP subjects was derived from the full 6-month data from the pivotal Study 20090 in which 113 subjects were treated at baseline (after randomization in a 2:1 ratio) with either aflibercept 0.4 mg per eye (75 subjects) or laser (38 subjects).

Additionally, a pre-planned evidence synthesis study, as well as the results from a pre-planned interim analysis of the extension Study 20275 were provided to bring supportive evidences.

Methods

Study design

Core Study 20090

This was a phase 3, multicenter, open-label, randomized, 2-arm controlled study to assess the efficacy, safety, and tolerability of IVT aflibercept compared to laser photocoagulation in subjects with ROP. The study consisted of screening/baseline visit(s) (which could have been on the same day or within 10 days of each other), a 23-week treatment period (including retreatment and rescue treatment), and a final

visit at week 24 (could have been between weeks 25 and 27 for subjects treated between weeks 21 and 23). Study duration was planned for at least 24 weeks.

Subjects were randomized in a 2:1 ratio to baseline treatment with aflibercept 0.4 mg or laser per eligible eye. After baseline treatment, retreatment and rescue treatment (laser for the aflibercept -treated subjects, aflibercept for the laser-treated subjects) was permitted according to pre-defined retreatment and rescue treatment criteria. Retreatment with aflibercept at the same single dose of 0.4 mg at least 28 days after the previous injection in either eye was allowed, up to 2 additional injections per eye. In case multiple laser sessions were necessary within 1 week from baseline, they were counted as a single treatment. Subjects for whom aflibercept rescue treatment was initiated were thereafter managed according to the aflibercept arm treatment regimen.

One or both eyes could be treated according to the investigator's assessment of the study's eligibility criteria. The second eye of subjects who started the study with one eligible eye was kept under observation according to the local ROP screening guidelines or at every study visit, whichever was more frequent. Second eyes that developed ROP requiring treatment during the study received treatment according to the randomization assignment of the first eye.

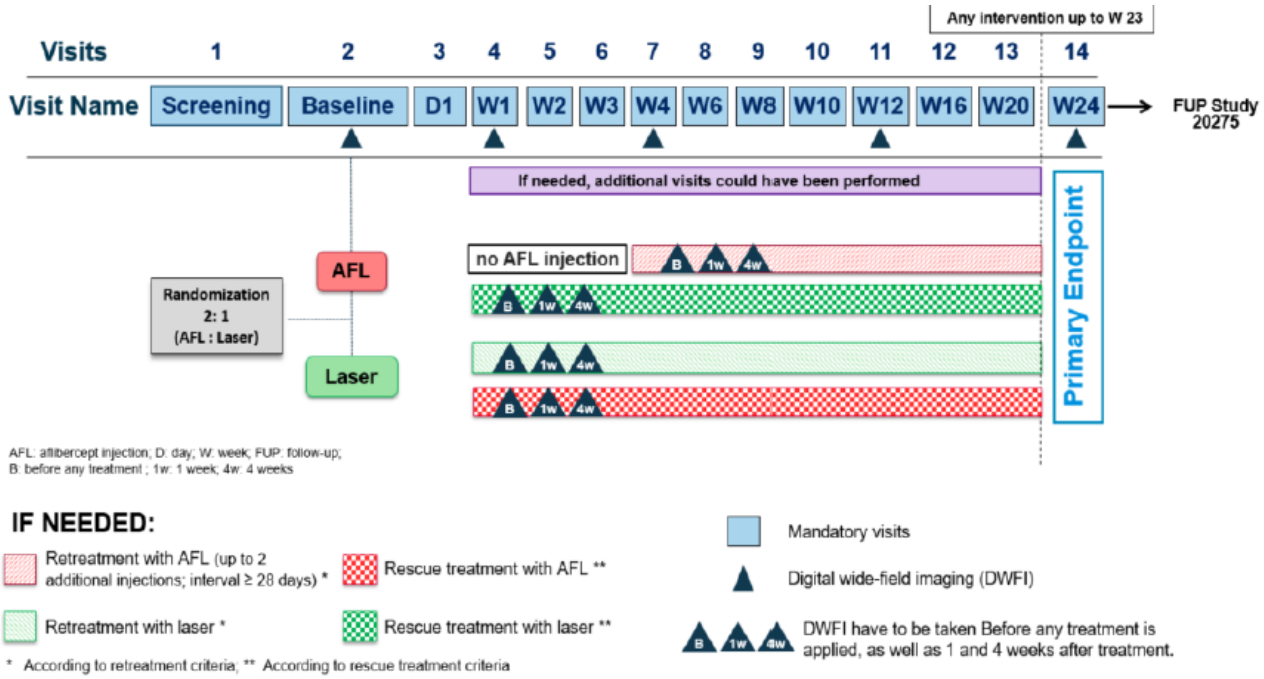


Figure 5.5.1 - Study design of Core Study 20090

The overall designed is acceptable and in agreement with the PIP discussed with the PDCO.

Subjects were randomised in two aflibercept 0.4 mg/0.01 mL or laser photocoagulation treatment arm in a 2:1 ratio.

The laser photocoagulation has been chosen as comparator. This option was considered as part of the standard of care at the time of starting the clinical development and was acceptable from an ethical point of view. However, the MAH did not discuss the inclusion of another comparator (anti-VEGF-agent). This point was raised and discussed with agreement at the Day 120 PDCO discussion for the Applicant to provide an historical/ published evidence study with other anti-VEGF.
One or both eyes were treated, and included in the study based on the study eligibility criteria as assessed by the investigator, at baseline or later during the study. Considering that this has been

taken into account in the statistical analysis plan (see comment further below), together with the fact both eyes received the same treatment, the approach does not raise concerns. As a note, in the aflibercept group, the injection should have been performed in both eyes on the same day.

Participants were treated at baseline. However, retreatment or rescue could be administrated from Week 1 and for the following 23 weeks the study as per the defined criteria.

Retreatment

- In the aflibercept group, up to 2 additional IVT injections may have been administered in each eye at a minimum interval of 28 days between injections and in case further pre-specified retreatment criteria were met (see further below, under subheading "Treatments").
- In the Laser arm, subjects randomized to laser photocoagulation underwent treatment in each eligible eye at baseline. Laser ablation should have been as complete as possible as judged by the investigator. If multiple sessions were necessary within 1 week from baseline, they were counted as a single laser treatment.

Rescue therapy

If needed, patients could receive rescue treatment switching to another treatment (patients who received aflibercept as initial treatment could switch to laser therapy and vice versa). Once rescue treatment is applied to an eye, treatment in that eye with the subject's randomized treatment cannot be reinitiated. However, the fellow eye can still receive the subject's randomized study intervention, if retreatment criteria are met, which is acceptable.

<u>Extension Study 20275</u>

Study 20275 is an ongoing, phase 3b, multicenter, extension study to evaluate the long-term outcomes of subjects who received treatment (aflibercept and/or laser) for ROP in Study 20090. All subjects who were treated in Study 20090 were eligible for enrollment and are being followed for ocular, neurodevelopmental, and overall clinical outcomes until 5 years of chronological age. No study treatment will be administered. The treatments to be evaluated in this study were administered in Study 20090. Subjects enrolled into this study will be followed until the age of 5 years.

The screening/baseline visit (visit 1a) of Study 20275 was conducted concomitantly with the week 24 visit or the last follow-up visit of Study 20090, whichever was later, or at a later point between this date and before the subject was 13 months of chronological age. Visit 1b was scheduled when the subject was 40 weeks of chronological age. Additional visits are scheduled according to the subject's yearly birthday, with the last visit at the subject's 5th birthday.

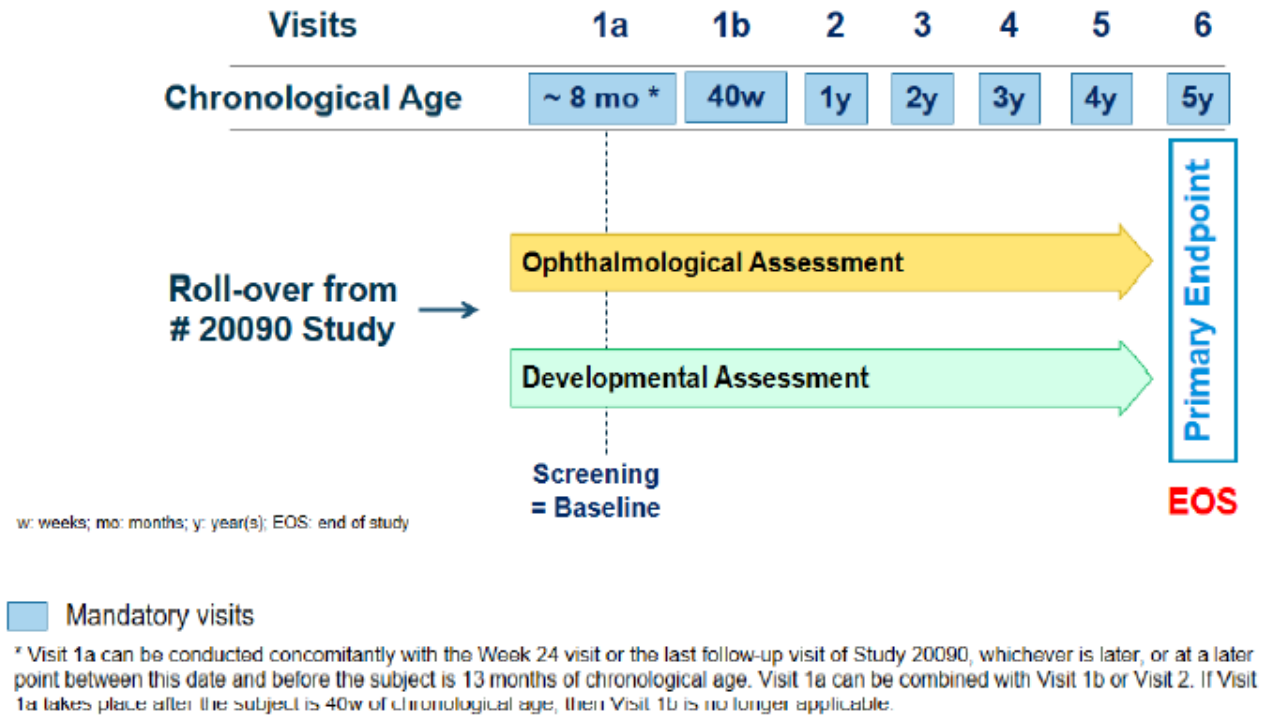


Figure 5.5.2 - Study design of Extension Study 20275

The overall designed is acceptable.

Study participants

Core Study 20090

The study population consisted of male and female preterm infants with ROP at least in one eye who required treatment. A minimum of 102 preterm infants were planned to be randomized to achieve at least 102 subjects evaluable for the primary analysis.

Inclusion criteria

Patients eligible for inclusion had to fulfil all of the following criteria prior to receiving the first investigational treatment:

1. Gestational age at birth ≤ 32 weeks or birth weight ≤ 1500 g
2. Subjects with treatment-naïve ROP classified according to the International Classification for ROP in at least one eye as:
   - Zone I Stage 1 plus, or 2 plus, or 3 non-plus or 3 plus, or
   - Zone II Stage 2 plus or 3 plus, or
   - AP-ROP
3. Weight at baseline (day of treatment) ≥ 800 g
4. Male or female
5. Signed informed consent from parent(s) or legal guardian(s), in compliance with local requirements

Exclusion criteria

Patients fulfilling any of the following criteria prior to receiving the first investigational treatment were not eligible for inclusion in this study.

1. Known or suspected chromosomal abnormality, genetic disorder or syndrome

2. Previous exposure to any IVT or systemic anti-VEGF agent, including maternal exposure during pregnancy and/or during breastfeeding

3. Clinically significant neurological disease (eg, intraventricular hemorrhage grade 3 or higher, periventricular leukomalacia, congenital brain lesions significantly impairing optic nerve function, severe hydrocephalus with significantly increased intracranial pressure)

4. Pediatric conditions rendering the infant ineligible for study intervention at baseline or for repeated blood draws as evaluated by a NICU specialist and a study ophthalmologist

5. Presence of active ocular infection within 5 days of the first treatment

6. Advanced stages of ROP with partial or complete retinal detachment (ROP Stages 4 and 5)

7. ROP involving only Zone III

8. Ocular abnormalities that may interfere with the administration of study intervention or assessment of the study primary endpoint

9. Postnatal treatment with oral or intravenous corticosteroids at an equivalent dose of prednisone $\geq$ 1 mg/kg/day for > 2 weeks within 14 days of the first study intervention

10. Previous surgical or nonsurgical treatment for ROP (IVT anti-VEGF injection, ablative laser therapy, cryotherapy, and vitrectomy)

11. Participation of the subject or the mother in other clinical trials requiring administration of investigational treatments (other than vitamins and minerals) at the time of screening, or within 30 days or 5 half-lives of administration of the previous study drug, whichever is longer.

Extension study 20275

The study population consisted of male and female preterm infants with ROP at least in one eye who required treatment. The number of subjects is not predefined. All subjects who were treated in Study 20090 are eligible for enrollment into this long-term follow-up study. Approximately 100 subjects are expected to be enrolled in Study 20090.

Inclusion criteria

1. Subject was treated in Study 20090

2. Age less than 13 months of chronological age

3. Signed informed consent from parent(s) or legal guardian(s), in compliance with local requirements

Exclusion Criteria

Subject has a condition preventing participation in the study, or performance of study procedures

Treatments

Test product (Aflibercept arm), dose and mode of administration: Single IVT injection of aflibercept 0.4 mg/0.01 mL per eligible eye at baseline were received by subjects. The injection were performed in both eyes on the same day, if applicable. Thereafter, up to 2 additional IVT injections of aflibercept 0.4 mg/0.01 mL may have been administered in each eye in case retreatment criteria were met:

- Presence of ROP requiring treatment AND

- The interval since the last aflibercept IVT injection was 28 or more days

Rescue treatment with laser may have been performed if one of the following conditions was met:

- Worsening of ROP compared to the examination before the previous injection during the 27 days following that IVT aflibercept injection

- Presence of ROP requiring treatment after the subject already received a total of 3 aflibercept injections and the interval since the last IVT injection was 28 or more days

The rationale for dose selection and the proposed initial dose of 0.4 mg of aflibercept was selected considering existing clinical data and geometric modelling. In order to limit drug exposure, the lowest dose for which positive efficacy was reported was selected for this study. It should be highlighted that the results of these analysis indicate a higher systemic exposures that are expected in neonates compared to adults. Therefore the lowest dose for which positive efficacy was reported (0.4 mg) was selected for this study.

More importantly, discussion on whether in light of the existing clinical uncertainties, the proposed single dose is agreeable or whether 2 dose levels should be investigated or a dose-finding study should be performed prior to the efficacy and safety study. The proposed dose and dosing regimen considerations were confirmed to be agreeable with PDCO.

Reference therapy (Laser photocoagulation arm), dose and mode of administration:

Subjects randomized to laser photocoagulation underwent treatment in each eligible eye at baseline. If multiple sessions of laser ablation were necessary within 1 week from baseline, they were counted as a single treatment. Treatment was applied to the entire avascular peripheral retina and was to be kept well away from the fovea. Supplementary laser treatments were allowed during the study. Retreatment with laser was allowed if both of the following criteria were met:

- Presence of ROP requiring treatment

- Fundus examination revealed laser treatment was incomplete as judged by the investigator

Rescue treatment with aflibercept 0.4 mg/0.01 mL was allowed if the fundus examination revealed laser treatment was complete as judged by the investigator and if one of the following conditions was met:

- Worsening of ROP compared to the prelaser examination

- Persistence of ROP requiring treatment 28 or more days after laser treatment

Subjects who initiated aflibercept rescue treatment were thereafter managed according to the aflibercept arm treatment regimen.

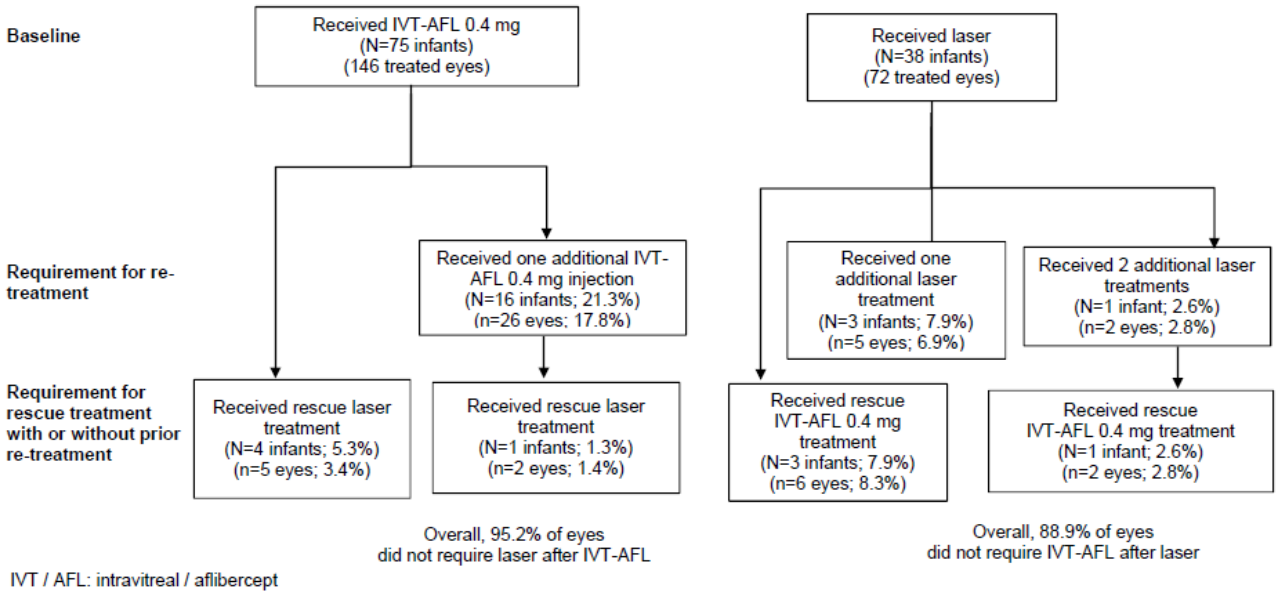
For both treatment arms, once rescue treatment was applied to an eye, treatment in that eye with the subject's randomized treatment could not be reinitiated.

The Applicant was requested to address a detailed description regarding the retreatment/rescue treatment applied during the study and provide further clarifications especially regarding the number of

retreatment in laser arm authorised before switching patient to rescue treatment (aflibercept 0.4 mg). The Applicant provided data of retreatment and rescued treatment in the laser group during the study (see figure below).

The Applicant also clarified that multiple laser photocoagulation treatment were possible within the first week and counted as the baseline treatment, and indeed one patient had 3 laser treatments each in both eyes, and two patients had 2 laser treatments each in both eyes. After the first treatment, based on the Applicant responses, up to 2 laser retreatment were performed before the rescue treatment was administrated. The information provided by the Applicant is considered satisfactory.

Figure 3: Treatments in Study 20090



Extension Study 20275

No study treatment will be administered. The treatments to be evaluated in this study were administered in Study 20090. Subjects enrolled into this study will be followed until the age of 5 years.

Objectives

Study 20090

The *primary objective* of the study was to assess the efficacy of aflibercept in subjects diagnosed with ROP in comparison to laser.

The *secondary objectives* were to:

1. Assess the safety and tolerability of aflibercept
2. Assess the treatment burden of aflibercept and laser
3. Describe the systemic exposure to aflibercept

Other prespecified objectives were to:

4. Characterize further aspects of the effect of aflibercept in the treatment of ROP

5. Further investigate the study intervention and similar drugs (i.e. mode-of-action-related effects and/or safety) and to further investigate pathomechanisms deemed relevant to diseases of the eye and associated health problems

As indicated above, at the end of the FIREFLEYE trial, if continued treatment was deemed beneficial by the investigator, an extension study was proposed (FIREFLEYE extension).

Study 20275

The *primary objective* is to evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for ROP.

The *secondary objective* is to describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP.

The *other pre-specified objective* is to explore further metrics for description of visual function and overall development of subjects included in Study 20090 for treatment for ROP.

Outcomes/endpoints

Core Study 20090

The *primary efficacy variable* was the absence of active ROP and absence of unfavourable structural outcomes at 24 weeks after starting study treatment, as assessed by the Investigator. Unfavorable structural outcome is defined as retinal detachment, macular dragging, macular fold, or retrolental opacity. Furthermore, eyes are considered non-responders if rescue treatment was given. The *secondary endpoints addressing primary objective* were the :

- Requirement for intervention with a second treatment modality from baseline to Week 24

- Recurrence of ROP from baseline to Week 24

- To explore new Retinopathy of Prematurity Activity Scale proposed by the International Neonatal Consortium

Secondary endpoints variables included:

- Number of aflibercept administrations from baseline to Week 24

- Number of laser treatments from baseline to Week 24

- Proportion of participants with ocular TEAEs and SAEs from baseline to Week 24

- Proportion of participants with systemic TEAEs and SAEs from baseline to Week 24

- Systemic exposure to free aflibercept (at expected maximum plasma concentration and during elimination period from plasma) determined by sparse sampling

- Presence of anti-drug antibodies before and 12 weeks afteraflibercept injection

Other pre-specified endpoints variables included:

- Evaluation of visual function at Week 24

- Time required to perform treatment

- Requirement for sedation or general anesthesia

- Requirement for treatment with more than one aflibercept injection

- Time to intervention with a second treatment modality for ROP or development of unfavorable structural outcomes

- Time to recurrence of ROP

- Regression of plus disease, regression of pre-retinal-vascularized ridge and progression of retinal vascularization beyond the ridge from baseline to Week 24

- Progression to Stage 4 or 5 ROP from baseline to Week 24

- Completion of vascularization of the peripheral retina to within one disc diameter of the ora serrata at Week 24

- Time to completion of vascularization

- Number of visits required up to Week 24

- Systemic exposure to total aflibercept determined by sparse sampling

- Various biomarkers (eg, diagnostic, safety, pharmacodynamics, monitoring, or potentially predictive biomarkers)

The presence of fundus features was assessed in both eyes by the Investigator before any treatment was applied, using wide-field digital retinal photography (images taken by eg, RetCam, Phoenix ICON Camera) or as assessed by indirect ophthalmoscopy, according to protocol.

Safety was assessed based on AEs, vital signs, physical findings, clinical safety laboratory assessments and Central Nervous System Imaging.

<u>Extension Study 20275</u>

The *primary efficacy variable* include Binocular best-corrected visual acuity (BCVA) in Snellen equivalent score at 5 years of age. The *secondary endpoints addressing primary objective* is the proportion of subjects with ocular and/or systemic AEs and SAEs through 5 years of age.

The *secondary endpoints* variables include:

- 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

- BCVA 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, BSID-III, DAS-II, WPPSI-IV, 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

Other pre-specified endpoints variables included:

- Evaluation of visual function and refraction and structural-outcomes through 5 years of age

- Analysis of ocular extrinsic motility through 5 years of age

- Stereopsis and visual field at 5 years of age

- Proportion of subjects with complete vascularization assessed by indirect ophthalmoscopy through 5 years of age

- Neurodevelopmental outcomes through 5 years of age using standardized development tests (eg, BSID-III, DAS-II, WPPSI-IV, VABS-II)

- Evaluation of ROP outcomes according to the International Neonatal Consortium ROP activity scale

- Growth and development through 5 years of age

Sample size

The sample size rationale was based on the primary efficacy endpoint "absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment" and the success criterion defined as response probability for aflibercept is greater than the one for laser minus 5 percentage points with at least 95% probability. This criterion assumes a Bayesian primary analysis, and would be met if the lower limit of the one-sided 95% credible interval for the treatment difference (aflibercept – laser) was greater than -5%.

When non-informative prior distributions are used (as planned for the primary analysis), this success criterion corresponds to a frequentist non-inferiority test with a non-inferiority margin of 5 percentage points with a one-sided type I error control at 5%.

It should be noted that the control of the type I error, as defined in the study protocol, is more relaxed than what would be typically expected in a confirmatory phase III trial (i.e. 2.5% one-sided).

A broad discussion on sample size took place during the evaluation of the PIP. This final proposal of sample size considerations and associated success criterion were confirmed to be agreeable in that context.

With at least 102 subjects evaluable for the primary analysis in the FAS and a randomization ratio of 2:1 (active:control) to receive either treatment with aflibercept or laser photocoagulation (68 and 34 subjects, respectively), the defined success criterion would be achieved with a power of 81% under following assumptions:

1. The laser response probability for the study is similar to historic data: a Bayesian meta-analytical prediction based on BEAT-ROP and RAINBOW resulted in a posterior predictive distribution described by a beta(34.7, 13.8) distribution. For the power simulations, the true response probability for laser photocoagulation in this trial was drawn from this distribution for each simulation run.

2. And the response probability for aflibercept is 15 percentage points higher than for laser, but not higher than 95%.

Respective power simulations were performed using package rjags (Plummer, 2016) in the statistical software R (R Core Team, 2016).

No interim analysis was planned. During the study, an external data safety monitoring board performed regular safety assessments to determine if the study showed unacceptable risks for the subjects, and issued recommendations to proceed or terminate the study.

Randomisation

Eligible subjects were randomized 2:1 to receive either treatment with aflibercept or laser photocoagulation, respectively, stratified by Japanese and non-Japanese sites as well as by ROP

classification in Zone I, Zone II, or AP-ROP according to investigator assessment. If both eyes met the eligibility criteria of the study after screening, the eye with the more severe disease was considered for stratification. Subjects were centrally assigned to randomized study intervention using the IVRS/IWRS.

The randomisation process and associated stratification factors are deemed appropriate.

Statistical methods

Analysis populations

In general, a subject was assigned to an analysis set if at least 1 eye met the respective criteria. Eye level analyses include only eyes that met the respective criteria (i.e. a single eye could have been excluded from an analysis while the subject was valid for the analysis).

The primary efficacy variable was analysed using the full analysis set (FAS), modified full analysis set (mFAS), and the per protocol analysis set (PPS). The secondary and explorative efficacy variables were analysed using the FAS and mFAS. The FAS analysis was considered to be the primary analysis in both cases, while the mFAS and PPS were considered supportive. Safety variables were analysed based on the safety analysis set (SAF). Pharmacokinetic-related analyses were performed based on the pharmacokinetic analysis set (PKS).

The **FAS** included all subjects who received any study treatment and had a baseline and at least one post-baseline assessment of efficacy. The analysis on the FAS was performed according to the treatment assigned at baseline (as randomized).

The **mFAS** included all subjects with central reading centre positive confirmed disease stages meeting the inclusion criteria who completed baseline treatment, had a baseline and at least one post-baseline central reading centre assessment of efficacy. The analysis on the mFAS was performed according to the treatment assigned at baseline (as randomized).

The **PPS** included all subjects in the mFAS who had no validity findings or important deviations that could have affected the primary efficacy variable. The analysis of the PPS was performed according to the treatment the subject actually received (as treated; determined by the first study treatment that the subject actually received during the study).

The **SAF** included all subjects who received any type of study treatment. The analysis of the SAF was performed according to the treatment the subject actually received (as treated; determined by the first study treatment that the subject actually received during the study).

The **PKS** included all subjects who received aflibercept treatment at the baseline visit and who had at least one nonmissing PK assessment following the first dose of study drug.

Immunogenicity analysis sets: ADA data were analyzed using the ADA analysis set (**AAS**) and neutralizing antibody (NAb) data was analyzed using the NAb analysis set (**NAS**).

The AAS included all subjects who received aflibercept at baseline and had at least 1 nonmissing result in the ADA assay following the first study dose. The NAS included all subjects who received aflibercept at baseline and with at least 1 nonmissing result in the NAb assay. Subjects who were with negative ADA response and those who were with positive but not treatment-emergent ADA response were set to negative in the NAS. Analysis of both immunogenicity analysis sets were performed according to the treatment the subject actually received (as treated).

Success criterion and type I error control

The success criterion is derived from the Bayesian primary analysis and is defined as "response probability for aflibercept is greater than the one for laser minus 5 percentage points with at least 95% probability", i.e.:

P(response probability for aflibercept > (response probability for laser -5%)) ≥ 95%.

This is the case if the lower limit of the one-sided 95% credible interval for the treatment difference (aflibercept – laser) is greater than -5%. As noninformative prior distributions were used for the analysis this success criterion corresponds to a frequentist non-inferiority test with a non-inferiority margin of 5 percentage points and a one-sided type I error control at 5%.

The posterior distribution of both response probabilities, as well as the difference in response probabilities are displayed using normal kernel densities.

If the success criterion was met, in a second step superiority of aflibercept over laser was evaluated by comparing the lower limit of the 95% one-sided credible interval with 0.

There was no type I error control for secondary endpoint analyses.

Primary endpoint analysis

The following conditions were followed in the analysis of the data:

1. Primary analysis: The data was analysed by a Bayesian statistical model.
2. Success criterion defined as "response probability for aflibercept is greater than the one for laser minus 5 percentage points with at least 95% probability"
3. One eye or both eyes of a patient were included into the analysis to determine the primary endpoint on a patient level, if treated and meeting the inclusion criteria.
4. 90% credible intervals were provided for the probability of response.

The primary efficacy endpoint was the proportion of patients with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment, based on the investigator's assessment. Active ROP was ROP (according to the inclusion criterion) requiring treatment and unfavourable structural outcome was defined as retinal detachment, macular dragging, macular fold, or retrolental opacity.

Data of a second eye of subjects who started the study with 1 eligible eye and that developed ROP during study were included in the efficacy analyses only if treated before or on visit 9 (approximately 8 weeks from baseline).

All subjects requiring rescue treatment were counted as missing the primary endpoint.

A subject for whom both eyes were included in the analysis was defined as a responder if both eyes showed the defined absence. If only one eye was treated this fact was accounted for by the statistical model.

The number and percentage of eyes with active ROP or any of the unfavourable structural outcomes (overall and by type of unfavourable structural outcome) defined for the assessment of this endpoint at week 24 were displayed separately by treatment group using descriptive statistics.

Primary analysis/Bayesian statistical model/success criterion

The primary analysis for this endpoint was based on the investigator's assessment of ROP and analysed for FAS and repeated for mFAS and PPS.

As it was assumed that in most subjects both eyes would be treated, this was accounted for by using the following bivariate binomial model:

l_i ~ Bernoulli (p): response of subject i in left eye

r_i ~ Bernoulli (p): response of subject i in right eye

l_i and r_i are correlated with correlation coefficient ρ

Bivariate probability distribution:

left eye / right eye	Response (r_i=1)	No response (r_i=0)	
Response (l_i=1)	$p^2+ \rho\ p(1-p)$	$p(1-p)(1- \rho)$	p
No response (l_i=0)	$p(1-p)(1- \rho)$	$(1-p)(1-p(1- \rho))$	1-p
	p	1-p	

Based on this model the probability for a subject to be a responder was

$\pi = p^2+ \rho\ p(1-p)$

Primary analysis: the data were analysed by a Bayesian statistical model

Data were analysed by a Bayesian statistical model with a noninformative prior probability distribution for the response probability for a single eye (p). For the correlation coefficient (ρ), an informative prior distribution allowing positive values only was assumed. The model was based on following distribution assumptions:

p ~ beta(1,1): noninformative prior for the response probability in 1 eye

ρ ~ beta(1,1): prior for the correlation between the 2 eyes of 1 subject (allowing only a positive correlation)

Based on this model, the primary endpoint proportion of patients with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment (e.g. response on a subject level, i.e. π = p2+ ρ p(1-p)) was analysed for each of the 2 treatment groups.

The Bayesian statistical model itself is deemed appropriate, and was previously supported by the PDCO. The study success criterion for the primary endpoint was defined as the response probability for aflibercept to be greater than the one for laser minus 5 percentage points with at least 95% probability. It would have been met if the lower limit of the one-sided 95% credible interval for the treatment difference (aflibercept – laser) was greater than -5%. When non-informative prior distributions are used (as planned for the primary analysis), it should be noted that this success criterion corresponds to a frequentist non-inferiority test with a non-inferiority margin of 5 percentage points with a one-sided type I error control at 5%. As mentioned in the sample size section, it should be noted that the control of the type I error, as defined in the study protocol, is more relaxed than what would be typically expected in a confirmatory phase III trial (i.e. 2.5% one-sided). Nevertheless, these sample size considerations and associated success criterion were confirmed to be agreeable at the Day 120 PDCO discussion.

<u>Handling of missing data for the primary analysis</u>

All subjects were required to have efficacy assessments 24 weeks (±7 days) after starting study intervention. Missing week 24 data for a treated eye was imputed as follows as long as the respective eye did not have had an unfavourable structural outcome or rescue treatment before dropping out, as in these cases the eye was considered as nonresponding:

1. If at the last visit before dropping out the subject had no active ROP and Zone II was completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects) the respective eye was considered as responding.

2. Otherwise, if the subject dropped out at or after week 16, the last nonmissing postbaseline ROP staging before dropping out was carried forward and used for determining the response in this eye (last observation carried forward approach).

3. If the subject dropped out before week 16, the missing information was imputed as follows:

    a. If there was a clear documentation that the subject dropped out due to lack of efficacy, the respective eye was considered as nonresponding.

    b. Otherwise, a multiple imputation approach was used giving the same probability of success as subject's having the same treatment group and initial staging (Zone I versus Zone II versus AP-ROP).

As requested, the Applicant provided a summary of missing data for the primary endpoint and secondary efficacy endpoints (requirement for intervention with a second treatment modality from baseline to week 24, recurrence of ROP from baseline to week 24), with associated type of data imputation. Some differences can be noted in the frequency of specific data imputation rules, however, due to the small numbers, it is difficult to draw any meaningful conclusions.

Sensitivity analyses

A sensitivity analysis was performed where the central reading center data was used instead of the investigator's assessment of ROP at week 24 for FAS, mFAS, and PPS.

A sensitivity analysis was also conducted evaluating the impact of missing data considering all dropouts as nonresponders unless completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects) for FAS, mFAS, and PPS (worst case imputation).

As a further sensitivity analysis, the proportion of patients with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment according to the investigator's assessment was analyzed by the corresponding frequentist approach for FAS.

Reading center results were analyzed for mFAS and PPS.

Asymptotic 90% confidence intervals for the difference in response rates were calculated based on a 2x2 contingency table for response (yes, no) versus treatment (aflibercept injection, laser). If both eyes of a subject were treated, the subject was considered a responder if both eyes responded; if 1 eye was treated, the subject was considered a responder if this eye responded. Aflibercept was considered to be noninferior to laser with regards to the sensitivity analysis if the 90% confidence interval of the difference was above -5%.

Asymptotic 90% confidence intervals were presented in addition for the Mantel-Haenszel weighted treatment difference calculated using normal approximation and adjusting for each individual stratification factor (baseline ROP classification and Japan vs non-Japan).

It is acknowledged that a sensitivity analysis was conducted to assess the impact of missing data considering all dropouts as non-responders unless completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects). Another sensitivity analysis was requested on the FAS where all subjects with missing data are considered non-responders regardless of complete vascularisation or laser treatment completion. The suggested sensitivity analysis has been performed. As a result of the imputation, lower proportions of patients with absence of active ROP or unfavourable

structural outcomes at 24 weeks can be observed in both treatment arms. It is noted that the difference between treatment groups is close to zero.

Secondary endpoint analyses

Requirement for intervention with a second treatment modality from baseline to week 24

A second treatment modality for ROP was either rescue treatment or treatment with any other surgical or nonsurgical treatment for ROP (e.g. IVT anti-VEGF injection, ablative laser therapy, cryotherapy, or vitrectomy) captured as concomitant medication or surgeries after start of study treatment.

Second treatment modalities other than rescue treatment were identified by:

1. Any concomitant medication starting after start of study treatment with standardized medication term in ("bevacizumab," "pegaptanib," "ranibizumab," "aflibercept," and "brolucizumab")
2. Any ocular surgery after start of study treatment assessed by the medical experts as second treatment modality

The same Bayesian statistical model as described for the primary analysis of the primary endpoint was used to estimate probabilities for a requirement of intervention with a second treatment modality between baseline and week 24. As for the primary analysis, a subject might have contributed with a single eye or with both eyes. Analyses are presented for the FAS, mFAS, and PPS.

Missing data regarding requirements for intervention with a second treatment modality were imputed analogously to the approach used for the primary endpoint.

Recurrence of ROP from baseline to week 24

Recurrence of ROP until week 24 aimed to monitor the disease activity during the study and was defined as a need for retreatment or rescue treatment in cases where the question presence of active ROP requiring treatment had been previously answered with no. This binary endpoint was analysed using the same Bayesian statistical model as described for the primary analysis of the primary endpoint. Analyses are presented for the FAS, mFAS, and PPS.

Missing data regarding recurrence of ROP was imputed analogously to the approach used for the primary endpoint

Number of aflibercept administrations from Baseline to Week 24 and number of laser treatments from Baseline to Week 24

The number of aflibercept and laser treatments from baseline to week 24 were described descriptively per treatment arm in frequency tables. In case multiple sessions of laser treatment were necessary within 1 week from baseline, they were counted as a single treatment. The same approach was planned for the analysis of laser treatment as retreatment or rescue treatment (however, was not applicable).

Accounting for eventual reduced follow-up times due to dropping out of subjects, the number of aflibercept and laser treatments from baseline to week 24 were also displayed descriptively for treatment completers

To explore new Retinopathy of Prematurity Activity Scale proposed by the International Neonatal Consortium

Based on the ICROP classification (IC-ROP 2005), the ROP Activity Scale and severity classification of ROP (mild, moderate, severe) were derived using the assessments from the central reading centre (Smith et al., 2018).

The distribution and changes from baseline over time of the ROP Activity Scale and the 3 subcategories (mild, moderate, and severe) using the assessments from the central reading centre were described descriptively per eye by summary statistics (including quartiles), frequency and shift tables. The number and percentage of subjects with at least a 2-step decrease by visit are presented for the FAS, mFAS, and PPS.

Subgroup analyses

For the primary and secondary efficacy endpoints, subgroup analyses were performed for the following groups: baseline ROP in Zone I (excluding AP-ROP), baseline ROP in Zone II (excluding AP-ROP), and baseline AP-ROP. The subgroups were defined twice: based on the investigator assessment and the central reading centre assessment.

Changes to planned analyses

Protocol amendments are not thought to have affected the analysis of efficacy data.

The original version of the statistical analysis plan (SAP) was finalised before the first subject first visit. Subsequent versions of the SAP were finalised close to or after the last subject last visit, which was on 12 February 2021.

Changes to the statistical analysis plan are summarised below.

SAP version	Change description
1.0, 10 July 2019	First version
2.0, 9 February 2021	Addition of COVID-19 pandemic related analyses Addition of frequentist analysis approach for primary efficacy variable Addition of further exploratory endpoint: "Recurrence following complete regression of ROP from Baseline to Week 24" Further details on analyses of PK and immunogenicity data
3.0, 24 February 2021	Definition of screen failure added
4.0 10 May 2021	Addition of data rules to correct the AP-ROP assessment of the RC to follow the RC charter Editorial changes to the PK figures

An additional SAP, version 1.0, dated 28 May 2021, described post-hoc analyses that were performed, which include additional subgroup analyses for the primary efficacy endpoint, an update to the calculation of spherical equivalent, a summary of re- and rescue treatments, additional summary tables for the ROP Activity Scale, analyses for PK, and summary of all aflibercept-related and photocoagulation-related AEs.

Estimands

The Applicant provided a description of the estimand corresponding to the primary analysis. The strategy for the intercurrent event of rescue therapy was clarified as a composite strategy, meaning that patients with rescue treatment were considered as non-responders.

Upon request, an additional analysis was performed where a treatment policy is followed for patients with rescue treatment instead. As expected, this analysis provided a slightly higher proportion of patients with absence of active ROP or unfavourable structural outcomes at 24 weeks in both arms. Of note, the difference between treatment groups is smaller than in the primary analysis (0.2% vs 3.6%).

Historical/published evidence synthesis study

The statistical analysis of the historical/published evidence study was done in two steps for primary and secondary endpoints, as follows:

1. Development of a prior distribution for laser photocoagulation based on published data

2. Bayesian analysis comparing aflibercept with laser photocoagulation using the prior distribution for laser photocoagulation.

Primary endpoint

Development of a prior distribution

For the development of the prior distribution for the effect of laser photocoagulation, only randomized controlled studies of a reasonable size that reported results on the primary endpoint of FIREFLEYE were selected. Therefore, historic data for ROP laser treatment from large clinical trials, including data from BEAT-ROP and RAINBOW study were used as control (Mintz-Hittner et al. 2011, Stahl et al. 2019).

As the prior distribution for the Bayesian analysis, the distribution of the potential treatment effect of laser photocoagulation in future studies was derived by the meta-analytical predication (MAP) method (Neuenschwander et al. 2010). This method is based on a Bayesian random-effects meta-analysis of published studies and accounts for the between trial variability. Further details are available in the technical report / evidence synthesis study report.

Bayesian analysis comparing aflibercept with laser photocoagulation

The Bayesian analysis comparing aflibercept with laser photocoagulation for the primary and secondary endpoint followed the same methodology described for the study primary analysis. The main difference to the study level analysis was the use of the informative prior for the response probability for laser photocoagulation derived as outlined above instead of a non-informative prior. The handling of missing data was the same.

Sensitivity analyses

To facilitate the assessment of the impact of a potential discrepancy between the historic and the newly collected data, the following sensitivity analyses were planned

(a) An analysis with a robust prior (eg, Schmidli et al. 2014): The derived prior was weighted down to 80 or 90% or even down to 50% and mixed with a uniform distribution on the interval [0, 1]. With this approach, if the data collected in study 20090 and the historic data are in-line, the prior information will be reflected in the derivation of the posterior distribution and thus will be considered when interpreting the data. If there is a major conflict between the newly collected data and the historic data, i.e. if the data deviates significantly from the prior data, the posterior distribution resulting from the Bayesian analysis with robust prior will shift almost completely towards the newly collected data and with this the historic data will be partly or fully discarded in the outcome.

(b) A tipping-point type analysis, where the weight of the prior information is gradually reduced.

Secondary endpoint

Only the RAINBOW study (Stahl et al. 2019) was identified to provide information on the secondary endpoint (Recurrence of ROP requiring any postbaseline intervention until Week 24). As this does not allow for a meta-analysis as described for the primary endpoint, for the secondary endpoint a beta-distributed prior for the probability of not experiencing a recurrence was derived directly from the results reported in RAINBOW.

In general, the same Bayesian model as used for the primary endpoint analysis was also used for the secondary endpoint.

The conduct of an evidence synthesis study, based on a Bayesian analysis using historical data and taking between-trial variability into account, was supported by the PDCO. The use of a prior distribution following the meta-analytical prediction (MAP) method for the primary endpoint is, in principle, agreeable.

However, it should be noted that only 2 trials (BEAT-ROP and RAINBOW) are used to develop the MAP prior. It is therefore doubtful that the between-trial variability was appropriately taken into account. As a result, an informative prior had to be used for the MAP prior parameter of inter-study variability.

A reasonable set of sensitivity analyses was planned by the Applicant to assess the impact of the prior distribution, mainly by down-weighting the prior distribution in a stepwise manner (i.e., a tipping point analysis). Robust priors were also investigated as part of the sensitivity analyses (MAP prior mixed with a uniform distribution), which allow for the prior to possibly shift to the study data when it is in conflict with the historical MAP prior.

For the secondary endpoint (recurrence of ROP requiring any post-baseline intervention until Week 24), only one study (RAINBOW) was used to derive the prior distribution. This is ignoring the presence of inter-study variability. A sensitivity analysis with a 50% down-weighted prior distribution has been performed to assess the impact of the historical prior on the posterior distribution.

It is acknowledged that the use of historical data as prior distribution allow for additional relevant information to be incorporated in the same Bayesian model as planned for the primary analysis. Indeed, the non-informative prior distributions used for the study-level analyses are replaced with informative priors based on historical data in this evidence synthesis study.

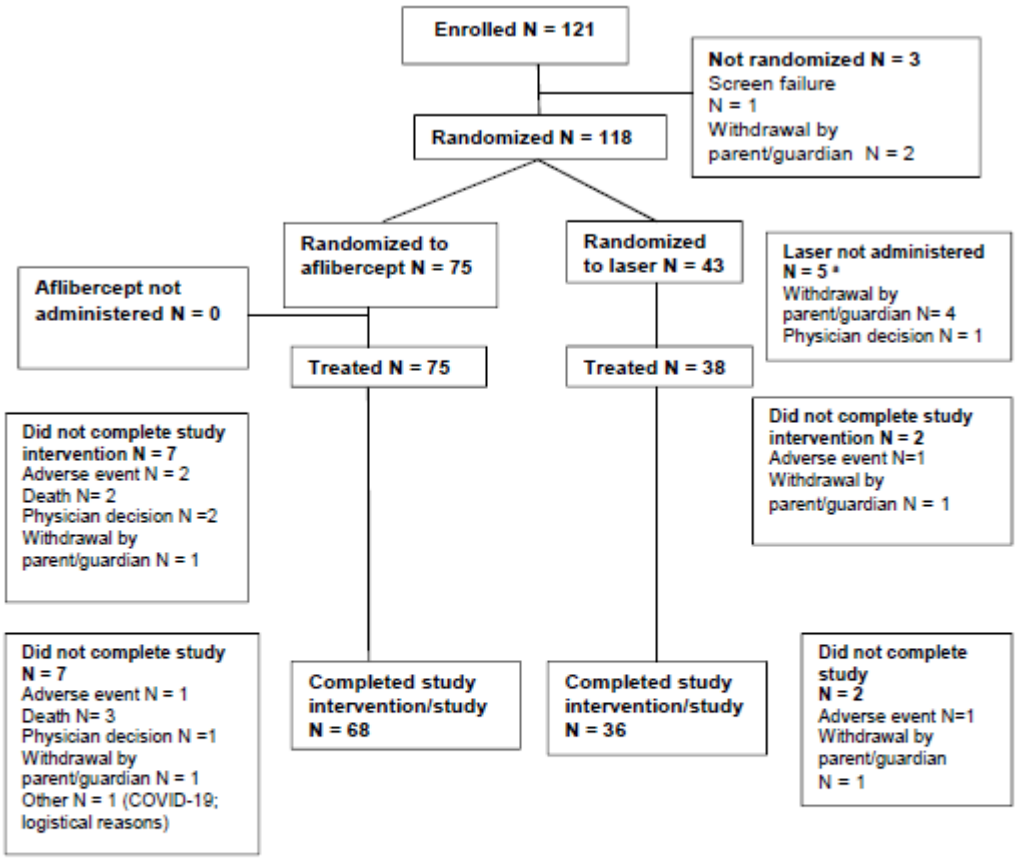
It was unclear whether the distribution of ROP categories (Zone I, Zone II, or AP-ROP) and possibly other baseline characteristics were similar in the historical trials in comparison with Study 20090. The Applicant was requested to provide a summary of baseline characteristics in the trials used as historical evidence. Some differences could be observed, notably for the BEAT-ROP trial which included patients with lower birth weights compared to Study 20090, as well as a higher proportion of patients with Zone 1 baseline ROP. It cannot be excluded that other baseline characteristics (possibly not reported in the published data) differ between trials.

As requested, the Applicant also performed an additional analysis with separate priors for different ROP categories. These could not differentiate AP-ROP as another category as this information was not available in the BEAT-ROP trial. This analysis by baseline ROP category did not lead to different conclusions, as a positive treatment difference could be observed in both categories, with higher proportions of responders generally observed in Zone II compared to Zone I. However, the Applicant could not provide analyses accounting for other baseline characteristics due to the absence of such subgroup results in the published data. As a consequence, the potential for bias remains of concern, especially as the proportion of responders is higher in the historical evidence. More generally, there are

some clear limitations that should be taken into account when interpreting these results, due to the inclusion of non-randomised control data. Indeed, the MAP prior used for the primary endpoint, while accounting for inter-study variability, still relies on the assumption of exchangeability of control arm parameters across trials. This is a strong and unverifiable assumption which would lead to bias when it is violated. The same obviously applies to the secondary endpoint analysis which is based on a single study and does not account for between-study variability. The robust prior is an effort to reduce such bias by increasing the uncertainty in case of a clear prior-data conflict, but it can still occur for the same reason.

4.5.2. Results

Participant flow



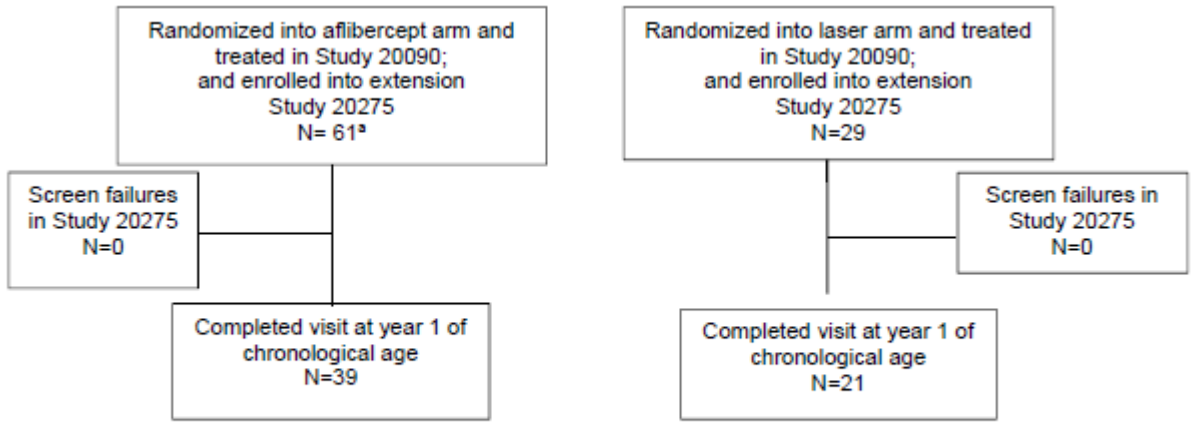
[a] For the 4 subjects who were withdrawn by parent/guardian, the parents decided against laser because they preferred treatment with anti-VEGF treatment. The withdrawal by physician was based on a decision to avoid treatment burden related to laser (data on file).

Intervention completed = subject had assessments of retreatment/rescue criteria up to and including week 20 (or week 23 if performed due to retreatment or rescue treatment) and received all intended treatments (retreatment and rescue treatment) as described in the protocol. A subject is considered as intervention completer if treatment was completed for at least 1 eye.

Study completion = subject completed week 24 or week 27 if applicable due to retreatment or rescue treatment.

COVID-19 = coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus).

Figure 5.5.3 - Subject disposition (all enrolled subjects) in Core Study 20090



*Data cut-off for interim analysis: 01 MAR 2021

[a] One subject (from the aflibercept arm in Study 20090) with a signed informed consent is not included in the analysis set as no study visit had taken place at the time of the cut-off date of this interim analysis report. This subject is not considered a screen failure according to the definition of a screen failure in the protocol.

Figure 5.5.4 - Subject disposition (all enrolled subjects) in Core Study 20090

Recruitment / Numbers analysed

Core Study 20090

FIREFLEYE study was conducted in 64 sites across 27 countries. The first subject was enrolled on 25 SEP 2019. Recruitment was completed on 28 AUG 2020. Last patient last visit was on 12 FEB 2021.

A total of 121 subjects were screened and 118 subjects were randomized, 75 to the aflibercept arm and 43 to the laser arm. Five randomized subjects were withdrawn prior to receiving any study intervention (all were randomized to laser). In all cases either the parents or physician had decided against treatment with laser. Thus, at baseline, 75 subjects were treated with aflibercept and 38 subjects were treated with laser, and all were valid for the safety analysis set (SAF) and full analysis set (FAS). Therefore, at baseline, 75 (100%) subjects were treated with aflibercept and 38 (88.4%) were treated with laser. A total of 104 (88.1%) subjects completed the study, 68 (90.7%) in the aflibercept arm and 36 (83.7%) in the laser arm.

The analysis populations are summarised in **Error! Reference source not found.**. The FAS was the analysis population used for the efficacy analyses (mFAS and PPS were considered as supportive) and the SAF (all randomised subjects except 5 laser subjects randomized but not treated) was used for the safety analyses.

	Aflibercept N=75 (100%)	Laser N=43 (100%)	Total N=118 (100%)
Subjects valid for SAF	75 (100.0%)	38 (88.4%)	113 (95.8%)
Subjects valid for FAS	75 (100.0%)	38 (88.4%)	113 (95.8%)
Subjects valid for mFAS	68 (90.7%)	35 (81.4%)	103 (87.3%)
Subjects valid for PPS	66 (88.0%)	35 (81.4%)	101 (85.6%)
Subjects valid for PKS	75 (100.0%)	0	75 (63.6%)

FAS = full analysis set, mFAS = modified full analysis set, PKS = pharmacokinetic analysis set, PPS = per protocol analysis set, SAF = safety analysis set

Table 5.5.1 - Subject validity (all randomized subjects)

A total 118 were randomized of which among them 5 patients did not receive treatment and 9 patients discontinued after the initial treatment at baseline (9 in total, including 2 deaths in the aflibercept arm). The FAS population included 113 patients and the SAF population 113 patients.

Extension Study 20275

A total of 90 subjects who received study treatment in Study 20090 were enrolled at the time of the data cut-off date (01 MAR 2021) into the extension Study 20275, of which 61 subjects were in the aflibercept arm and 29 subjects were in the laser arm of Study 20090. One subject in the aflibercept arm with a signed informed consent is not included in the analysis set as no study visit took place at the time of the cut-off date of this interim analysis report. No subjects were screen failures, and no subjects discontinued the study prior to the visit at year 1 of chronological age.

At the time of data cut-off date (01 MAR 2021) of this interim analysis, data until 1 year of chronological age was available from 89 subjects (60 treated with aflibercept and 29 with laser at baseline of Study 20090). Of these 89 subjects, 60 subjects had data at 1 year of chronological age (39 treated with aflibercept and 21 with laser at baseline of Study 20090).

Conduct of the study

Amendment

The original protocol (dated 22 MAR 2019) had one globally implemented amendment (version 2, dated 23 JUN 2020), in order to add at weeks 8, 12, and 24 pharmacokinetic samples to further characterize the PK profile in subjects treated with aflibercept, document the further elimination of free (pharmacologically active) aflibercept and bound aflibercept from plasma, and provide estimates of the elimination half-life.

The MAH precise that, several amendments were valid for centers located in individual countries:

Amendment JPN-1 (specific to Japan, dated 09 MAY 2019) addressed the regulatory requirements of the PMDA, and included the following key specification:

- The primary success criterion agreed with PMDA (demonstration of superiority in response proportion over 66% in the aflibercept group with a two-sided exact test at a 5% significance level) and the associated plans for statistical analysis was added.

- The target enrollment of at least 18 Japanese subjects (12 in the aflibercept arm and 6 in the laser photocoagulation arm) was specified.

Amendment SWE-1 (specific to Sweden, dated 04 JUN 2019) addressed feedback from the Swedish Medical Products Agency (MPA), and added a stipulation that protocol amendments that are considered substantial require approval from the appropriate competent authorities.

Amendment PRT-1 (specific to Portugal, dated 18 JUL 2019) addressed feedback from the health authority in Portugal (INFARMED). The underlined text was added to exclusion criterion number 5 to align with the Summary of Product Characteristics: Presence of active ocular or periocular infection within 5 days of the first treatment.

Amendment KOR-1 (specific to South Korea, dated 18 JUL 2019) addressed feedback from the South Korean Ministry of Food and Drug Safety (MFDS). In order to assess the suitability of the Bayesian method, a sensitivity analysis according to the frequentist approach was added.

Protocol deviation

Of the 118 randomized subjects, 49 (65.3%) subjects in the aflibercept arm and 18 (41.9%) subjects in the laser arm (total 67 patients) had important protocol deviations, most of which were due to procedure deviations.

In total, 38 of the enrolled subjects had important protocol deviations relating to the COVID-19 pandemic (24 subjects in the aflibercept arm and 14 subjects in the laser arm). Upon request, the Applicant clarified that for these 38 patients affected by the pandemic, a total of 152 pandemic-related protocol deviations were reported all of which were of procedural nature (such as missed or delayed visits or skipped assessments). Importantly for the patients, none of the pandemic-related protocol deviations led to any missed or delayed ROP treatments. For one additional patient in the aflibercept group, asymptomatic COVID-19 without any related protocol deviation was reported.

Protocol Deviation Category	Aflibercept N=75 (100%)	Laser N=43 (100%)	Total N=118 (100%)
Subjects with any important deviation	49 (65.3%)	18 (41.9%)	67 (56.8%)
Other protocol deviations	1 (1.3%)	0	1 (0.8%)
Procedure deviations	48 (64.0%)	18 (41.9%)	66 (55.9%)
Time schedule deviations	0	1 (2.3%)	1 (0.8%)
Treatment deviations	3 (4.0%)	2 (4.7%)	5 (4.2%)

Subjects may have more than one protocol deviation but are only counted once within each deviation category.

Table 5.5.2 - Number of subjects with important protocol deviations (all randomized subjects)

Extension Study 20275

Amendment

The original protocol (dated 22 MAR 2019) of the ongoing long-term follow-up Study 20275 had one globally implemented, non-substantial amendment (version 2.0, dated 27 NOV 2019), which consist in the addition of the VABS-II to further standardized neurodevelopmental assessment test and a visit at week 40 of chronological age, in order to close the gap between the end of Study 20090 and the visit at 1 year of chronological age.

Protocol deviation

Protocol deviations were not analyzed in this interim analysis.

Baseline data

Core Study 20090

Patient demographic and baseline data are summarised in the tables below. The number of male subjects (54.7%) was slightly higher than female subjects (45.3%) in the aflibercept arm but were equally distributed in the laser arm, 50% males and 50% females. The majority of subjects were White (73.5%), while 23.0% were Asian (of which 14.2% were from Japan). The gestational age at birth ranged from 23 to 31 weeks (median 26 weeks, 0 days; mean ± SD: 26 weeks 2 days ± 1.9), with the majority of subjects in the < 28 weeks category (83.2% subjects overall). At the time of treatment, the mean (standard deviation [SD]) chronological age was 10.3 weeks and the mean body weight was 1965.3 g (mean weight at the time of birth: 862.1 g). Nearly half of the subjects had an Apgar score of 4 to 7, inclusive, at both 1 and 5 minutes after birth.

	Aflibercept N=75 (100%)	Laser N=38 (100%)	Total N=113 (100%)
Sex			
Male	41 (54.7%)	19 (50.0%)	60 (53.1%)
Female	34 (45.3%)	19 (50.0%)	53 (46.9%)
Race			
WHITE	55 (73.3%)	28 (73.7%)	83 (73.5%)
BLACK OR AFRICAN AMERICAN	2 (2.7%)	0	2 (1.8%)
ASIAN	17 (22.7%)	9 (23.7%)	26 (23.0%)
ASIAN INDIAN	0	2 (5.3%)	2 (1.8%)
ASIAN: OTHER	1 (1.3%)	0	1 (0.9%)
CHINESE	4 (5.3%)	0	4 (3.5%)
JAPANESE	10 (13.3%)	6 (15.8%)	16 (14.2%)
KOREAN	2 (2.7%)	1 (2.6%)	3 (2.7%)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (2.6%)	1 (0.9%)
MULTIPLE	1 (1.3%)	0	1 (0.9%)
Region			
Japan	10 (13.3%)	6 (15.8%)	16 (14.2%)
non Japan	65 (86.7%)	32 (84.2%)	97 (85.8%)
Gestational age at birth (weeks)			
n	75	38	113
Mean (SD)	26w 3d (2.1)	26w 0d (1.6)	26w 2d (1.9)
Median	26w 0d	26w 0d	26w 0d
Min, Max	23, 31	24, 31	23, 31
Chronological age at baseline (weeks)			
n	75	38	113
Mean (SD)	10.4 (2.8)	10.2 (2.3)	10.3 (2.6)
Median	10.3	10.0	10.0
Min, Max	4, 19	6, 16	4, 19
Gestational age group (2-level)			
< 28 weeks	60 (80.0%)	34 (89.5%)	94 (83.2%)
>= 28 to < 32 weeks	15 (20.0%)	4 (10.5%)	19 (16.8%)
Gestational age group (3-level)			
<24 weeks	4 (5.3%)	3 (7.9%)	7 (6.2%)
>=24 to <27 weeks	45 (60.0%)	25 (65.8%)	70 (61.9%)
>=27 weeks	26 (34.7%)	10 (26.3%)	36 (31.9%)
Birth Weight (g)			
n	75	38	113
Mean (SD)	881.1 (305.6)	824.6 (230.8)	862.1 (282.9)
Median	820.0	790.0	820.0
Min, Max	410, 1780	467, 1500	410, 1780
Birth weight group			
<500 g	5 (6.7%)	3 (7.9%)	8 (7.1%)
500 g - < 1000 g	49 (65.3%)	28 (73.7%)	77 (68.1%)
1000 g - < 1500 g	18 (24.0%)	6 (15.8%)	24 (21.2%)
1500 g - < 2000 g	3 (4.0%)	1 (2.6%)	4 (3.5%)
Baseline weight (g)			
n	75	38	113
Mean (SD)	2027.8 (675.69)	1842.1 (554.18)	1965.3 (641.00)
Median	1862.0	1735.5	1815.0
Min, Max	800.0, 3800	898.0, 3608	800.0, 3800
Baseline weight group			
500 g - < 1000 g	3 (4.0%)	1 (2.6%)	4 (3.5%)
1000 g - < 1500 g	11 (14.7%)	9 (23.7%)	20 (17.7%)
1500 g - < 2000 g	30 (40.0%)	14 (36.8%)	44 (38.9%)
2000 g - < 2500 g	12 (16.0%)	12 (31.6%)	24 (21.2%)
>= 2500 g	19 (25.3%)	2 (5.3%)	21 (18.6%)
Apgar score 1 minute after birth			
0-3	27 (36.0%)	14 (36.8%)	41 (36.3%)
4-7	36 (48.0%)	20 (52.6%)	56 (49.6%)
8-10	8 (10.7%)	3 (7.9%)	11 (9.7%)
Not done	4 (5.3%)	1 (2.6%)	5 (4.4%)
Apgar score 5 minutes after birth			
0-3	8 (10.7%)	5 (13.2%)	13 (11.5%)
4-7	35 (46.7%)	20 (52.6%)	55 (48.7%)
8-10	27 (36.0%)	9 (23.7%)	36 (31.9%)
Not done	5 (6.7%)	4 (10.5%)	9 (8.0%)

Max = maximum, Min = minimum, SAF = safety analysis set, SD = standard deviation.

Table 5.5.3 - Demographics (SAF)

The ROP of the majority of subjects was classified by the investigators as Zone II (63.7% subjects; excluding AP-ROP), followed by Zone I (excluding AP-ROP) (19.5%) and AP-ROP (16.8%) based on the assessment of the more severe eye in case that both eyes were eligible. Within Zone I and Zone II categories, most subjects had ROP Stage 3 plus disease (Zone II: 52.2% and Zone I: 11.5%). In the AP-ROP category, most subjects were classified as Zone I (14.2%). In summary, the most frequent type of ROP at baseline was Zone II stage 3 plus disease (52.2%), followed by Zone I stage 3 plus (11.5%) and AP-ROP (16.8%; [Zone I: 14.2% and Zone II: 2.7%]).

	Aflibercept/N=75 (100%)	**Laser/N=38 (100%)**	**Total/N=113 (100%)**
Detailed ROP classification by investigator			
Zone I	15 (20.0%)	7 (18.4%)	22 (19.5%)
Stage 1 plus	1 (1.3%)	0	1 (0.9%)
Stage 2 plus	2 (2.7%)	2 (5.3%)	4 (3.5%)
Stage 3	3 (4.0%)	1 (2.6%)	4 (3.5%)
Stage 3 plus	9 (12.0%)	4 (10.5%)	13 (11.5%)
Zone II	46 (61.3%)	26 (68.4%)	72 (63.7%)
Stage 2	0	1 (2.6%)	1 (0.9%)
Stage 2 plus	7 (9.3%)	5 (13.2%)	12 (10.6%)
Stage 3 plus	39 (52.0%)	20 (52.6%)	59 (52.2%)
AP-ROP	14 (18.7%)	5 (13.2%)	19 (16.8%)
Zone I	12 (16.0%)	4 (10.5%)	16 (14.2%)
Zone II	2 (2.7%)	1 (2.6%)	3 (2.7%)
Detailed ROP classification by reading center			
Zone I	23 (30.7%)	10 (26.3%)	33 (29.2%)
Stage 2 plus	1 (1.3%)	0	1 (0.9%)
Stage 3	2 (2.7%)	2 (5.3%)	4 (3.5%)
Stage 3 plus	20 (26.7%)	8 (21.1%)	28 (24.8%)
Zone II	28 (37.3%)	16 (42.1%)	44 (38.9%)
Stage 2	1 (1.3%)	0	1 (0.9%)
Stage 2 plus	2 (2.7%)	2 (5.3%)	4 (3.5%)
Stage 3	1 (1.3%)	2 (5.3%)	3 (2.7%)
Stage 3 plus	24 (32.0%)	12 (31.6%)	36 (31.9%)
AP-ROP	21 (28.0%)	11 (28.9%)	32 (28.3%)
Zone I	19 (25.3%)	8 (21.1%)	27 (23.9%)
Zone II	2 (2.7%)	3 (7.9%)	5 (4.4%)
MISSING	2 (2.7%)	0	2 (1.8%)

If both eyes met the eligibility criteria of the study after screening, the eye with the more severe disease was considered for stratification.
AP =aggressive posterior, ROP = retinopathy of prematurity, SAF = safety analysis set.

Table 5.5.4 - Baseline characteristics per subject (SAF) for Core Study 20090

	Aflibercept/N=146 (100%)	Laser/N=72 (100%)	Total/N=218 (100%)
Detailed ROP classification by investigator			
ZONE I	28 (19.2%)	13 (18.1%)	41 (18.8%)
Stage 1 plus	1 (0.7%)	0	1 (0.5%)
Stage 2 plus	4 (2.7%)	5 (6.9%)	9 (4.1%)
Stage 3	6 (4.1%)	1 (1.4%)	7 (3.2%)
Stage 3 plus	17 (11.6%)	7 (9.7%)	24 (11.0%)
ZONE II	90 (61.6%)	49 (68.1%)	139 (63.8%)
Stage 2	0	1 (1.4%)	1 (0.5%)
Stage 2 plus	17 (11.6%)	11 (15.3%)	28 (12.8%)
Stage 3 plus	73 (50.0%)	37 (51.4%)	110 (50.5%)
AP-ROP	28 (19.2%)	10 (13.9%)	38 (17.4%)
Zone I	23 (15.8%)	8 (11.1%)	31 (14.2%)
Zone II	5 (3.4%)	2 (2.8%)	7 (3.2%)
Detailed ROP classification by reading center			
ZONE I	44 (30.1%)	22 (30.6%)	66 (30.3%)
Stage 2	1 (0.7%)	0	1 (0.5%)
Stage 2 plus	2 (1.4%)	1 (1.4%)	3 (1.4%)
Stage 3	5 (3.4%)	7 (9.7%)	12 (5.5%)
Stage 3 plus	36 (24.7%)	13 (18.1%)	49 (22.5%)
Stage 4 A	0	1 (1.4%)	1 (0.5%)
ZONE II	58 (39.7%)	31 (43.1%)	89 (40.8%)
Stage 2	2 (1.4%)	1 (1.4%)	3 (1.4%)
Stage 2 plus	5 (3.4%)	5 (6.9%)	10 (4.6%)
Stage 3	4 (2.7%)	3 (4.2%)	7 (3.2%)
Stage 3 plus	47 (32.2%)	22 (30.6%)	69 (31.7%)
AP-ROP	36 (24.7%)	17 (23.6%)	53 (24.3%)
Zone I	28 (19.2%)	13 (18.1%)	41 (18.8%)
Zone II	8 (5.5%)	4 (5.6%)	12 (5.5%)

AP =aggressive posterior, ROP = retinopathy of prematurity, SAF = safety analysis set.

Table 5.5.5 - Baseline characteristics per eye (SAF) for Core Study 20090

Overall, most of baseline demographics and disease characteristics were well balanced over treatment arms. Males represented 53.1% of the population. Gestational age at birth ranged from 23 to 31 weeks (mean 26 weeks, 0 days; mean ± SD: 26 weeks 2 days ± 1.9). At the time of treatment, the mean chronological age was 10.3 weeks and the mean body weight was 1965.3 g (mean weight at the time of birth: 862.1 g).

The Applicant was asked to discuss and interpret the impact of the baseline weight on efficacy results between the two groups of treatment and included the different origin (Japanese, non-Japanese). The Applicant provided tables regarding baseline infant's data by region (Japanese and not-Japanese) and groups of treatment (aflibercept and laser) (see below).

Table 3: Birthweight, baseline ROP and bodyweight at baseline treatment in Japanese vs. non-Japanese patients (Study 20090), Demographics by Region (full analysis set)

	Region: Japan			non-Japan		
	Aflibercept N=10 (100%)	Laser N=6 (100%)	Total N=16 (100%)	Aflibercept N=65 (100%)	Laser N=32 (100%)	Total N=97 (100%)
Sex						
Male	4 (40.0%)	3 (50.0%)	7 (43.8%)	37 (56.9%)	16 (50.0%)	53 (54.6%)
Female	6 (60.0%)	3 (50.0%)	9 (56.3%)	28 (43.1%)	16 (50.0%)	44 (45.4%)
Race						
WHITE	0	0	0	55 (84.6%)	28 (87.5%)	83 (85.6%)
BLACK OR AFRICAN AMERICAN	0	0	0	2 (3.1%)	0	2 (2.1%)
ASIAN	10 (100.0%)	6 (100.0%)	16 (100.0%)	7 (10.8%)	3 (9.4%)	10 (10.3%)
ASIAN INDIAN	0	0	0	0	2 (6.3%)	2 (2.1%)
ASIAN: OTHER	0	0	0	1 (1.5%)	0	1 (1.0%)
CHINESE	0	0	0	4 (6.2%)	0	4 (4.1%)
JAPANESE	10 (100.0%)	6 (100.0%)	16 (100.0%)	0	0	0
KOREAN	0	0	0	2 (3.1%)	1 (3.1%)	3 (3.1%)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0	0	1 (3.1%)	1 (1.0%)
MULTIPLE	0	0	0	1 (1.5%)	0	1 (1.0%)
Gestational age at birth (weeks)						
n	10	6	16	65	32	97
Mean (SD)	25w 0d (1.3)	25w 3d (1.4)	25w 1d (1.3)	26w 5d (2.1)	26w 0d (1.7)	26w 3d (2.0)
Median	24w 6d	25w 3d	25w 1d	26w 2d	26w 0d	26w 1d
Min, Max	23, 27	24, 27	23, 27	24, 31	24, 31	24, 31
Gestational age group (2-level)						
< 28 weeks	10 (100.0%)	6 (100.0%)	16 (100.0%)	50 (76.9%)	28 (87.5%)	78 (80.4%)
>= 28 to < 32 weeks	0	0	0	15 (23.1%)	4 (12.5%)	19 (19.6%)
Gestational age group (3-level)						
<24 weeks	2 (20.0%)	1 (16.7%)	3 (18.8%)	2 (3.1%)	2 (6.3%)	4 (4.1%)
>=24 to <27 weeks	7 (70.0%)	4 (66.7%)	11 (68.8%)	38 (58.5%)	21 (65.6%)	59 (60.8%)
>=27 weeks	1 (10.0%)	1 (16.7%)	2 (12.5%)	25 (38.5%)	9 (28.1%)	34 (35.1%)
Birth Weight (g)						
n	10	6	16	65	32	97
Mean (SD)	672.2 (170.4)	732.2 (177.5)	694.7 (169.8)	913.3 (309.9)	841.9 (237.8)	889.7 (288.8)
Median	661.0	738.5	667.5	859.0	790.0	835.0
Min, Max	445, 1020	467, 949	445, 1020	410, 1780	470, 1500	410, 1780
Birth weight group						
<500 g	2 (20.0%)	1 (16.7%)	3 (18.8%)	3 (4.6%)	2 (6.3%)	5 (5.2%)
500 g - < 1000 g	7 (70.0%)	5 (83.3%)	12 (75.0%)	42 (64.6%)	23 (71.9%)	65 (67.0%)
1000 g - < 1500 g	1 (10.0%)	0	1 (6.3%)	17 (26.2%)	6 (18.8%)	23 (23.7%)
1500 g - < 2000 g	0	0	0	3 (4.6%)	1 (3.1%)	4 (4.1%)
Baseline weight (g)						
n	10	6	16	65	32	97
Mean (SD)	1452.3 (491.87)	1877.5 (828.08)	1611.8 (647.25)	2116.3 (658.92)	1835.4 (505.64)	2023.7 (624.20)
Median	1342.0	1671.0	1368.5	1940.0	1742.5	1870.0
Min, Max	930.0, 2534	1142, 3422	930.0, 3422	800.0, 3800	898.0, 3608	800.0, 3800
Baseline weight group						
500 g - < 1000 g	2 (20.0%)	0	2 (12.5%)	1 (1.5%)	1 (3.1%)	2 (2.1%)
1000 g - < 1500 g	5 (50.0%)	2 (33.3%)	7 (43.8%)	6 (9.2%)	7 (21.9%)	13 (13.4%)
1500 g - < 2000 g	2 (20.0%)	2 (33.3%)	4 (25.0%)	28 (43.1%)	12 (37.5%)	40 (41.2%)
2000 g - < 2500 g	0	1 (16.7%)	1 (6.3%)	12 (18.5%)	11 (34.4%)	23 (23.7%)
>= 2500 g	1 (10.0%)	1 (16.7%)	2 (12.5%)	18 (27.7%)	1 (3.1%)	19 (19.6%)
ROP classification by investigator						
Zone I	5 (50.0%)	3 (50.0%)	8 (50.0%)	10 (15.4%)	4 (12.5%)	14 (14.4%)
Zone II	4 (40.0%)	3 (50.0%)	7 (43.8%)	42 (64.6%)	23 (71.9%)	65 (67.0%)
AP-ROP	1 (10.0%)	0	1 (6.3%)	13 (20.0%)	5 (15.6%)	18 (18.6%)
Zone I	1 (10.0%)	0	1 (6.3%)	11 (16.9%)	4 (12.5%)	15 (15.5%)
Zone II	0	0	0	2 (3.1%)	1 (3.1%)	3 (3.1%)

Source: Bayer: /var/swan/root/bhc/865321/20090/stat/query05/prod/pgms/t_14_1_4_2_adsl_basechar.sas 21MAY2021 10:51

Overall, the difference in baseline weight between Regions does not allow to disentangle any possible impact of ethnicity itself. Moreover, results for both Region in term of absence of active ROP and unfavorable structural outcomes at 24 weeks tend to be numerically in favour of aflibercept, with with a:

- mean difference of 0.190 (SD 0.175, 90% Credible Interval: -0.072, 0.505) in Japanese
- mean difference of 0.014 (SD 0.084, 90% Credible Interval: -0.112, 0.153) in non-Japanese.

Regarding the selected population, patients with ROP in one or both eye with Zone I, stage 1+, 2+, 3 or 3+ disease, or Zone II, stage 2+ or 3+ disease, or AP-ROP (aggressive posterior retinopathy of prematurity) were included. Overall, distribution of ROP patients depending on the Zone/stage presented appear to differ depending on whether the classification was done by Investigator or reading center. The Applicant discussed the inconsistency between ROP classification by Investigator and by reading center: the discrepancy resulted from the fact that the investigator's disease assessment relies on multiple exams contrary to the reading center which only relies on retinal photography. This is an acceptable explanation.

Moreover, the MAH's proposal of indication in the SmPC do not appear adequate given the available data. Indeed, the indication "retinopathy of prematurity (ROP)" appears broader because it includes more severe stage of the disease not being assessed or for which even more limited results were observed. Therefore, the Applicant was requested to specifically justify including more severe stage of the disease in the claimed indication, or restrict the indication. Consequently, the Applicant amended the indication (section 4.1 of the SmPC) in order to reflect more closely the studied patient population, as follows:

"EYLEA is indicated in preterm infants for the treatment of

- retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease".

However, regarding AP-ROP population, the Applicant was asked to justify that a positive Benefit/risk has been demonstrated for all subgroups included in the proposed indication (i.e. ROP with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP disease). The Applicant discussed the results of responders patients observed in more severe stage of ROP for which a total of 19 patients were included. The descriptive primary efficacy outcomes at 24 weeks (absence of active ROP and absence of unfavourable structural outcomes at 24 weeks) were considered to assess patients as responders/non-responders. Overall, AP-ROP is an even more rare and severe subtype of the ROP disease in preterm infants (rare disease), which explain the limited inclusion. Given the lack of patients treated for AP-ROP, the results appear to be difficult to interpret from a statistical point of view and transpose them to the general population, even more given the numerically higher observed response in the laser group for the AP-ROP Zone I patients and in the aflibercept group for the AP-ROP Zone II patients. The response rate is still considered to be high for patients with AP-ROP Zone I, even if not numerically higher. It is to note, that there were slightly more patients included in the aflibercept group (14 patients, 18.7%) than in the laser group (5 patients, 13.2%), this could also potentially bias the outcomes. Therefore, the indication has been accepted.

Extension Study 20275

Baseline demographics of patients in the Extension Study are coherent with the core study 20090 and comparable across treatment groups.

Outcomes and estimation

Core Study 20090

Primary endpoint results

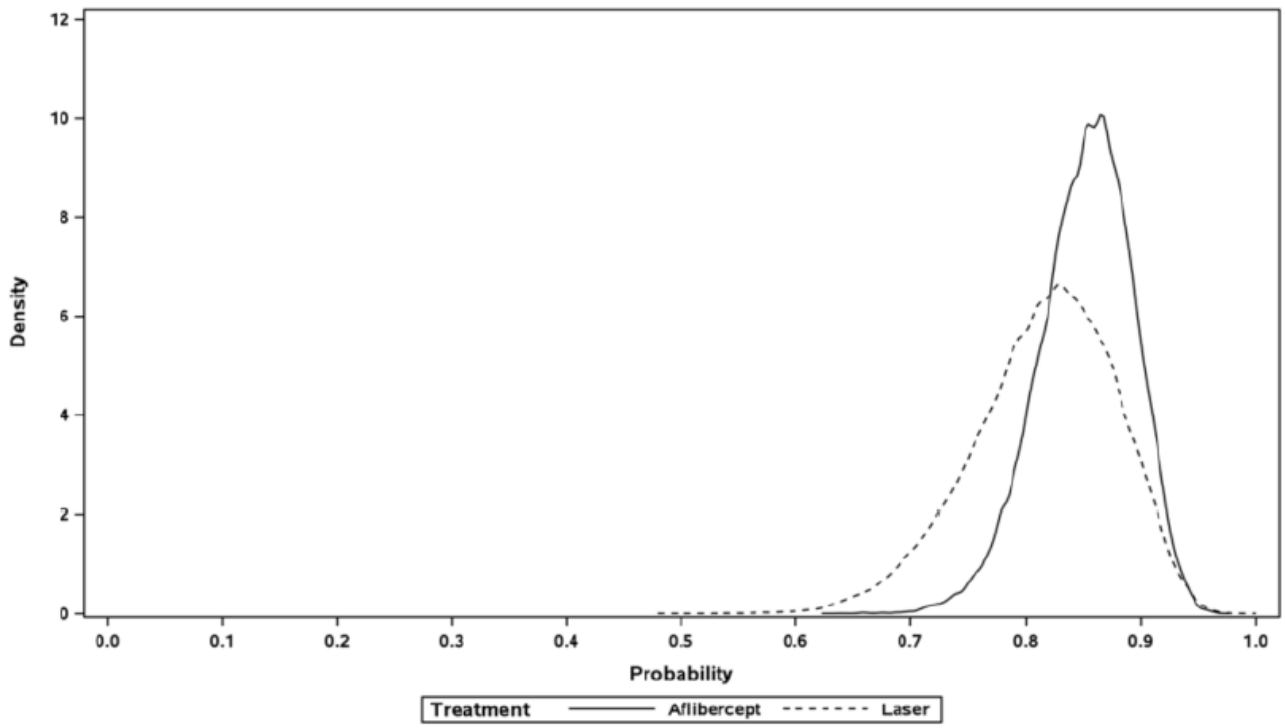
The primary efficacy endpoint was the proportion of patients with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on the investigator's assessment. Active ROP was defined as ROP (according to the inclusion criteria) requiring treatment. Unfavorable structural outcomes included retinal detachment, macular dragging, macular fold, or retrolental opacity. One eye or both eyes of a patient were included into the analysis to determine the primary endpoint on a patient level, if treated and meeting the inclusion criteria. Subjects receiving rescue treatment were considered nonresponders with respect to the primary endpoint. The primary efficacy endpoint analysis was based on the FAS, which included all subjects who received any study treatment and had a baseline and at least one post-baseline assessment of efficacy.

Using a Bayesian model, the estimated response probability (median of the posterior distribution) for meeting the response criterion absence of active ROP and unfavourable structural outcomes at 24 weeks was 85.5% in the aflibercept treatment arm and 82.1% for the laser treatment arm (Table 5.5.6). As the 90% credible interval for the treatment difference (-8.0%; 16.2%) does not exclude -5%, non-inferiority of aflibercept compared to laser treatment (pre-defined success criterion) could not be concluded, although the aflibercept arm numerically showed slightly better outcomes. The posterior probability that the response rate for aflibercept is greater than that for laser minus 5 percentage points was 88.4%.

	Mean	Standard Deviation	90% Credible Interval [a]	Median	Mode [b]	Probability for difference ≥-0.05%
Aflibercept n = 75	0.852	0.041	(0.780 , 0.913)	0.855	0.864	
Laser n = 38	0.816	0.062	(0.705 , 0.908)	0.821	0.827	
Difference	0.036	0.073	(-0.080 , 0.162)	0.034	0.029	0.884

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes (i.e. if a subject had 2 treated eyes, both needed to respond).
Response probability modeled as $pi = p^2 + r*p*(1-p)$, with p response probability of an individual eye and r = correlation between 2 eyes.
Success criterion: P(response probability for aflibercept > (response probability for laser -5%)) ≥ 95%.
a 90% equal tail credible intervals for posterior proportion are presented.
b Half-sample mode
FAS = full analysis set, ROP = retinopathy of prematurity.

Table 5.5.6 - Bayesian model for proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment (FAS)



FAS = full analysis set, ROP = retinopathy of prematurity.

Figure 5.5.5 - Posterior probability density for proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator's assessment (FAS)

According to the investigator's assessment, treatment success occurred in 126 (86.3%) of 146 eyes in the aflibercept arm and 61 (84.7%) of 72 eyes in the laser arm (Table 5.5.7). The type(s) of unfavorable structural outcome per subject and per eye based on the investigators' assessment can be found in *Module 5.3.5.1 (ROP), Report PH-41617, Table 14.2.1.1/1*. Retinal detachment was the most frequent of unfavorable structural outcome (5 subjects (6.7%) in the aflibercept arm and in 2 (5.3%) in the laser arm).

	Aflibercept N=75	Laser N=38
Number of subjects	75 (100.0%)	38 (100.0%)
Number of subjects both eyes eligible	71 (94.7%)	34 (89.5%)
At least 1 eye not fully assessable	2 (2.7%)	0 (0.0%)
Response 1 eye	0 (0.0%)	0 (0.0%)
Both eyes fully assessable	69 (92.0%)	34 (89.5%)
Response both eyes	59 (78.7%)	28 (73.7%)
Response 1 eye	4 (5.3%)	1 (2.6%)
Number of subjects with 1 eye eligible	4 (5.3%)	4 (10.5%)
Eye not fully assessable	0 (0.0%)	0 (0.0%)
Response 1 eye	4 (5.3%)	4 (10.5%)
Number of eyes	146 (100.0%)	72 (100.0%)
Eyes meeting response criterion	126 (86.3%)	61 (84.7%)
Eye not fully assessable	4 (2.7%)	0 (0.0%)
Active ROP	9 (6.2%)	2 (2.8%)
Unfavorable structural outcome	10 (6.8%)	4 (5.6%)
Rescue treatment received	7 (4.8%)	8 (11.1%)

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes.
Subjects receiving rescue treatment are considered nonresponders.
Eye is not fully assessable if dropped out prior to week 16 where neither response (no active ROP and either fully vascularized or laser treatment completed) nor nonresponse could be clearly assigned.
An eye is considered eligible, in case it meets the inclusion and exclusion criteria and treatment started prior to, or at visit 9 (week 8).
FAS = full analysis set, ROP = retinopathy of prematurity.

Table 5.5.7 - Absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment – investigator's assessment (FAS)

	Aflibercept N=68	Laser N=35
Number of subjects (a)	68 (100.0%)	35 (100.0%)
Number of subjects both eyes eligible	64 (94.1%)	33 (94.3%)
At least one eye not fully assessable (b)	2 (2.9%)	0 (0.0%)
Response one eye	0 (0.0%)	0 (0.0%)
Both eyes fully assessable (b)	62 (91.2%)	33 (94.3%)
Response both eyes	54 (79.4%)	27 (77.1%)
Response one eye	3 (4.4%)	1 (2.9%)
Number of subjects with one eye eligible	4 (5.9%)	2 (5.7%)
Eye not fully assessable (b)	0 (0.0%)	0 (0.0%)
Response one eye	4 (5.9%)	2 (5.7%)
Number of eyes	132 (100.0%)	68 (100.0%)
Eyes meeting response criterion	115 (87.1%)	57 (83.8%)
Eye not fully assessable (b)	4 (3.0%)	0 (0.0%)
Active ROP	9 (6.8%)	2 (2.9%)
Unfavorable structural outcome	10 (7.6%)	4 (5.9%)
Rescue treatment received	4 (3.0%)	8 (11.8%)

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes.
All subjects receiving rescue treatment are counted as non responders.
(a) All subjects of the respective analysis set.
(b) Eye is not fully assessable if dropped out prior to week 16 where neither response (no active ROP and either fully vascularized or laser treatment completed) nor non response can be clearly assigned.
An eye is considered eligible, in case it meets the inclusion and exclusion criteria and treatment started prior to, or at Visit 9 (week 8).
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity

Table 5.5.8 - Number of subjects with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment based on investigator assessment (modified full analysis set)

	Aflibercept N=66	Laser N=35
Number of subjects (a)	66 (100.0%)	35 (100.0%)
Number of subjects both eyes eligible	62 (93.9%)	33 (94.3%)
At least one eye not fully assessable (b)	0 (0.0%)	0 (0.0%)
Response one eye	0 (0.0%)	0 (0.0%)
Both eyes fully assessable (b)	62 (93.9%)	33 (94.3%)
Response both eyes	54 (81.8%)	27 (77.1%)
Response one eye	3 (4.5%)	1 (2.9%)
Number of subjects with one eye eligible	4 (6.1%)	2 (5.7%)
Eye not fully assessable (b)	0 (0.0%)	0 (0.0%)
Response one eye	4 (6.1%)	2 (5.7%)
Number of eyes	128 (100.0%)	68 (100.0%)
Eyes meeting response criterion	115 (89.8%)	57 (83.8%)
Eye not fully assessable (b)	0 (0.0%)	0 (0.0%)
Active ROP	8 (6.3%)	2 (2.9%)
Unfavorable structural outcome	10 (7.8%)	4 (5.9%)
Rescue treatment received	4 (3.1%)	8 (11.8%)

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes.
All subjects receiving rescue treatment are counted as non responders.
(a) All subjects of the respective analysis set.
(b) Eye is not fully assessable if dropped out prior to week 16 where neither response (no active ROP and either fully vascularized or laser treatment completed) nor non response can be clearly assigned.
An eye is considered eligible, in case it meets the inclusion and exclusion criteria and treatment started prior to, or at Visit 9 (week 8).
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity

Table 5.5.9 - Number of subjects with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment based on investigator assessment (per protocol set)

The primary efficacy endpoint based on the investigator's assessment was analyzed by baseline ROP classification (AP-ROP, Zone I [excluding AP-ROP] and Zone II [excluding AP-ROP]). Applying the Bayesian model, the best response seen in both arms was in Zone II.

In all 3 subgroups, the aflibercept arm showed numerically higher efficacy. The estimated response probabilities (median of the posterior distribution) by baseline ROP classification were (*Module 5.3.5.1 [ROP], Report PH-41617, Tables 14.2.1.1/14, 14.2.1.1/15, and 14.2.1.1/16*):

- AP-ROP: 73.3% (aflibercept arm) and 72.2% (laser arm)

- Zone I (excluding AP-ROP): 70.8% (aflibercept arm) and 64.4% (laser arm)

- Zone II (excluding AP-ROP): 92.0% (aflibercept arm) and 84.9% (laser arm)

The type(s) of unfavorable structural outcome per eye based on the investigators' assessment can be found in *Module 5.3.5.1 (ROP), Report PH-41617, Table 14.2.1.1/40*.

It should be noted that the control of the type I error, as defined in the study protocol, is more relaxed than what would be typically expected in a confirmatory phase III trial (i.e. 2.5% one-sided). Nevertheless, the success criterion (non-inferiority of IVT aflibercept therapy to conventional laser therapy) is not considered to be statistically met (90% credible interval for treatment difference was −8.0% to +16.2% and did not exclude the pre-specified margin of -5%), although treatment success was numerically slightly higher with IVT aflibercept (85.5%) compared to laser (82.1%) at Week 24.

Therefore, it cannot be concluded that aflibercept is non-inferior to the laser treatment, despite the less conservative less stringent statistical approach than usual. Consequently, there are true concerns on the

efficacy of aflibercept in ROP, and it cannot be excluded that the treatment is inferior to the laser photocoagulation, meaning the risk of loss of chance for the patient. All the more, the sensitivity analysis, including the Per Protocol analysis, are consistent with this results and do not show more favourable outcomes; using a frequentist approach no numerically trend in favour of Aflibercept could be observed anymore. However, considering the totality of evidence, including the consistency across endpoints and the possibility that laser had by chance a high response rate in this study (which is to some extent accounted for in the evidence synthesis study, see below), it can be concluded that aflibercept does have a clinically relevant level of efficacy in the target population. This was also discussed by the Applicant who submitted literature supporting the clinical relevance endpoint used to assess visual function, the assessment of the fixation and ability to follow a 5cm toy (Bowman, 2016; International Neonatal Consortium, Smith et al., 2019).

Moreover, in order to further reduce the uncertainty, the Applicant was asked to implement a post approval study. The Applicant commits – as implemented in the RMP - to submit further results until 5 years of chronological age. Additionally, the applicant co-funded a ROP registry in Europe aiming the collection of data (eg. baseline demographics, ROP disease and treatment characteristics as well as ophthalmological outcomes from infants treated). The age-related ocular developpement and difficulty to perform exams are well understood.

Sensitivity analyses

Three sensitivity analyses were performed on the primary efficacy endpoint:

- using the central reading center data instead of the investigator's assessment of ROP at week 24;

- evaluating the impact of missing data considering all dropouts as non-responders unless completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects) (worst case imputation);

- the proportion of patients with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment according to the investigator's assessment was analyzed by the corresponding frequentist approach.

Using the reading center's assessments, the estimated response probability (median of the posterior distribution) was 80.9% of subjects in the aflibercept arm and 77.5% subjects in the laser arm (*Table 5.5.10).* The response rates based on the reading center's assessment was slightly lower than those obtained by the investigator's assessment (85.5% and 82.1%) because less subjects were evaluable, as not all subjects had images that were assessed by the reading center.

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	75	0.805	0.053	(0.711 , 0.885)	0.809	0.824
Laser	38	0.770	0.070	(0.646 , 0.876)	0.775	0.789
Difference		0.035	0.087	(-0.104 , 0.182)	0.033	0.040

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both need to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.10 - Bayesian model for Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on central reading center assessment (FAS)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	68	0.808	0.054	(0.712 , 0.891)	0.812	0.823
Laser	35	0.751	0.072	(0.625 , 0.862)	0.756	0.761
Difference		0.057	0.090	(-0.088 , 0.207)	0.055	0.059

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both need to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.11 - Bayesian model for Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on central reading center assessment (mFAS)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	66	0.809	0.053	(0.716 , 0.890)	0.812	0.828
Laser	35	0.757	0.073	(0.628 , 0.868)	0.762	0.781
Difference		0.052	0.090	(-0.092 , 0.204)	0.050	0.050

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both need to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.12 - Bayesian model for Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on central reading center assessment (PPS)

For the evaluation of the impact of missing data, the estimated response probability (median of the posterior distribution) was 79.2% of subjects in the aflibercept arm and 82.6% subjects in the laser arm (*Table 5.5.13*). This approach favored the laser arm as complete laser treatment is easier to achieve than complete vascularization.

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	75	0.789	0.047	(0.707 , 0.861)	0.792	0.804
Laser	38	0.821	0.060	(0.713 , 0.911)	0.826	0.844
Difference		-0.031	0.075	(-0.151 , 0.095)	-0.034	-0.035

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both need to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
All drop-outs unless completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects) are considered as non-responders.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.13 - Bayesian model for Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment - worst case imputation (FAS)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	68	0.814	0.046	(0.733 , 0.885)	0.817	0.834
Laser	35	0.807	0.065	(0.690 , 0.903)	0.812	0.833
Difference		0.007	0.079	(-0.118 , 0.143)	0.004	-0.005

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both need to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
All drop-outs unless completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects) are considered as non-responders.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.14 - Bayesian model for Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment - worst case imputation (mFAS)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	66	0.836	0.046	(0.756 , 0.905)	0.839	0.833
Laser	35	0.804	0.066	(0.686 , 0.901)	0.809	0.816
Difference		0.032	0.079	(-0.094 , 0.168)	0.030	0.010

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both need to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental opacity
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
All drop-outs unless completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects) are considered as non-responders.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.15 - Bayesian model for Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment - worst case imputation (PPS)

Similar to the primary analysis, in the analyses based on a frequentist approach estimating asymptotic 90% confidence intervals for the treatment difference as a sensitivity analysis, non-inferiority of aflibercept compared to laser could not be concluded as the 90% confidence interval includes -5% (90% CI: -12.2, 11.8). Different to the primary analysis where the response of unilaterally-treated subjects was handled model-based, these subjects were considered responders if they met the response criterion in the one treated eye.

For further details on the sensitivity analyses, see Module 5.3.5.1 (ROP), Report PH-41617, Section 9.2.1.1.2. The analysis of the sensitivity analyses by baseline ROP classification can be found in Module 5.3.5.1 (ROP), Report PH-41617, Section 9.2.2.1.2.

Supportive assessment

The primary success criterion agreed with the Japanese health authority, PMDA, was to show that the response probability for aflibercept is significantly higher than 66%, which is the one reported for laser treatment in the literature (Stahl et al. 2019).

As for the primary analysis, this analysis was based on the investigator's assessment at 24 weeks. This analysis demonstrated superiority of aflibercept over the historic laser rate of 66% (p=0.0021), which can also be seen by the lower limit of the 2-sided 95% confidence interval of the aflibercept arm (95%

CI: 72.2, 90.4) being higher than the threshold value of 66% (Table 5.5.16).

	Aflibercept	Laser
Number of subjects	75	38
Number of responders	62	32
Percentage of responders	82.7	84.2
95% CI [a]	(72.2, 90.4)	(68.7, 94.0)
p-value [b]	0.0021	
Treatment difference	-1.5	
95% CI [c]	(-16.0, 12.9)	

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes (i.e. if a subject had 2 study eyes, both needed to respond).
a Exact Clopper-Pearson CIs
b Exact 2-sided binomial test of responder proportion against fixed threshold of 0.66
c Asymptotic 2-sided CIs.
CI = confidence interval, FAS = full analysis set, ROP = retinopathy of prematurity.

Table 5.5.16 - Supportive assessment for proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment (FAS)

Secondary efficacy analysis results

The analysis of the secondary efficacy variables by baseline ROP classification can be found in *Module 5.3.5.1 (ROP), Report PH-41617, Section 9.2.2.2.*

Requirement for intervention with a second treatment modality from baseline to week 24 (*secondary endpoints addressing primary objective)*

A second treatment modality for ROP was either rescue treatment or any other surgical or nonsurgical treatment for ROP (e.g. IVT anti-VEGF injection, ablative laser therapy, cryotherapy, or vitrectomy) captured as concomitant medication or surgery after study start.

Using a similar Bayesian model as for the primary analysis, the estimated median probability for a subject to require an intervention with a second modality from baseline until week 24 was 7.2% of subjects in the aflibercept arm and 9.6% subjects in the laser arm (*Table 5.5.17*).

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	75	0.076	0.028	(0.036 , 0.127)	0.072	0.072
Laser	38	0.102	0.044	(0.042 , 0.184)	0.096	0.085
Difference		-0.027	0.048	(-0.110 , 0.046)	-0.023	-0.017

A second treatment modality is either rescue treatment as defined per protocol or any other surgical or nonsurgical treatment for ROP.
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.17 - Bayesian model for Proportion of subjects requiring an intervention with a second treatment modality from baseline until week 24 (full analysis set)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	68	0.069	0.029	(0.029 , 0.123)	0.064	0.059
Laser	35	0.116	0.049	(0.047 , 0.208)	0.110	0.098
Difference		-0.047	0.052	(-0.141 , 0.031)	-0.043	-0.038

A second treatment modality is either rescue treatment as defined per protocol or any other surgical or nonsurgical treatment for ROP.
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.18 - Bayesian model for Proportion of subjects requiring an intervention with a second treatment modality from baseline until week 24 (modified full analysis set)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	66	0.058	0.027	(0.023 , 0.108)	0.055	0.052
Laser	35	0.112	0.049	(0.045 , 0.204)	0.106	0.089
Difference		-0.054	0.052	(-0.147 , 0.022)	-0.049	-0.039

A second treatment modality is either rescue treatment as defined per protocol or any other surgical or nonsurgical treatment for ROP.
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.19 - Bayesian model for Proportion of subjects requiring an intervention with a second treatment modality from baseline until week 24 (per protocol set)

Recurrence of ROP from baseline to week 24 (*secondary endpoints addressing primary objective)*

Recurrence of ROP until week 24 was defined as the need for retreatment or rescue treatment in the opinion of the investigator in cases where the question presence of active ROP requiring treatment had been previously answered by the investigator as "no".

Using a Bayesian model, the estimated response probability (median of the posterior distribution) for recurrence of ROP was 16.1% of subjects in the aflibercept arm and 6.3% subjects in the laser arm (*Table 5.5.20).*

This secondary endpoint needs to be interpreted with caution. Based on the protocol definition of recurrence only subjects who previously experienced an improvement to a ROP stage that did not require treatment could classify for having ROP recurrence. The higher recurrence rate in the aflibercept arm of Study 20090 does not imply that aflibercept treatment is inferior.

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	75	0.165	0.041	(0.102 , 0.237)	0.161	0.148
Laser	38	0.068	0.033	(0.025 , 0.131)	0.063	0.057
Difference		0.096	0.048	(0.019 , 0.175)	0.096	0.088

Recurrence of ROP until Week 24 is defined as a need for retreatment or rescue treatment in cases where the question presence of active ROP requiring treatment had been previously answered with 'No'.
Response probability modeled as pi = p^2 + r*p*(1-p), with p probability of absence of recurrence of ROP of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.20 - Bayesian model for Proportion of subjects with recurrence of ROP from baseline until week 24 (FAS)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	68	0.152	0.042	(0.090 , 0.225)	0.149	0.139
Laser	35	0.077	0.037	(0.028 , 0.145)	0.071	0.061
Difference		0.075	0.050	(-0.006 , 0.158)	0.075	0.070

Recurrence of ROP until Week 24 is defined as a need for retreatment or rescue treatment in cases where the question presence of active ROP requiring treatment had been previously answered with 'No'.
Response probability modeled as pi = p^2 + r*p*(1-p), with p probability of absence of recurrence of ROP of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.21 - Bayesian model for Proportion of subjects with recurrence of ROP from baseline until week 24 (mFAS)

Treatment	n	Mean	SD	90% Credible interval (a)	Median	Mode (b)
Aflibercept	66	0.152	0.043	(0.089 , 0.227)	0.148	0.138
Laser	35	0.077	0.037	(0.028 , 0.146)	0.072	0.058
Difference		0.075	0.051	(-0.008 , 0.159)	0.074	0.075

Recurrence of ROP until Week 24 is defined as a need for retreatment or rescue treatment in cases where the question presence of active ROP requiring treatment had been previously answered with 'No'.
Response probability modeled as pi = p^2 + r*p*(1-p), with p probability of absence of recurrence of ROP of an individual eye and r = correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
(a) 90% Equal Tail credible intervals for posterior proportion are presented.
(b) Half-sample mode.

Table 5.5.22 - Bayesian model for Proportion of subjects with recurrence of ROP from baseline until week 24 (PPS)

To explore new Retinopathy of Prematurity Activity Scale proposed by the International Neonatal Consortium (*secondary endpoints addressing primary objective)*

The ROP Activity Scale and the severity classifications (mild, moderate, severe) were derived for each eye using the assessments from the central reading center as described in *Module 5.3.5.1 [ROP], Report PH-41617, Section 7.6.4.2.4.* ROP Activity Scale values of 0 to 7 are considered mild, 8 to 12 are moderate, and 13 to 22 are severe.

The mean (SD) ROP Activity Scale values at baseline were similar between the 2 treatment arms: 16.20 (2.81) for the aflibercept arm and 15.63 (3.53) for the laser arm (*Table 5.5.23*). At each post-baseline visit, mean decreases from baseline were seen in both arms with the exception of week 3 in the laser arm. At week 24, the mean (SD) decrease from baseline was -15.42 (4.46) in the aflibercept arm and -14.77 (4.19) in the laser arm.

Treatment group	Visit	Value at visit					Change from baseline				
		n	Mean (SD)	Median	Q1, Q3	Min, Max	n	Mean (SD)	Median	Q1, Q3	Min, Max
Aflibercept (N=75)	BASELINE	136	16.20 (2.81)	18.00	14.00, 19.00	7.0, 19.0					
	WEEK 1	135	11.44 (5.41)	13.00	8.00, 16.00	0.0, 21.0	113	-5.06 (5.58)	-4.00	-8.00, 0.00	-19.0, 2.0
	WEEK 2	7	9.57 (7.30)	14.00	0.00, 14.00	0.0, 18.0	7	-7.57 (8.18)	-4.00	-19.00, 0.00	-19.0, 0.0
	WEEK 3	2	16.50 (3.54)	16.50	14.00, 19.00	14.0, 19.0	2	-1.50 (3.54)	-1.50	-4.00, 1.00	-4.0, 1.0
	WEEK 4	125	5.59 (5.64)	7.00	0.00, 8.00	0.0, 19.0	108	-10.79 (6.49)	-12.00	-18.00, -6.00	-19.0, 6.0
	WEEK 5	4	12.50 (3.00)	14.00	11.00, 14.00	8.0, 14.0	4	-4.00 (2.71)	-5.00	-5.50, -2.50	-6.0, 0.0
	WEEK 6	6	12.80 (7.43)	14.00	14.00, 18.00	0.0, 18.0	5	-4.00 (7.84)	-1.00	-1.00, 0.00	-18.0, 0.0
	WEEK 7	2	12.00 (5.66)	12.00	8.00, 16.00	8.0, 16.0	2	-7.00 (5.66)	-7.00	-11.00, -3.00	-11.0, -3.0
	WEEK 8	6	5.00 (6.27)	3.50	0.00, 10.00	0.0, 13.0	4	-11.00 (8.45)	-12.50	-18.00, -4.00	-18.0, -1.0
	WEEK 10	6	8.17 (5.27)	7.00	7.00, 14.00	0.0, 14.0	3	-7.33 (4.04)	-5.00	-12.00, -5.00	-12.0, -5.0
	WEEK 11	10	6.50 (6.95)	6.50	0.00, 13.00	0.0, 13.0	5	-11.40 (5.55)	-12.00	-14.00, -6.00	-19.0, -6.0
	WEEK 12	126	3.74 (5.51)	0.00	0.00, 7.00	0.0, 19.0	99	-12.63 (5.71)	-14.00	-18.00, -8.00	-19.0, 5.0
	WEEK 13	4	1.50 (1.73)	1.50	0.00, 3.00	0.0, 3.0	4	-17.50 (1.73)	-17.50	-19.00, -16.00	-19.0, -16.0
	WEEK 14	6	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 15	4	8.50 (6.35)	8.50	3.00, 14.00	3.0, 14.0	4	-10.50 (6.35)	-10.50	-16.00, -5.00	-16.0, -5.0
	WEEK 16	20	3.19 (5.10)	0.00	0.00, 5.00	0.0, 14.0	13	-15.08 (4.39)	-16.00	-19.00, -14.00	-19.0, -4.0
	WEEK 17	8	5.57 (5.59)	3.00	0.00, 13.00	0.0, 13.0	4	-15.25 (3.30)	-15.50	-17.50, -13.00	-19.0, -11.0
	WEEK 18	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-18.00 (0.00)	-18.00	-18.00, -18.00	-18.0, -18.0
	WEEK 20	10	4.11 (6.19)	0.00	0.00, 11.00	0.0, 13.0	7	-13.57 (5.53)	-14.00	-18.00, -6.00	-19.0, -6.0
	WEEK 24	117	0.93 (3.60)	0.00	0.00, 0.00	0.0, 20.0	90	-15.42 (4.46)	-17.50	-18.00, -14.00	-19.0, 6.0
	EARLY TERMINATION	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
Laser (N=38)	BASELINE	71	15.63 (3.53)	16.00	14.00, 19.00	0.0, 20.0					
	WEEK 1	71	5.64 (6.97)	0.00	0.00, 13.50	0.0, 19.0	64	-9.81 (7.47)	-13.00	-16.50, -1.50	-19.0, 7.0
	WEEK 2	4	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	4	-16.25 (3.20)	-16.50	-19.00, -13.50	-19.0, -13.0
	WEEK 3	2	19.00 (0.00)	19.00	19.00, 19.00	19.0, 19.0	2	0.50 (0.71)	0.50	0.00, 1.00	0.0, 1.0
	WEEK 4	67	2.70 (5.63)	0.00	0.00, 0.00	0.0, 19.0	64	-12.89 (5.97)	-14.00	-18.00, -11.00	-19.0, 0.0
	WEEK 5	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 6	10	8.10 (9.28)	3.50	0.00, 18.00	0.0, 21.0	10	-8.70 (8.25)	-12.00	-16.00, 0.00	-19.0, 3.0
	WEEK 7	2	9.00 (12.73)	9.00	0.00, 18.00	0.0, 18.0	2	-10.00 (12.73)	-10.00	-19.00, -1.00	-19.0, -1.0
	WEEK 8	4	5.25 (10.50)	0.00	0.00, 10.50	0.0, 21.0	4	-12.00 (10.10)	-16.00	-17.50, -6.50	-19.0, 3.0
	WEEK 9	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-17.00 (1.41)	-17.00	-18.00, -16.00	-18.0, -16.0
	WEEK 10	6	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	6	-18.00 (1.55)	-19.00	-19.00, -16.00	-19.0, -16.0
	WEEK 12	54	0.92 (3.86)	0.00	0.00, 0.00	0.0, 21.0	51	-14.33 (5.10)	-14.00	-18.00, -14.00	-19.0, 3.0
	WEEK 16	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 20	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-16.50 (3.54)	-16.50	-19.00, -14.00	-19.0, -14.0
	WEEK 24	63	0.48 (2.88)	0.00	0.00, 0.00	0.0, 21.0	60	-14.77 (4.19)	-14.00	-18.00, -14.00	-19.0, 3.0
	EARLY TERMINATION	2	10.50 (14.85)	10.50	0.00, 21.00	0.0, 21.0	2	-9.00 (14.14)	-9.00	-19.00, 1.00	-19.0, 1.0

n refers to number of eyes

Table 5.5.23 - Summary statistics for retinopathy of prematurity activity scale from central reading center and changes from baseline by visit (full analysis set)

Treatment group	Visit	Value at visit					Change from baseline				
		n	Mean (SD)	Median	Q1, Q3	Min, Max	n	Mean (SD)	Median	Q1, Q3	Min, Max
Aflibercept (N=75)	BASELINE	129	16.47 (2.50)	18.00	14.00, 19.00	8.0, 19.0					
	WEEK 1	129	11.43 (5.44)	13.00	8.00, 16.00	0.0, 21.0	112	-5.10 (5.59)	-4.00	-8.50, 0.00	-19.0, 2.0
	WEEK 2	7	9.57 (7.30)	14.00	0.00, 14.00	0.0, 18.0	7	-7.57 (8.18)	-4.00	-19.00, 0.00	-19.0, 0.0
	WEEK 3	2	16.50 (3.54)	16.50	14.00, 19.00	14.0, 19.0	2	-1.50 (3.54)	-1.50	-4.00, 1.00	-4.0, 1.0
	WEEK 4	121	5.59 (5.73)	7.00	0.00, 8.00	0.0, 19.0	106	-10.91 (6.49)	-12.00	-18.00, -6.00	-19.0, 6.0
	WEEK 5	4	12.50 (3.00)	14.00	11.00, 14.00	8.0, 14.0	4	-4.00 (2.71)	-5.00	-5.50, -2.50	-6.0, 0.0
	WEEK 6	6	12.80 (7.43)	14.00	14.00, 18.00	0.0, 18.0	5	-4.00 (7.84)	-1.00	-1.00, 0.00	-18.0, 0.0
	WEEK 7	2	12.00 (5.66)	12.00	8.00, 16.00	8.0, 16.0	2	-7.00 (5.66)	-7.00	-11.00, -3.00	-11.0, -3.0
	WEEK 8	6	5.00 (6.27)	3.50	0.00, 10.00	0.0, 13.0	4	-11.00 (8.45)	-12.50	-18.00, -4.00	-18.0, -1.0
	WEEK 10	4	8.75 (6.70)	10.50	3.50, 14.00	0.0, 14.0	3	-7.33 (4.04)	-5.00	-12.00, -5.00	-12.0, -5.0
	WEEK 11	6	5.20 (7.12)	0.00	0.00, 13.00	0.0, 13.0	5	-11.40 (5.55)	-12.00	-14.00, -6.00	-19.0, -6.0
	WEEK 12	114	3.61 (5.56)	0.00	0.00, 7.00	0.0, 19.0	97	-12.73 (5.72)	-14.00	-18.00, -9.00	-19.0, 5.0
	WEEK 13	4	1.50 (1.73)	1.50	0.00, 3.00	0.0, 3.0	4	-17.50 (1.73)	-17.50	-19.00, -16.00	-19.0, -16.0
	WEEK 14	4	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 15	4	8.50 (6.35)	8.50	3.00, 14.00	3.0, 14.0	4	-10.50 (6.35)	-10.50	-16.00, -5.00	-16.0, -5.0
	WEEK 16	18	2.64 (5.00)	0.00	0.00, 3.00	0.0, 14.0	13	-15.08 (4.39)	-16.00	-19.00, -14.00	-19.0, -4.0
	WEEK 17	6	2.60 (2.88)	3.00	0.00, 3.00	0.0, 7.0	4	-15.25 (3.30)	-15.50	-17.50, -13.00	-19.0, -11.0
	WEEK 18	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-18.00 (0.00)	-18.00	-18.00, -18.00	-18.0, -18.0
	WEEK 20	8	3.71 (6.34)	0.00	0.00, 13.00	0.0, 13.0	7	-13.57 (5.53)	-14.00	-18.00, -6.00	-19.0, -6.0
	WEEK 24	109	0.94 (3.74)	0.00	0.00, 0.00	0.0, 20.0	88	-15.60 (4.34)	-18.00	-18.00, -14.00	-19.0, 6.0
	EARLY TERMINATION	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
Laser (N=38)	BASELINE	68	15.99 (3.17)	16.00	14.00, 19.00	0.0, 20.0					
	WEEK 1	67	5.92 (7.03)	0.00	0.00, 14.00	0.0, 19.0	61	-9.92 (7.63)	-14.00	-17.00, -1.00	-19.0, 7.0
	WEEK 2	4	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	4	-16.25 (3.20)	-16.50	-19.00, -13.50	-19.0, -13.0
	WEEK 3	2	19.00 (0.00)	19.00	19.00, 19.00	19.0, 19.0	2	0.50 (0.71)	0.50	0.00, 1.00	0.0, 1.0
	WEEK 4	64	2.84 (5.74)	0.00	0.00, 0.00	0.0, 19.0	61	-13.15 (6.00)	-14.00	-18.00, -13.00	-19.0, 0.0
	WEEK 5	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 6	10	8.10 (9.28)	3.50	0.00, 18.00	0.0, 21.0	10	-8.70 (8.25)	-12.00	-16.00, 0.00	-19.0, 3.0
	WEEK 7	2	9.00 (12.73)	9.00	0.00, 18.00	0.0, 18.0	2	-10.00 (12.73)	-10.00	-19.00, -1.00	-19.0, -1.0
	WEEK 8	4	5.25 (10.50)	0.00	0.00, 10.50	0.0, 21.0	4	-12.00 (10.10)	-16.00	-17.50, -6.50	-19.0, 3.0
	WEEK 9	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-17.00 (1.41)	-17.00	-18.00, -16.00	-18.0, -16.0
	WEEK 10	6	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	6	-18.00 (1.55)	-19.00	-19.00, -16.00	-19.0, -16.0
	WEEK 12	52	0.96 (3.94)	0.00	0.00, 0.00	0.0, 21.0	50	-14.46 (5.07)	-14.00	-18.00, -14.00	-19.0, 3.0
	WEEK 16	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 20	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-16.50 (3.54)	-16.50	-19.00, -14.00	-19.0, -14.0
	WEEK 24	60	0.50 (2.93)	0.00	0.00, 0.00	0.0, 21.0	58	-15.02 (4.03)	-14.00	-18.00, -14.00	-19.0, 3.0
	EARLY TERMINATION	2	10.50 (14.85)	10.50	0.00, 21.00	0.0, 21.0	2	-9.00 (14.14)	-9.00	-19.00, 1.00	-19.0, 1.0

n refers to number of eyes

Table 5.5.24 - Summary statistics for retinopathy of prematurity activity scale from central reading center and changes from baseline by visit (modified full analysis set)

Treatment group	Visit	Value at visit					Change from baseline				
		n	Mean (SD)	Median	Q1, Q3	Min, Max	n	Mean (SD)	Median	Q1, Q3	Min, Max
Aflibercept (N=66)	BASELINE	125	16.41 (2.51)	18.00	14.00, 19.00	8.0, 19.0					
	WEEK 1	125	11.26 (5.41)	13.00	8.00, 15.00	0.0, 21.0	109	-5.21 (5.63)	-4.00	-9.00, 0.00	-19.0, 2.0
	WEEK 2	7	9.57 (7.30)	14.00	0.00, 14.00	0.0, 18.0	7	-7.57 (8.18)	-4.00	-19.00, 0.00	-19.0, 0.0
	WEEK 3	2	16.50 (3.54)	16.50	14.00, 19.00	14.0, 19.0	2	-1.50 (3.54)	-1.50	-4.00, 1.00	-4.0, 1.0
	WEEK 4	119	5.56 (5.78)	7.00	0.00, 8.00	0.0, 19.0	104	-10.89 (6.55)	-12.00	-18.00, -6.00	-19.0, 6.0
	WEEK 5	4	12.50 (3.00)	14.00	11.00, 14.00	8.0, 14.0	4	-4.00 (2.71)	-5.00	-5.50, -2.50	-6.0, 0.0
	WEEK 6	6	12.80 (7.43)	14.00	14.00, 18.00	0.0, 18.0	5	-4.00 (7.84)	-1.00	-1.00, 0.00	-18.0, 0.0
	WEEK 7	2	12.00 (5.66)	12.00	8.00, 16.00	8.0, 16.0	2	-7.00 (5.66)	-7.00	-11.00, -3.00	-11.0, -3.0
	WEEK 8	6	5.00 (6.27)	3.50	0.00, 10.00	0.0, 13.0	4	-11.00 (8.45)	-12.50	-18.00, -4.00	-18.0, -1.0
	WEEK 10	4	8.75 (6.70)	10.50	3.50, 14.00	0.0, 14.0	3	-7.33 (4.04)	-5.00	-12.00, -5.00	-12.0, -5.0
	WEEK 11	6	5.20 (7.12)	0.00	0.00, 13.00	0.0, 13.0	5	-11.40 (5.55)	-12.00	-14.00, -6.00	-19.0, -6.0
	WEEK 12	114	3.61 (5.56)	0.00	0.00, 7.00	0.0, 19.0	97	-12.73 (5.72)	-14.00	-18.00, -9.00	-19.0, 5.0
	WEEK 13	4	1.50 (1.73)	1.50	0.00, 3.00	0.0, 3.0	4	-17.50 (1.73)	-17.50	-19.00, -16.00	-19.0, -16.0
	WEEK 14	4	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 15	4	8.50 (6.35)	8.50	3.00, 14.00	3.0, 14.0	4	-10.50 (6.35)	-10.50	-16.00, -5.00	-16.0, -5.0
	WEEK 16	18	2.64 (5.00)	0.00	0.00, 3.00	0.0, 14.0	13	-15.08 (4.39)	-16.00	-19.00, -14.00	-19.0, -4.0
	WEEK 17	6	2.60 (2.88)	3.00	0.00, 3.00	0.0, 7.0	4	-15.25 (3.30)	-15.50	-17.50, -13.00	-19.0, -11.0
	WEEK 18	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-18.00 (0.00)	-18.00	-18.00, -18.00	-18.0, -18.0
	WEEK 20	8	3.71 (6.34)	0.00	0.00, 13.00	0.0, 13.0	7	-13.57 (5.53)	-14.00	-18.00, -6.00	-19.0, -6.0
	WEEK 24	109	0.94 (3.74)	0.00	0.00, 0.00	0.0, 20.0	88	-15.60 (4.34)	-18.00	-18.00, -14.00	-19.0, 6.0
	EARLY TERMINATION	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
Laser (N=35)	BASELINE	68	15.99 (3.17)	16.00	14.00, 19.00	0.0, 20.0					
	WEEK 1	67	5.92 (7.03)	0.00	0.00, 14.00	0.0, 19.0	61	-9.92 (7.63)	-14.00	-17.00, -1.00	-19.0, 7.0
	WEEK 2	4	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	4	-16.25 (3.20)	-16.50	-19.00, -13.50	-19.0, -13.0
	WEEK 3	2	19.00 (0.00)	19.00	19.00, 19.00	19.0, 19.0	2	0.50 (0.71)	0.50	0.00, 1.00	0.0, 1.0
	WEEK 4	64	2.84 (5.74)	0.00	0.00, 0.00	0.0, 19.0	61	-13.15 (6.00)	-14.00	-18.00, -13.00	-19.0, 0.0
	WEEK 5	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 6	10	8.10 (9.28)	3.50	0.00, 18.00	0.0, 21.0	10	-8.70 (8.25)	-12.00	-16.00, 0.00	-19.0, 3.0
	WEEK 7	2	9.00 (12.73)	9.00	0.00, 18.00	0.0, 18.0	2	-10.00 (12.73)	-10.00	-19.00, -1.00	-19.0, -1.0
	WEEK 8	4	5.25 (10.50)	0.00	0.00, 10.50	0.0, 21.0	4	-12.00 (10.10)	-16.00	-17.50, -6.50	-19.0, 3.0
	WEEK 9	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-17.00 (1.41)	-17.00	-18.00, -16.00	-18.0, -16.0
	WEEK 10	6	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	6	-18.00 (1.55)	-19.00	-19.00, -16.00	-19.0, -16.0
	WEEK 12	52	0.96 (3.94)	0.00	0.00, 0.00	0.0, 21.0	50	-14.46 (5.07)	-14.00	-18.00, -14.00	-19.0, 3.0
	WEEK 16	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-19.00 (0.00)	-19.00	-19.00, -19.00	-19.0, -19.0
	WEEK 20	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	2	-16.50 (3.54)	-16.50	-19.00, -14.00	-19.0, -14.0
	WEEK 24	60	0.50 (2.93)	0.00	0.00, 0.00	0.0, 21.0	58	-15.02 (4.03)	-14.00	-18.00, -14.00	-19.0, 3.0
	EARLY TERMINATION	2	10.50 (14.85)	10.50	0.00, 21.00	0.0, 21.0	2	-9.00 (14.14)	-9.00	-19.00, 1.00	-19.0, 1.0

n refers to number of eyes

Table 5.5.25 - Summary statistics for retinopathy of prematurity activity scale from central reading center and changes from baseline by visit (PPS)

During the study, very few eyes transitioned from baseline to a more severe ROP category: 1 eye at week 4 and 1 eye at week 12 (both aflibercept arm). At week 1, about 45% of aflibercept eyes and 62% of laser eyes transitioned to a less severe category (*Module 5.3.5.1 [ROP], Report PH-41617, Table 14.2.2/103*). At week 24, about 93% of aflibercept eyes and 95% of laser eyes transitioned to a less severe category.

The number of eyes with at least a 2-step increase or decrease from baseline in the ROP Activity Scale for the FAS is shown in *Table 5.5.26*.

Analysis Visit		Aflibercept (N=75)	Laser (N=38)	Total (N=113)
WEEK 1	Number of eyes	113 (100%)	64 (100%)	177 (100%)
	Number of eyes with >= 2 step decrease	65 (57.5%)	48 (75.0%)	113 (63.8%)
	Number of eyes with >= 2 step increase	2 (1.8%)	1 (1.6%)	3 (1.7%)
WEEK 2	Number of eyes	7 (100%)	4 (100%)	11 (100%)
	Number of eyes with >= 2 step decrease	5 (71.4%)	4 (100.0%)	9 (81.8%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 3	Number of eyes	2 (100%)	2 (100%)	4 (100%)
	Number of eyes with >= 2 step decrease	1 (50.0%)	0	1 (25.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 4	Number of eyes	108 (100%)	64 (100%)	172 (100%)
	Number of eyes with >= 2 step decrease	94 (87.0%)	57 (89.1%)	151 (87.8%)
	Number of eyes with >= 2 step increase	3 (2.8%)	0	3 (1.7%)
WEEK 6	Number of eyes	5 (100%)	10 (100%)	15 (100%)
	Number of eyes with >= 2 step decrease	1 (20.0%)	6 (60.0%)	7 (46.7%)
	Number of eyes with >= 2 step increase	0	1 (10.0%)	1 (6.7%)
WEEK 8	Number of eyes	4 (100%)	4 (100%)	8 (100%)
	Number of eyes with >= 2 step decrease	3 (75.0%)	3 (75.0%)	6 (75.0%)
	Number of eyes with >= 2 step increase	0	1 (25.0%)	1 (12.5%)
WEEK 10	Number of eyes	3 (100%)	6 (100%)	9 (100%)
	Number of eyes with >= 2 step decrease	3 (100.0%)	6 (100.0%)	9 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 12	Number of eyes	99 (100%)	51 (100%)	150 (100%)
	Number of eyes with >= 2 step decrease	93 (93.9%)	47 (92.2%)	140 (93.3%)
	Number of eyes with >= 2 step increase	1 (1.0%)	1 (2.0%)	2 (1.3%)
WEEK 16	Number of eyes	13 (100%)	2 (100%)	15 (100%)
	Number of eyes with >= 2 step decrease	13 (100.0%)	2 (100.0%)	15 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 20	Number of eyes	7 (100%)	2 (100%)	9 (100%)
	Number of eyes with >= 2 step decrease	7 (100.0%)	2 (100.0%)	9 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 24	Number of eyes	90 (100%)	60 (100%)	150 (100%)
	Number of eyes with >= 2 step decrease	88 (97.8%)	58 (96.7%)	146 (97.3%)
	Number of eyes with >= 2 step increase	2 (2.2%)	1 (1.7%)	3 (2.0%)

Two step decrease/increase refers to a change of at least 2 points compared to baseline in ROP activity scale.

Table 5.5.26 - Number of eyes with change in ROP activity scale from central reading center (full analysis set)

Analysis Visit		Aflibercept (N=68)	Laser (N=35)	Total (N=103)
WEEK 1	Number of eyes	112 (100%)	61 (100%)	173 (100%)
	Number of eyes with >= 2 step decrease	65 (58.0%)	45 (73.8%)	110 (63.6%)
	Number of eyes with >= 2 step increase	2 (1.8%)	1 (1.6%)	3 (1.7%)
WEEK 2	Number of eyes	7 (100%)	4 (100%)	11 (100%)
	Number of eyes with >= 2 step decrease	5 (71.4%)	4 (100.0%)	9 (81.8%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 3	Number of eyes	2 (100%)	2 (100%)	4 (100%)
	Number of eyes with >= 2 step decrease	1 (50.0%)	0	1 (25.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 4	Number of eyes	106 (100%)	61 (100%)	167 (100%)
	Number of eyes with >= 2 step decrease	92 (86.8%)	54 (88.5%)	146 (87.4%)
	Number of eyes with >= 2 step increase	3 (2.8%)	0	3 (1.8%)
WEEK 6	Number of eyes	5 (100%)	10 (100%)	15 (100%)
	Number of eyes with >= 2 step decrease	1 (20.0%)	6 (60.0%)	7 (46.7%)
	Number of eyes with >= 2 step increase	0	1 (10.0%)	1 (6.7%)
WEEK 8	Number of eyes	4 (100%)	4 (100%)	8 (100%)
	Number of eyes with >= 2 step decrease	3 (75.0%)	3 (75.0%)	6 (75.0%)
	Number of eyes with >= 2 step increase	0	1 (25.0%)	1 (12.5%)
WEEK 10	Number of eyes	3 (100%)	6 (100%)	9 (100%)
	Number of eyes with >= 2 step decrease	3 (100.0%)	6 (100.0%)	9 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 12	Number of eyes	97 (100%)	50 (100%)	147 (100%)
	Number of eyes with >= 2 step decrease	91 (93.8%)	46 (92.0%)	137 (93.2%)
	Number of eyes with >= 2 step increase	1 (1.0%)	1 (2.0%)	2 (1.4%)
WEEK 16	Number of eyes	13 (100%)	2 (100%)	15 (100%)
	Number of eyes with >= 2 step decrease	13 (100.0%)	2 (100.0%)	15 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 20	Number of eyes	7 (100%)	2 (100%)	9 (100%)
	Number of eyes with >= 2 step decrease	7 (100.0%)	2 (100.0%)	9 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 24	Number of eyes	88 (100%)	58 (100%)	146 (100%)
	Number of eyes with >= 2 step decrease	86 (97.7%)	56 (96.6%)	142 (97.3%)
	Number of eyes with >= 2 step increase	2 (2.3%)	1 (1.7%)	3 (2.1%)

Two step decrease/increase refers to a change of at least 2 points compared to baseline in ROP activity scale.

Table 5.5.27 - Number of eyes with change in ROP activity scale from central reading center (modified full analysis set)

Analysis Visit		Aflibercept (N=66)	Laser (N=35)	Total (N=101)
WEEK 1	Number of eyes	109 (100%)	61 (100%)	170 (100%)
	Number of eyes with >= 2 step decrease	64 (58.7%)	45 (73.8%)	109 (64.1%)
	Number of eyes with >= 2 step increase	2 (1.8%)	1 (1.6%)	3 (1.8%)
WEEK 2	Number of eyes	7 (100%)	4 (100%)	11 (100%)
	Number of eyes with >= 2 step decrease	5 (71.4%)	4 (100.0%)	9 (81.8%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 3	Number of eyes	2 (100%)	2 (100%)	4 (100%)
	Number of eyes with >= 2 step decrease	1 (50.0%)	0	1 (25.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 4	Number of eyes	104 (100%)	61 (100%)	165 (100%)
	Number of eyes with >= 2 step decrease	90 (86.5%)	54 (88.5%)	144 (87.3%)
	Number of eyes with >= 2 step increase	3 (2.9%)	0	3 (1.8%)
WEEK 6	Number of eyes	5 (100%)	10 (100%)	15 (100%)
	Number of eyes with >= 2 step decrease	1 (20.0%)	6 (60.0%)	7 (46.7%)
	Number of eyes with >= 2 step increase	0	1 (10.0%)	1 (6.7%)
WEEK 8	Number of eyes	4 (100%)	4 (100%)	8 (100%)
	Number of eyes with >= 2 step decrease	3 (75.0%)	3 (75.0%)	6 (75.0%)
	Number of eyes with >= 2 step increase	0	1 (25.0%)	1 (12.5%)
WEEK 10	Number of eyes	3 (100%)	6 (100%)	9 (100%)
	Number of eyes with >= 2 step decrease	3 (100.0%)	6 (100.0%)	9 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 12	Number of eyes	97 (100%)	50 (100%)	147 (100%)
	Number of eyes with >= 2 step decrease	91 (93.8%)	46 (92.0%)	137 (93.2%)
	Number of eyes with >= 2 step increase	1 (1.0%)	1 (2.0%)	2 (1.4%)
WEEK 16	Number of eyes	13 (100%)	2 (100%)	15 (100%)
	Number of eyes with >= 2 step decrease	13 (100.0%)	2 (100.0%)	15 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 20	Number of eyes	7 (100%)	2 (100%)	9 (100%)
	Number of eyes with >= 2 step decrease	7 (100.0%)	2 (100.0%)	9 (100.0%)
	Number of eyes with >= 2 step increase	0	0	0
WEEK 24	Number of eyes	88 (100%)	58 (100%)	146 (100%)
	Number of eyes with >= 2 step decrease	86 (97.7%)	56 (96.6%)	142 (97.3%)
	Number of eyes with >= 2 step increase	2 (2.3%)	1 (1.7%)	3 (2.1%)

Two step decrease/increase refers to a change of at least 2 points compared to baseline in ROP activity scale.

Table 5.5.28 - Number of eyes with change in ROP activity scale from central reading center (PPS)

Number of aflibercept administrations from baseline to week 24

The majority of subjects treated with aflibercept received a single injection per eye (78.7%) and were treated bilaterally (94.7%). No subject received more than 2 injections per eye (*Table 5.5.29*). Of the 75 subjects with evaluable eyes, 55 (73.3%) subjects received 2 injections, 10 (13.3%) subjects received 4 injections, 6 (8.0%) subjects received 3 injections, and 4 (5.3%) subjects received 1 injection.

	Aflibercept (N=75)	Laser (N=38)	Total (N=113)
Number of evaluable eyes for primary analysis	146 (100.0%)	72 (100.0%)	218 (100.0%)
Number of aflibercept administrations per evaluable eye for primary analysis			
0	0	64 (88.9%)	64 (29.4%)
1	120 (82.2%)	7 (9.7%)	127 (58.3%)
2	26 (17.8%)	1 (1.4%)	27 (12.4%)
Number of subjects with evaluable eyes for primary analysis	75 (100.0%)	38 (100.0%)	113 (100.0%)
Number of aflibercept administrations per subject with evaluable eyes for primary analysis			
0	0	34 (89.5%)	34 (30.1%)
1	4 (5.3%)	0	4 (3.5%)
2	55 (73.3%)	3 (7.9%)	58 (51.3%)
3	6 (8.0%)	1 (2.6%)	7 (6.2%)
4	10 (13.3%)	0	10 (8.8%)

Aflibercept administrations for the laser arm refer to rescue treatment.

Table 5.5.29 - Number of aflibercept administrations from baseline to week 24 (FAS)

	Aflibercept (N=68)	Laser (N=35)	Total (N=103)
Number of evaluable eyes for primary analysis	132 (100.0%)	68 (100.0%)	200 (100.0%)
Number of aflibercept administrations per evaluable eye for primary analysis			
0	0	60 (88.2%)	60 (30.0%)
1	110 (83.3%)	7 (10.3%)	117 (58.5%)
2	22 (16.7%)	1 (1.5%)	23 (11.5%)
Number of subjects with evaluable eyes for primary analysis	68 (100.0%)	35 (100.0%)	103 (100.0%)
Number of aflibercept administrations per subject with evaluable eyes for primary analysis			
0	0	31 (88.6%)	31 (30.1%)
1	4 (5.9%)	0	4 (3.9%)
2	50 (73.5%)	3 (8.6%)	53 (51.5%)
3	6 (8.8%)	1 (2.9%)	7 (6.8%)
4	8 (11.8%)	0	8 (7.8%)

Aflibercept administrations for the laser arm refer to rescue treatment.

Table 5.5.30 - Number of aflibercept administrations from baseline to week 24 (mFAS)

	Aflibercept (N=66)	Laser (N=35)	Total (N=101)
Number of evaluable eyes for primary analysis	128 (100.0%)	68 (100.0%)	196 (100.0%)
Number of aflibercept administrations per evaluable eye for primary analysis			
0	0	60 (88.2%)	60 (30.6%)
1	106 (82.8%)	7 (10.3%)	113 (57.7%)
2	22 (17.2%)	1 (1.5%)	23 (11.7%)
Number of subjects with evaluable eyes for primary analysis	66 (100.0%)	35 (100.0%)	101 (100.0%)
Number of aflibercept administrations per subject with evaluable eyes for primary analysis			
0	0	31 (88.6%)	31 (30.7%)
1	4 (6.1%)	0	4 (4.0%)
2	48 (72.7%)	3 (8.6%)	51 (50.5%)
3	6 (9.1%)	1 (2.9%)	7 (6.9%)
4	8 (12.1%)	0	8 (7.9%)

Aflibercept administrations for the laser arm refer to rescue treatment.

Table 5.5.31 - Number of aflibercept administrations from baseline to week 24 (PPS)

Of the 146 evaluable eyes in the aflibercept arm, 120 (82.2%) eyes received 1 injection and 26 (17.8%) eyes received 2 injections. The majority of eyes (95.2%) did not require laser rescue treatment. (*Table 5.5.32*).

	Aflibercept (N=75)	Laser (N=38)	Total (N=113)
Number of evaluable eyes for primary analysis	146 (100.0%)	72 (100.0%)	218 (100.0%)
Number of Laser treatments per evaluable eye for primary analysis			
0	139 (95.2%)	0	139 (63.8%)
1	7 (4.8%)	65 (90.3%)	72 (33.0%)
2	0	5 (6.9%)	5 (2.3%)
3	0	2 (2.8%)	2 (0.9%)
Number subjects with evaluable eyes for primary analysis	75 (100.0%)	38 (100.0%)	113 (100.0%)
Number of Laser treatments per subject with evaluable eyes for primary analysis			
0	70 (93.3%)	0	70 (61.9%)
1	3 (4.0%)	4 (10.5%)	7 (6.2%)
2	2 (2.7%)	30 (78.9%)	32 (28.3%)
3	0	1 (2.6%)	1 (0.9%)
4	0	2 (5.3%)	2 (1.8%)
6	0	1 (2.6%)	1 (0.9%)

Laser treatments for the aflibercept arm refer to rescue treatment.

Table 5.5.32 - Number of laser treatments from baseline to week 24 (full analysis set)

	Aflibercept (N=68)	Laser (N=35)	Total (N=103)
Number of evaluable eyes for primary analysis	132 (100.0%)	68 (100.0%)	200 (100.0%)
Number of Laser treatments per evaluable eye for primary analysis			
0	128 (97.0%)	0	128 (64.0%)
1	4 (3.0%)	61 (89.7%)	65 (32.5%)
2	0	5 (7.4%)	5 (2.5%)
3	0	2 (2.9%)	2 (1.0%)
Number subjects with evaluable eyes for primary analysis	68 (100.0%)	35 (100.0%)	103 (100.0%)
Number of Laser treatments per subject with evaluable eyes for primary analysis			
0	65 (95.6%)	0	65 (63.1%)
1	2 (2.9%)	2 (5.7%)	4 (3.9%)
2	1 (1.5%)	29 (82.9%)	30 (29.1%)
3	0	1 (2.9%)	1 (1.0%)
4	0	2 (5.7%)	2 (1.9%)
6	0	1 (2.9%)	1 (1.0%)

Laser treatments for the aflibercept arm refer to rescue treatment.

Table 5.5.33 - Number of laser treatments from baseline to week 24 (mFAS)

	Aflibercept (N=66)	Laser (N=35)	Total (N=101)
Number of evaluable eyes for primary analysis	128 (100.0%)	68 (100.0%)	196 (100.0%)
Number of Laser treatments per evaluable eye for primary analysis			
0	124 (96.9%)	0	124 (63.3%)
1	4 (3.1%)	61 (89.7%)	65 (33.2%)
2	0	5 (7.4%)	5 (2.6%)
3	0	2 (2.9%)	2 (1.0%)
Number subjects with evaluable eyes for primary analysis	66 (100.0%)	35 (100.0%)	101 (100.0%)
Number of Laser treatments per subject with evaluable eyes for primary analysis			
0	63 (95.5%)	0	63 (62.4%)
1	2 (3.0%)	2 (5.7%)	4 (4.0%)
2	1 (1.5%)	29 (82.9%)	30 (29.7%)
3	0	1 (2.9%)	1 (1.0%)
4	0	2 (5.7%)	2 (2.0%)
6	0	1 (2.9%)	1 (1.0%)

Laser treatments for the aflibercept arm refer to rescue treatment.

Table 5.5.34 - Number of laser treatments from baseline to week 24 (PPS)

Four subjects (8 eyes) in the laser arm received rescue treatment with aflibercept: 3 (7.9%) subjects received 2 injections and 1 (2.6%) subject received 3 injections. No eye received more than 2 injections.

Number of laser treatments from baseline to week 24

If multiple sessions of laser treatment were necessary within 1 week from baseline, they were counted as a single treatment.

Of the 146 evaluable eyes in the aflibercept arm, 139 (95.2%) eyes did not receive any rescue treatment with laser, and 7 (4.8%) eyes received 1 laser treatment (*Table 5.5.35*). Of the 5 subjects with evaluable eyes who received rescue treatment, 3 (4.0%) subjects received 1 treatment and 2 (2.7%) subjects received 2 treatments.

Of the 72 evaluable eyes in the laser arm, 65 (90.3%) eyes received 1 laser treatment, 5 (6.9%) eyes received 2 treatments, and 2 (2.8%) eyes received 3 treatments. Of the 38 subjects with evaluable eyes, 30 (78.9%) subjects received 2 treatments, 4 (10.5%) subjects received 1 treatment, 2 (5.3%) subjects received 4 treatments, 1 (2.6%) subject received 3 treatments, and 1 (2.6%) subject received 6 treatments.

	Aflibercept (N=75)	Laser (N=38)	Total (N=113)
Number of evaluable eyes for primary analysis	146 (100.0%)	72 (100.0%)	218 (100.0%)
Number of Laser treatments per evaluable eye for primary analysis			
0	139 (95.2%)	0	139 (63.8%)
1	7 (4.8%)	65 (90.3%)	72 (33.0%)
2	0	5 (6.9%)	5 (2.3%)
3	0	2 (2.8%)	2 (0.9%)
Number subjects with evaluable eyes for primary analysis	75 (100.0%)	38 (100.0%)	113 (100.0%)
Number of Laser treatments per subject with evaluable eyes for primary analysis			
0	70 (93.3%)	0	70 (61.9%)
1	3 (4.0%)	4 (10.5%)	7 (6.2%)
2	2 (2.7%)	30 (78.9%)	32
3	0	1 (2.6%)	1
4	0	2 (5.3%)	2
6	0	1 (2.6%)	1 (0.9%)

Laser treatments for the aflibercept arm refer to rescue treatment.

Table 5.5.35 - Number of laser treatments from baseline to week 24 (FAS)

	Aflibercept (N=68)	Laser (N=35)	Total (N=103)
Number of evaluable eyes for primary analysis	132 (100.0%)	68 (100.0%)	200 (100.0%)
Number of Laser treatments per evaluable eye for primary analysis			
0	128 (97.0%)	0	128 (64.0%)
1	4 (3.0%)	61 (89.7%)	65 (32.5%)
2	0	5 (7.4%)	5 (2.5%)
3	0	2 (2.9%)	2 (1.0%)
Number subjects with evaluable eyes for primary analysis	68 (100.0%)	35 (100.0%)	103 (100.0%)
Number of Laser treatments per subject with evaluable eyes for primary analysis			
0	65 (95.6%)	0	65 (63.1%)
1	2 (2.9%)	2 (5.7%)	4 (3.9%)
2	1 (1.5%)	29 (82.9%)	30 (29.1%)
3	0	1 (2.9%)	1 (1.0%)
4	0	2 (5.7%)	2 (1.9%)
6	0	1 (2.9%)	1 (1.0%)

Laser treatments for the aflibercept arm refer to rescue treatment.

Table 5.5.36 - Number of laser treatments from baseline to week 24 (mFAS)

	Aflibercept (N=66)	Laser (N=35)	Total (N=101)
Number of evaluable eyes for primary analysis	128 (100.0%)	68 (100.0%)	196 (100.0%)
Number of Laser treatments per evaluable eye for primary analysis			
0	124 (96.9%)	0	124 (63.3%)
1	4 (3.1%)	61 (89.7%)	65 (33.2%)
2	0	5 (7.4%)	5 (2.6%)
3	0	2 (2.9%)	2 (1.0%)
Number subjects with evaluable eyes for primary analysis	66 (100.0%)	35 (100.0%)	101 (100.0%)
Number of Laser treatments per subject with evaluable eyes for primary analysis			
0	63 (95.5%)	0	63 (62.4%)
1	2 (3.0%)	2 (5.7%)	4 (4.0%)
2	1 (1.5%)	29 (82.9%)	30 (29.7%)
3	0	1 (2.9%)	1 (1.0%)
4	0	2 (5.7%)	2 (2.0%)
6	0	1 (2.9%)	1 (1.0%)

Laser treatments for the aflibercept arm refer to rescue treatment.

Table 5.5.37 - Number of laser treatments from baseline to week 24 (PPS)

The requirement for intervention with a second treatment modality from baseline to week 24 was slightly higher in laser arm (9.6% vs 7.2% in aflibercept arm).

Regarding the secondary endpoints results, concerns on efficacy are further strengthened by a higher estimated probability for recurrence of ROP from Baseline to Week 24 in the Aflibercept group (16.1%; 90% Credible Interval [10.2, 23.7]) compared to (6.8%; 90% Credible Interval [2.5, 13.1]).

From baseline to week 24, Aflibercept was administered in the 146 evaluable eyes study and the majority received 1 injection (120 eyes - 82.2%). No subject received more than 2 injections per eye. The majority of eyes (95.2%) did not require laser rescue treatment. However, 4 subjects (8 eyes) in the laser arm received rescue treatment with aflibercept (no eye received more than 2 injections).

Moreover, multiple supplementary laser treatments were allowed for both eyes until 3 days after the Day 8 assessment and such treatments were considered part of the complete laser treatment. On the 72 evaluable eyes in the laser arm, the majority received 1 laser treatment (65 eyes - 90.3%) and 7 (4.8%) eyes from aflibercept arm received 1 laser treatment (rescue treatment).

Extension Study 20275

No study treatment is administered in Study 20275. Any study treatment for ROP was administered in the completed Study 20090. Treatment for ROP in Study 20275 was indicated per investigator according to local standards of care.

Results on structural abnormalities from a pre-specified interim analysis (as of 01 MAR 2021) are primarily presented for the 60 subjects with data available at 1 year of chronological age (39 in the aflibercept and 21 laser arms).

In addition, relevant further information on ocular efficacy from a total of 89 subjects with data available beyond the end of Study 20090 was taken into consideration. These included data related to ROP requiring treatment during the follow-up study, visual function, refraction, ocular extrinsic motility, strabismus, cataract and myopia, and complete vascularization. Furthermore, data from the full analysis set of Study 20090 (75 subjects in the aflibercept and 38 subjects in the laser arm) are presented to provide relevant efficacy outcomes of all subjects who received treatment for ROP in Study 20090 irrespective of whether they were enrolled in Study 20275.

Unfavorable ocular structural outcomes/ocular structural abnormalities

As in Study 20090, unfavorable ocular structural outcomes/ocular structural abnormalities in Study 20275 included retinal detachment, macular dragging, macular fold, or retrolental opacity as assessed by the investigator.

In the group of subjects with available 1-year of chronological age data, none of the 39 (100%) subjects (75 eyes) in the aflibercept arm had any new unfavorable structural outcomes. Of the 21 (100%) subjects (40 eyes) in the laser arm, 1 (4.8%) subject experienced an unfavourable structural outcome, which was retinal detachment in 1 (2.5%) eye (*Table 5.5.38*). Results were the same for the time up until the visit at 1 year of chronological age.

		Aflibercept (N=39)	Laser (N=21)
At age 1 year visit	Number of subjects	39 (100.0%)	21 (100.0%)
	Not done	0 (0.0%)	0 (0.0%)
	None	39 (100.0%)	20 (95.2%)
	Retinal detachment	0 (0.0%)	1 (4.8%)
	Macular dragging	0 (0.0%)	0 (0.0%)
	Macular Fold	0 (0.0%)	0 (0.0%)
	Retrolental opacity	0 (0.0%)	0 (0.0%)
	Any unfavorable structural outcome	0 (0.0%)	1 (4.8%)
	Number of eyes	75 (100.0%)	40 (100.0%)
	Not done	0 (0.0%)	0 (0.0%)
	None	75 (100.0%)	39 (97.5%)
	Retinal detachment	0 (0.0%)	1 (2.5%)
	Macular dragging	0 (0.0%)	0 (0.0%)
	Macular Fold	0 (0.0%)	0 (0.0%)
	Retrolental opacity	0 (0.0%)	0 (0.0%)
	Any unfavorable structural outcome	0 (0.0%)	1 (2.5%)
At any time until age 1 year	Number of subjects	39 (100.0%)	21 (100.0%)
	None	39 (100.0%)	20 (95.2%)
	Retinal detachment	0 (0.0%)	1 (4.8%)
	Macular dragging	0 (0.0%)	0 (0.0%)
	Macular Fold	0 (0.0%)	0 (0.0%)
	Retrolental opacity	0 (0.0%)	0 (0.0%)
	Any unfavorable structural outcome	0 (0.0%)	1 (4.8%)
	Number of eyes	75 (100.0%)	40 (100.0%)
	None	75 (100.0%)	39 (97.5%)
	Retinal detachment	0 (0.0%)	1 (2.5%)
	Macular dragging	0 (0.0%)	0 (0.0%)
	Macular Fold	0 (0.0%)	0 (0.0%)
	Retrolental opacity	0 (0.0%)	0 (0.0%)
	Any unfavorable structural outcome	0 (0.0%)	1 (2.5%)

Study intervention as in previous study 20090
At any time until 1 year of chronological age includes unfavorable structural outcome from treatment start in study 20090 until the 1 year of chronological age visit in study 20275.
A subject can report multiple events of unfavorable structural outcomes per eye.

Table 5.5.38 - Number of subjects with unfavorable structural outcomes at age 1 year based on investigator assessment (all subjects who completed visit at 1 year of chronological age)

The subject in the laser arm, Subject 510090001, who experienced retinal detachment in Study 20090, was treated bilaterally with laser at baseline of Study 20090 for bilateral ROP Zone I stage 3 plus, re-treated with laser twice on each eye (after 8 and 10 days from the previous laser treatment) and rescued with aflibercept once on each eye (3 days after last laser re-treatment). Unilateral (right) retinal detachment (ROP stage 4A) was reported at the week 4 visit and progressed to ROP stage 4B at the week 10 visit of Study 20090 (as reported in the subject's narrative, in *Module 5.3.5.1 [ROP], Report PH-41617, Section 15*).

Absence of active ROP and unfavorable ocular structural outcomes/ocular structural abnormalities

Absence of active ROP was defined as the absence of "ROP requiring treatment (according to the inclusion criteria of Study 20090)".

The number of subjects with absence of ROP and unfavorable structural outcomes based on investigator assessment at the visit at 1 year of chronological age is summarized in *Table 5.5.39*.

Of the 39 subjects in the aflibercept arm who reached the 1 year of age visit, 36 (92.3%) subjects were treated bilaterally in Study 20090 and 3 (7.7%) subjects were treated unilaterally. Of the 36 bilaterally-treated subjects, 35 (97.2%) subjects showed response in both eyes and 1 (2.8%) subject showed response in 1 eye after bilateral treatment received in Study 20090; 3 subjects showed response in their single eye.

Of the 21 subjects in the laser arm who reached the 1 year of age visit, 19 (90.5%) subjects were treated bilaterally in Study 20090 and 2 (9.5%) subjects were treated unilaterally. Of the 19 bilaterally-treated subjects in the laser arm, 17 (89.5%) subjects showed response in both eyes and no subjects showed response in 1 eye after bilateral treatment in Study 20090; both unilaterally-treated subjects showed response in their single eye.

ROP treatment after entry into the follow-up Study 20275 was not indicated by the investigators for any subjects with data available at the visit at 1 year of chronological age.

	Aflibercept (N=39)	Laser (N=21)
Number of subjects [a]	39 (100.0)	21 (100.0)
Number of subjects both eyes eligible	36 (92.3)	19 (90.5)
Number of subjects with response both eyes	35 (89.7)	17 (81.0)
Number of subjects with response one eye	1 (2.6)	0 (0.0)
Number of subjects with one eye eligible	3 (7.7)	2 (9.5)
Number of subjects with response one eye	3 (7.7)	2 (9.5)
Number of eyes	75 (100.0)	40 (100.0)
Eyes meeting response criterion	74 (98.7)	36 (90.0)
Active ROP	0 (0.0)	1 (2.5)
Unfavorable structural outcome	0 (0.0)	1 (2.5)
Rescue treatment received per protocol during 20090	1 (1.3)	4 (10.0)
Need for ROP treatment during Study 20275	0 (0.0)	0 (0.0)

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 1 year of chronological age based on investigator assessment for both eyes. Subjects receiving rescue treatment were considered non-responders with respect to the primary endpoint.
Active ROP is defined as ROP requiring treatment (according to the inclusion criteria of Study 20090).
Unfavorable structural outcome is defined as retinal detachment, macular dragging, macular fold, or retrolental opacity.
An eye is considered eligible, if it met the inclusion criteria and did not meet the exclusion criteria of Study 20090 and treatment started prior to visit 9 (week 8).
[a] All subjects of the respective analysis set.
Study intervention groups reflecting randomized intervention groups in the completed Study 20090.

Table 5.5.39 - Number of subjects with absence of active ROP and unfavourable structural outcomes at 1 year of chronological age visit based on investigator assessment (all subjects who completed visit at 1 year of chronological age)

Table 5.5.40 displays the number of subjects with absence of active ROP and unfavorable structural outcomes until 1 year of chronological age based on the investigator assessment based on all available data for all subjects in the FAS of Study 20090, i.e., for all subjects that had been treated at baseline in Study 20090. Of the 75 subjects in the aflibercept arm in the FAS of Study 20090, 71 (94.7%) subjects were bilaterally-treated in Study 20090 and 4 (5.3%) subjects were unilaterally-treated in Study 20090. Of the 71 bilaterally-treated subjects, 59 (83.1%) showed response in both eyes and 4 (5.6%) subjects showed response in 1 eye after bilateral treatment received in Study 20090; all 4 unilaterally-treated subjects showed response in their single eye.

	Aflibercept (N=75)	Laser (N=38)
Number of subjects (a)	75 (100.0%)	38 (100.0%)
Number of subjects both eyes eligible	71 (94.7%)	34 (89.5%)
Number of subjects with response both eyes	59 (78.7%)	28 (73.7%)
Number of subjects with response one eye	4 (5.3%)	1 (2.6%)
Number of subjects with one eye eligible	4 (5.3%)	4 (10.5%)
Number of subjects with response one eye	4 (5.3%)	4 (10.5%)
Number of eyes	146 (100.0%)	72 (100.0%)
Eyes meeting response criterion	126 (86.3%)	61 (84.7%)
Active ROP	10 (6.8%)	2 (2.8%)
Unfavorable structural outcome	10 (6.8%)	4 (5.6%)
Rescue treatment received per protocol during 20090	7 (4.8%)	8 (11.1%)
Need for ROP treatment during study 20275	6 (4.1%)	0 (0.0%)

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at age 1 year based on investigator assessment for both eyes.
Active ROP is defined as ROP requiring treatment (according to the inclusion criteria of study 20090).
Unfavorable structural outcome is defined as retinal detachment, macular dragging, macular fold, or retrolental opacity.
(a) All subjects of the respective analysis set.
An eye is considered eligible, if it meets the inclusion criteria and does not meet the exclusion criteria of study 20090 and treatment started prior to Visit 9 (Week 8).
Study intervention as in previous study 20090

Table 5.5.40 - Number of subjects with absence of active ROP and unfavorable structural outcomes at 1 year of chronological age visit based on investigator assessment (full analysis set of 20090)

Of the 38 subjects in the laser arm in the FAS of Study 20090, 34 (89.5%) subjects were bilaterally-treated and 4 (10.5%) subjects were unilaterally-treated in Study 20090. Of the 34 bilaterally-treated subjects, 28 (82.4%) subjects showed response in both eyes and 1 subject (2.9%) showed response in 1 eye after bilateral treatment in Study 20090; all 4 unilaterallytreated subjects showed response in their single eye.

For 3 subjects (6 [4.1%] of 146 eyes) treated with aflibercept at baseline in Study 20090, ROP treatment Study 20275 was indicated by the investigator (*Table 5.5.40* and *5.5.41*). All 3 subjects were already non-responders for the primary endpoint in Study 20090.

	Aflibercept (N=60)	Laser (N=29)
Number of subjects	60 (100.0%)	29 (100.0%)
Number of subjects with re-treatment during 20090	10 (16.7%)	2 (6.9%)
Number of subjects with rescue treatment during 20090	4 (6.7%)	3 (10.3%)
Number of subjects with re- or rescue treatment during 20090	13 (21.7%)	4 (13.8%)
Number of subjects requiring treatment for ROP during 20275	3 (5.0%)	0 (0.0%)
Number of subjects with re- or rescue treatment during 20090 or requiring treatment for ROP in 20275	14 (23.3%)	4 (13.8%)

Only eyes treated up until Visit 9 / Week 8 of study 20090 are included in the analysis.
Rescue treatment for aflibercept was laser, rescue treatment for laser was aflibercept.
Study intervention as in previous study 20090

Table 5.5.41 - Number of subjects requiring further treatment until 1 year of age (all subjects entering extension)

Subjects requiring treatment for ROP during extension Study 20275

None of the subjects in Study 20275 who completed the visit at 1 year of chronological age visit in the aflibercept and laser arms required treatment for ROP during Study 20275.

Among the 89 subjects who entered the extension Study 20275, 3 (5.0%) of the 60 subjects in the aflibercept arm, and no subjects in the laser arm required treatment for ROP after transition to Study 20275 and before the visit at 1 year of chronological age. Each of these 3 subjects was treated upon investigators' discretion in Study 20275 for ROP outcomes already present in the Study 20090, i.e. all 3 subjects were non-responders and represented treatment failures in Study 20090. They are summarized

as follows: 1 subject received bilateral anti-VEGF treatment (ranibizumab) and unilateral laser at screening/baseline in Study 20275; 1 subject required treatment at an unscheduled visit after screening/baseline (vitrectomy of the left eye); the other subject required bilateral laser treatment at an unscheduled visit after visit 1b (i.e. after visit at 40 weeks of chronological age) and received bilateral laser treatment.

Details of these subjects can be found in *Module 5.3.5.1 (ROP), Report PH-41618, Section 9.2.1.3.*

Subjects requiring ophthalmological treatment

Ophthalmological treatment was defined as either reported co-medication for an eye or as surgical procedure of an eye that is beyond study treatment or study procedures.

At 1 year of chronological age, 3 (7.7%) of the 39 subjects in the aflibercept arm and 1 (4.8%) of 21 subjects in the laser arm had ophthalmological treatment during the extension study (Table *5.5.42).*

	Aflibercept (N=39)	Laser (N=21)
Number of subjects	39 (100.0%)	21 (100.0%)
Number of subjects with opthalmologic treatment during 20275	3 (7.7%)	1 (4.8%)

Ophthalmologic treatment is defined as either reported comedication for an eye or as surgical procedures of an eye which is beyond study treatment or procedures.
Study intervention as in previous study 20090

Table 5.5.42 - Number of subjects with ophthalmologic treatment during the extension until 1 year of age (all subjects who completed visit at 1 year of chronological age)

Of all 89 subjects who entered the ongoing extension Study 20275, 6 (10.0%) of 60 subjects in the aflibercept arm and 1 (3.4%) of 29 subjects in the laser arm had ophthalmological treatment during the extension study (*Table 5.5.43*).

	Aflibercept (N=60)	Laser (N=29)
Number of subjects	60 (100.0%)	29 (100.0%)
Number of subjects with opthalmologic treatment during 20275	6 (10.0%)	1 (3.4%)

Ophthalmologic treatment is defined as either reported comedication for an eye or as surgical procedures of an eye which is beyond study treatment or procedures.
Study intervention as in previous study 20090

Table 5.5.43 - Number of subjects with ophthalmologic treatment during the extension until 1 year of age (all subjects entering extension)

Evaluation of visual function and refraction and structural outcomes

At the 1 year of chronological age time point, all 75 eyes in the aflibercept arm were reported with normal retina, attached to periphery and 39 (97.5%) out of 40 eyes in the laser arm were reported with normal retina, attached to periphery; similar proportions were seen at week 24 (end of Study 20090*)(Table 5.5.44*). The percentages are based on the number of eyes with reported data.

Time point			Aflibercept (N=39)	Laser (N=21)	Total (N=60)
Week 24	Normal retina, attached to periphery?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	0	1 (2.6%)	1 (0.9%)
		Yes	73 (100.0%)	38 (97.4%)	111 (99.1%)
	Normal central retina, peripheral retina scarred?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	70 (95.9%)	3 (7.7%)	73 (65.2%)
		Yes	3 (4.1%)	36 (92.3%)	39 (34.8%)
	Normal central retina, peripheral retina not vascularized?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	35 (47.9%)	17 (43.6%)	52 (46.4%)
		Yes	36 (49.3%)	22 (56.4%)	58 (51.8%)
		Unknown	2 (2.7%)	0	2 (1.8%)
	Fibrovascular organization?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	69 (94.5%)	38 (97.4%)	107 (95.5%)
		Yes	4 (5.5%)	1 (2.6%)	5 (4.5%)
		1 Quadrant affected	4 (5.5%)	0	4 (3.6%)
		2 Quadrants affected	0	1 (2.6%)	1 (0.9%)
		3 Quadrants affected	0	0	0
		4 Quadrants affected	0	0	0
		Not assessable	0	0	0
	Dense vitreous or preretinal hemorrhage?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	73 (100.0%)	36 (92.3%)	109 (97.3%)
		Yes	0	3 (7.7%)	3 (2.7%)
1 Year of age	Normal retina, attached to periphery?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	0	1 (2.5%)	1 (0.9%)
		Yes	75 (100.0%)	39 (97.5%)	114 (99.1%)
	Normal central retina, peripheral retina scarred?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	70 (93.3%)	1 (2.5%)	71 (61.7%)
		Yes	5 (6.7%)	39 (97.5%)	44 (38.3%)
	Normal central retina, peripheral retina not vascularized?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	52 (69.3%)	20 (50.0%)	72 (62.6%)
		Yes	23 (30.7%)	20 (50.0%)	43 (37.4%)
	Fibrovascular organization?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	72 (96.0%)	39 (97.5%)	111 (96.5%)
		Yes	3 (4.0%)	1 (2.5%)	4 (3.5%)
		1 Quadrant affected	3 (4.0%)	1 (2.5%)	4 (3.5%)
		2 Quadrants affected	0	0	0
		3 Quadrants affected	0	0	0
		4 Quadrants affected	0	0	0
		Not assessable	0	0	0
	Dense vitreous or preretinal hemorrhage?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	75 (100.0%)	40 (100.0%)	115 (100.0%)
		Yes	0	0	0

n refers to number of eyes, not subjects.
Study intervention as in previous study 20090

Table 5.5.44 - Visual function per eye at Week 24 (end of study 20090) and at 1 year of chronological age (study 20275): Abnormalities of the retina (all subjects who completed visit at 1 year of chronological age)

At the 1 year of chronological age time point, no eyes in either arm had optic nerve hypoplasia or optic nerve atrophy; these results were identical to week 24 (end of Study 20090)(*Table 5.5.45*). The number of eyes with large excavation of optic disc did not change from the end of Study 20090 to 1 year of chronological age for both aflibercept (5 [6.8%]) and laser (0 [0.0%]) arms. At the end of Study 20090, 1 (2.6%) eye in the laser arm had posterior subcapsular cataract of 1+ density at week 24 (for which surgery was applied), but no cataracts were reported at 1 year of chronological age; no cataracts were reported in the aflibercept arm at either time point.

Time point			Aflibercept (N=39)	Laser (N=21)	Total (N=60)
Week 24	Optic nerve hypoplasia?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	73 (100.0%)	39 (100.0%)	112 (100.0%)
		Yes	0	0	0
	Optic nerve atrophy?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	73 (100.0%)	37 (94.9%)	110 (98.2%)
		Yes	0	0	0
		Unknown	0	2 (5.1%)	2 (1.8%)
	Large excavation of optic disc?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	68 (93.2%)	39 (100.0%)	107 (95.5%)
		Yes	5 (6.8%)	0	5 (4.5%)
	Normal clear lens?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	0	1 (2.6%)	1 (0.9%)
		Yes	73 (100.0%)	38 (97.4%)	111 (99.1%)
	Cataract?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	73 (100.0%)	38 (97.4%)	111 (99.1%)
		Yes	0	1 (2.6%)	1 (0.9%)
	Cataract yes, localization?	Anterior polar	0	0	0
		Cortical	0	0	0
		Nuclear	0	0	0
		Posterior sub-capsular	0	1 (2.6%)	1 (0.9%)
		Total	0	0	0
	Cataract yes, density?	1+	0	1 (2.6%)	1 (0.9%)
		2+	0	0	0
		3+	0	0	0
		4+	0	0	0
1 Year of age	Optic nerve hypoplasia?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	75 (100.0%)	40 (100.0%)	115 (100.0%)
		Yes	0	0	0
	Optic nerve atrophy?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	75 (100.0%)	40 (100.0%)	115 (100.0%)
		Yes	0	0	0
	Large excavation of optic disc?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	70 (93.3%)	40 (100.0%)	110 (95.7%)
		Yes	5 (6.7%)	0	5 (4.3%)
	Normal clear lens?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	1 (1.3%)	1 (2.5%)	2 (1.7%)
		Yes	74 (98.7%)	39 (97.5%)	113 (98.3%)
	Cataract?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	74 (98.7%)	40 (100.0%)	114 (99.1%)
		Yes	0	0	0
		Unknown	1 (1.3%)	0	1 (0.9%)
	Cataract yes, localization?	Anterior polar	0	0	0
		Cortical	0	0	0
		Nuclear	0	0	0
		Posterior sub-capsular	0	0	0
		Total	0	0	0
	Cataract yes, density?	1+	0	0	0
		2+	0	0	0
		3+	0	0	0
		4+	0	0	0

n refers to number of eyes, not subjects.
Study intervention as in previous study 20090

Table 5.5.45 - Visual function per eye at Week 24 (end of study 20090) and at 1 year of chronological age (study 20275): Abnormalities of the optic nerve (all subjects who completed visit at 1 year of chronological age)

At the week 24 (end of Study 20090) time point, all eyes in the aflibercept and laser arms had light reaction; these results were identical to 1 year of chronological age time point (*Table 5.5.46*). All eyes in the aflibercept arm had central fixation and the ability to fix and follow a 5-cm toy at week 24 of Study 20090 and at the 1 year of chronological age time point. In the laser arm, 2 (5.1%) eyes were reported with no central fixation and no ability to fix and follow a 5-cm toy at week 24; at 1 year of age, 1 (2.5%) eye was reported with these results. There were no reported abnormal visual evoked potentials at week 24 in either arm. At the 1 year of chronological age time point in Study 20275, no eyes in the aflibercept arm were reported with abnormal visual evoked potentials and 2 eyes in laser arm was reported with abnormal visual evoked potentials. No eyes were reported with ocular palsy at the end of Study 20090; at the 1 year of chronological age time point in Study 20275, 1 (1.3%) eye in the aflibercept arm had ocular palsy of the cranial nerve VI (abducens nerve).

Time point			Aflibercept (N=39)	Laser (N=21)	Total (N=60)
Week 24	Light reaction?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	0	0	0
		Yes	73 (100.0%)	39 (100.0%)	112 (100.0%)
	Fixation Central?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	0	2 (5.1%)	2 (1.8%)
		Yes	73 (100.0%)	35 (89.7%)	108 (96.4%)
		Unknown	0	2 (5.1%)	2 (1.8%)
	Is the patient able to fix and follow a 5-cm toy?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	0	2 (5.1%)	2 (1.8%)
		Yes	73 (100.0%)	36 (92.3%)	109 (97.3%)
		Unknown	0	1 (2.6%)	1 (0.9%)
	Visual evoked potentials	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		Normal	5 (6.8%)	4 (10.3%)	9 (8.0%)
		Abnormal	0	0	0
		Unknown	68 (93.2%)	35 (89.7%)	103 (92.0%)
	Ocular palsy?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	70 (95.9%)	39 (100.0%)	109 (97.3%)
		Yes, nerve III (Oculomotor nerve)	0	0	0
		Yes, nerve IV (Trochlear nerve)	0	0	0
		Yes, nerve VI (Abducens nerve)	0	0	0
		Unknown	3 (4.1%)	0	3 (2.7%)
1 Year of age	Light reaction?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	0	0	0
		Yes	75 (100.0%)	40 (100.0%)	115 (100.0%)
	Fixation Central?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	0	1 (2.5%)	1 (0.9%)
		Yes	75 (100.0%)	39 (97.5%)	114 (99.1%)
	Is the patient able to fix and follow a 5-cm toy?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	0	1 (2.5%)	1 (0.9%)
		Yes	75 (100.0%)	39 (97.5%)	114 (99.1%)
	Visual evoked potentials	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		Normal	4 (5.3%)	10 (25.0%)	14 (12.2%)
		Abnormal	0	2 (5.0%)	2 (1.7%)
		Unknown	71 (94.7%)	28 (70.0%)	99 (86.1%)
	Ocular palsy?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	73 (97.3%)	40 (100.0%)	113 (98.3%)
		Yes, nerve III (Oculomotor nerve)	0	0	0
		Yes, nerve IV (Trochlear nerve)	0	0	0
		Yes, nerve VI (Abducens nerve)	1 (1.3%)	0	1 (0.9%)
		Unknown	1 (1.3%)	0	1 (0.9%)

n refers to number of eyes, not subjects.
Study intervention as in previous study 20090

Table 5.5.46 - Visual function per eye at Week 24 (end of study 20090) and at 1 year of chronological age (study 20275): Fixation (all subjects who completed visit at 1 year of chronological age)

For cycloplegic refraction, the refractive spherical equivalent (SE) was calculated as: sphere + ½ cylinder.

In the aflibercept arm, mean SE (SD) at week 24 (end of Study 20090)2 and at 1 year of chronological age in Study 20275 were +0.80 (2.72) diopters (D) and -0.22 (2.93) D respectively. The SE range were -10.62 D to +6.00 D at week 24 (end of Study 20090) and - 13.00 D to +3.50 D at 1 year of chronological age in Study 20275.

For laser arm, mean SE (SD) at week 24 (end of Study 20090) and at 1 year of chronological age in Study 20275 were +0.35 (3.35) D and -0.56 (2.88) D respectively. The SE range were - 11.00 D to +5.50 D at week 24 (end of Study 20090) and -10.25 D to +4.50 D at 1 year of chronological age in Study 20275 (*Module 5.3.5.1 [ROP], Report PH-41618, post-hoc Table 16.4.1.1/1*).

Mean (SD) axis values were similar at 1 year of chronological age in Study 20275 and at week 24 of Study 20090 in the aflibercept arm (112.89 [67.21] degrees and 100.42 [70.02] degrees, respectively) as well as in the laser arm (87.65 [74.98] and 88.33 [69.62], respectively) (*Table 5.5.47*).

Time point			Aflibercept (N=39)	Laser (N=21)	Total (N=60)
Week 24	Axis (deg)	n	55	33	88
		Nmiss	18	6	24
		Mean (SD)	100.4182 (70.0166)	88.3333 (69.6149)	95.8864 (69.7134)
		Median	90.0000	90.0000	90.0000
		Q1, Q3	23.0000, 177.0000	15.0000, 165.0000	18.0000, 172.5000
		Min, Max	0.000, 180.000	0.000, 180.000	0.000, 180.000
1 Year of age	Axis (deg)	n	61	31	92
		Nmiss	14	9	23
		Mean (SD)	112.8852 (67.2082)	87.6452 (74.9811)	104.3804 (70.5376)
		Median	120.0000	90.0000	104.0000
		Q1, Q3	50.0000, 180.0000	4.0000, 175.0000	30.0000, 179.5000
		Min, Max	0.000, 180.000	0.000, 180.000	0.000, 180.000

n refers to number of eyes, not subjects
Study intervention as in previous study 20090

Table 5.5.47 - Visual function per eye at Week 24 (end of study 20090) and at 1 year of chronological age (study 20275): Cycloplegic Refraction - Axis (all subjects who completed visit at 1 year of chronological age)

The majority of eyes in the aflibercept arm had no manifest strabismus at 1 year of chronological age and at week 24 (end of Study 20090); the proportion was similar at both time points but slightly higher at the 1 year of chronological age time point (72 [96.0%] eyes, as compared to 66 [90.4%] eyes at week 24 of Study 20090). In the laser arm, 33 (84.6%) eyes were without manifest strabismus at the week 24 in Study 20090, as compared to 34 (85.0%) eyes at the 1 year of chronological age time point. No eyes in the aflibercept arm had nystagmus in primary position at either time point; in the laser arm, the majority of eyes had no nystagmus in primary position, though the proportion was slightly higher at the 1 year of chronological age time point (38 [95.0%] eyes, as compared to 35 [89.7%] eyes at week 24 of Study 20090) (*Table 5.5.48*).

Time point			Aflibercept (N=39)	Laser (N=21)	Total (N=60)
Week 24	Manifest strabismus? (a)	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		Esotropia	3 (4.1%)	2 (5.1%)	5 (4.5%)
		Exotropia	2 (2.7%)	4 (10.3%)	6 (5.4%)
		Hypertropia	0	0	0
		Hypotropia	0	0	0
		Cyclotropia	0	0	0
		None	66 (90.4%)	33 (84.6%)	99 (88.4%)
		Unknown	2 (2.7%)	0	2 (1.8%)
	Nystagmus in primary position?	n	73 (100.0%)	39 (100.0%)	112 (100.0%)
		No	73 (100.0%)	35 (89.7%)	108 (96.4%)
		Yes	0	4 (10.3%)	4 (3.6%)
1 Year of age	Manifest strabismus? (a)	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		Esotropia	3 (4.0%)	4 (10.0%)	7 (6.1%)
		Exotropia	0	2 (5.0%)	2 (1.7%)
		Hypertropia	0	2 (5.0%)	2 (1.7%)
		Hypotropia	0	0	0
		Cyclotropia	0	0	0
		None	72 (96.0%)	34 (85.0%)	106 (92.2%)
	Nystagmus in primary position?	n	75 (100.0%)	40 (100.0%)	115 (100.0%)
		No	75 (100.0%)	38 (95.0%)	113 (98.3%)
		Yes	0	2 (5.0%)	2 (1.7%)

(a) All that apply are ticked.
Study intervention as in previous study 20090

Table 5.5.48 - Visual function per eye at Week 24 (end of study 20090) and at 1 year of chronological age (study 20275): Ocular motility (all subjects who completed visit at 1 year of chronological age)

2 Week 24 (end of Study 20090) data obtained from *Module 5.3.5.1 (ROP), Report PH- 41617, post-hoc Table 16.4.1.2/7.*

ROP outcomes according to the Neonatal Consortium ROP activity scale

The ROP Activity Scale values were derived for each eye by investigator assessment as displayed in *Module 5.3.5.1 (ROP), Report PH-41618, Section 7.6.4.5*. ROP Activity Scale values of 0 to 7 are considered as mild, 8 to 12 moderate, and 13 to 22 severe ROP activity.

Considering all subjects who completed visit at 1 year of chronological age, the mean (SD) ROP Activity Scale values by eye were similar between the 2 treatment arms at baseline in Study 20090 (15.00 [2.11] for the aflibercept arm and 14.88 [2.49] for the laser arm. At the screening/baseline visit for the 20275 study, a mean decrease in ROP Activity Scale values from baseline of Study 20090 was observed in both the aflibercept arm (-14.08 [3.04]) and the laser arm (-13.90 [3.71]). These decreases were sustained through the visit at 1 year of chronological age; at this visit, a mean decrease in ROP Activity Scale values from baseline of Study 20090 of -14.67 (2.43) was observed for the aflibercept arm and a mean decrease of -14.35 (3.72) was observed for the laser arm (*Table 5.5.49*).

			Value at visit					Change from baseline of study 20090				
Treatment Group	Study	Visit	n	Mean (SD)	Median	Q1, Q3	Min, Max	n	Mean (SD)	Median	Q1, Q3	Min, Max
Aflibercept (N=39)	20090	BASELINE	75	15.00 (2.11)	14.00	14.00, 16.00	13.0, 19.0					
		WEEK 0, DAY 1	75	14.09 (3.05)	14.00	13.00, 16.00	7.0, 19.0	75	-0.91 (2.00)	0.00	0.00, 0.00	-6.0, 0.0
		WEEK 1	74	9.14 (5.12)	8.00	7.00, 13.00	0.0, 19.0	74	-5.88 (4.53)	-6.00	-7.00, -1.00	-19.0, 0.0
		WEEK 1, DAY 1	2	7.50 (0.71)	7.50	7.00, 8.00	7.0, 8.0	2	-6.50 (0.71)	-6.50	-7.00, -6.00	-7.0, -6.0
		WEEK 2	72	7.10 (5.95)	7.00	1.50, 8.00	0.0, 19.0	72	-7.97 (5.52)	-7.00	-13.00, -6.00	-19.0, 0.0
		WEEK 3	75	5.89 (5.96)	3.00	0.00, 8.00	0.0, 19.0	75	-9.11 (5.53)	-10.00	-14.00, -6.00	-19.0, 0.0
		WEEK 4	73	5.00 (5.56)	3.00	0.00, 7.00	0.0, 19.0	73	-10.03 (5.03)	-11.00	-14.00, -6.00	-19.0, 0.0
		WEEK 4, DAY 1	2	5.50 (3.54)	5.50	3.00, 8.00	3.0, 8.0	2	-11.50 (3.54)	-11.50	-14.00, -9.00	-14.0, -9.0
		WEEK 5	2	5.00 (2.83)	5.00	3.00, 7.00	3.0, 7.0	2	-12.00 (2.83)	-12.00	-14.00, -10.00	-14.0, -10.0
		WEEK 6	73	4.52 (5.82)	3.00	0.00, 7.00	0.0, 19.0	73	-10.51 (5.00)	-12.00	-14.00, -7.00	-19.0, 0.0
		WEEK 6, DAY 1	2	9.50 (13.44)	9.50	0.00, 19.00	0.0, 19.0	2	-9.50 (13.44)	-9.50	-19.00, 0.00	-19.0, 0.0
		WEEK 7	2	3.00 (0.00)	3.00	3.00, 3.00	3.0, 3.0	2	-16.00 (0.00)	-16.00	-16.00, -16.00	-16.0, -16.0
		WEEK 8	71	3.49 (4.81)	2.00	0.00, 7.00	0.0, 19.0	71	-11.59 (4.69)	-13.00	-14.00, -7.00	-18.0, 0.0
		WEEK 10	69	3.07 (4.83)	0.00	0.00, 3.00	0.0, 19.0	69	-11.87 (4.70)	-14.00	-14.00, -10.00	-19.0, 0.0
		WEEK 10, DAY 1	4	4.75 (3.95)	5.50	1.50, 8.00	0.0, 8.0	4	-11.75 (6.75)	-11.00	-17.50, -6.00	-19.0, -6.0
		WEEK 11	4	7.50 (6.35)	7.50	2.00, 13.00	2.0, 13.0	4	-7.50 (5.20)	-7.50	-12.00, -3.00	-12.0, -3.0
		WEEK 11, DAY 1	2	13.00 (0.00)	13.00	13.00, 13.00	13.0, 13.0	2	-3.00 (0.00)	-3.00	-3.00, -3.00	-3.0, -3.0
		WEEK 12	73	2.66 (4.31)	1.00	0.00, 3.00	0.0, 19.0	73	-12.23 (4.19)	-13.00	-14.00, -11.00	-19.0, 0.0
		WEEK 14	4	2.75 (4.19)	1.00	0.50, 5.00	0.0, 9.0	4	-11.25 (4.19)	-13.00	-13.50, -9.00	-14.0, -5.0
		WEEK 14, DAY 1	2	4.50 (6.36)	4.50	0.00, 9.00	0.0, 9.0	2	-9.50 (6.36)	-9.50	-14.00, -5.00	-14.0, -5.0
		WEEK 15	4	7.25 (4.92)	9.00	4.50, 10.00	0.0, 11.0	4	-9.25 (6.65)	-6.50	-13.50, -5.00	-19.0, -5.0
		WEEK 15, DAY 1	2	9.00 (0.00)	9.00	9.00, 9.00	9.0, 9.0	2	-5.00 (0.00)	-5.00	-5.00, -5.00	-5.0, -5.0
		WEEK 16	71	2.14 (3.84)	0.00	0.00, 3.00	0.0, 19.0	71	-12.77 (3.66)	-14.00	-14.00, -11.00	-19.0, 0.0
		WEEK 20	63	1.73 (4.04)	0.00	0.00, 1.00	0.0, 19.0	63	-13.24 (3.88)	-14.00	-14.00, -13.00	-19.0, 0.0
		WEEK 24	73	0.86 (2.62)	0.00	0.00, 0.00	0.0, 11.0	73	-14.19 (3.14)	-14.00	-14.00, -14.00	-19.0, -4.0
	20275	Screening/Baseline	59	0.61 (2.19)	0.00	0.00, 0.00	0.0, 10.0	59	-14.08 (3.04)	-14.00	-14.00, -14.00	-19.0, -4.0
		40 weeks of age	28	0.57 (1.83)	0.00	0.00, 0.00	0.0, 7.0	28	-13.39 (1.99)	-14.00	-14.00, -13.50	-16.0, -7.0
		1 year of age	73	0.22 (1.16)	0.00	0.00, 0.00	0.0, 7.0	73	-14.67 (2.43)	-14.00	-15.00, -14.00	-19.0, -7.0
Laser (N=21)	20090	BASELINE	40	14.88 (2.49)	14.00	14.00, 17.00	7.0, 19.0					
		WEEK 0, DAY 1	39	13.62 (4.83)	14.00	13.00, 18.00	0.0, 19.0	39	-1.46 (4.03)	0.00	0.00, 0.00	-14.0, 0.0
		WEEK 1	40	9.55 (6.89)	10.50	2.00, 14.00	0.0, 19.0	40	-5.33 (6.25)	-3.00	-10.00, 0.00	-19.0, 0.0
		WEEK 1, DAY 1	2	18.00 (0.00)	18.00	18.00, 18.00	18.0, 18.0	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0
		WEEK 2	40	8.23 (7.03)	8.00	0.00, 14.00	0.0, 19.0	40	-6.65 (6.36)	-6.00	-13.50, 0.00	-19.0, 0.0
		WEEK 3	40	7.38 (7.15)	7.00	0.00, 13.50	0.0, 19.0	40	-7.50 (6.80)	-7.00	-14.00, 0.00	-19.0, 0.0
		WEEK 3, DAY 1	2	18.00 (0.00)	18.00	18.00, 18.00	18.0, 18.0	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0
		WEEK 4	39	6.10 (7.05)	3.00	0.00, 13.00	0.0, 20.0	39	-8.97 (6.48)	-11.00	-14.00, 0.00	-19.0, 2.0
		WEEK 6	38	6.32 (7.49)	3.00	0.00, 14.00	0.0, 20.0	38	-8.61 (6.06)	-11.00	-14.00, -2.00	-18.0, 2.0
		WEEK 6, DAY 1	2	19.00 (0.00)	19.00	19.00, 19.00	19.0, 19.0	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0
		WEEK 8	33	2.88 (5.15)	0.00	0.00, 3.00	0.0, 20.0	33	-11.55 (4.65)	-14.00	-14.00, -11.00	-19.0, 2.0
		WEEK 10	32	1.78 (4.28)	0.00	0.00, 1.50	0.0, 21.0	32	-13.00 (4.14)	-14.00	-14.00, -11.00	-19.0, 3.0
		WEEK 10, DAY 1	2	8.00 (0.00)	8.00	8.00, 8.00	8.0, 8.0	2	-11.00 (0.00)	-11.00	-11.00, -11.00	-11.0, -11.0
		WEEK 12	32	2.06 (4.56)	0.00	0.00, 0.00	0.0, 21.0	32	-12.47 (4.28)	-14.00	-14.00, -12.00	-19.0, 3.0
		WEEK 16	34	1.21 (3.86)	0.00	0.00, 0.00	0.0, 21.0	34	-13.24 (3.99)	-14.00	-14.00, -13.00	-19.0, 3.0
		WEEK 20	31	0.87 (3.81)	0.00	0.00, 0.00	0.0, 21.0	31	-13.90 (3.71)	-14.00	-14.00, -14.00	-19.0, 3.0
		WEEK 24	39	0.85 (3.44)	0.00	0.00, 0.00	0.0, 21.0	39	-14.23 (3.74)	-14.00	-16.00, -13.00	-19.0, 3.0
	20275	Screening/Baseline	31	0.87 (3.81)	0.00	0.00, 0.00	0.0, 21.0	31	-13.90 (3.71)	-14.00	-14.00, -14.00	-19.0, 3.0
		40 weeks of age	12	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	12	-15.33 (2.39)	-14.00	-18.00, -14.00	-19.0, -13.0
		1 year of age	40	0.53 (3.32)	0.00	0.00, 0.00	0.0, 21.0	40	-14.35 (3.72)	-14.00	-15.00, -14.00	-19.0, 3.0

n refers to number of eyes
Study intervention as in previous study 20090

Table 5.5.49 - Summary statistics for Retinopathy of Prematurity Activity Scale from investigator assessment and changes from baseline of study 20090 by visit (all subjects who completed visit at 1 year of chronological age)

Considering all subjects who had entered the extension Study 20275, the mean (SD) ROP Activity Scale values by eye were similar between the 2 treatment arms at baseline in Study 20090 (15.62 [2.27] for the aflibercept arm and 14.87 [2.32] for the laser arm. At the screening/baseline visit for the 20275 study, a mean decrease in ROP Activity Scale values from baseline of Study 20090 was observed in both the aflibercept arm (-14.06 [4.71]) and the laser arm (-14.20 [3.24]). These decreases were sustained through the visit at 1 year of chronological age; at this visit, a mean decrease in ROP Activity Scale value from baseline of Study 20090 of -14.67 (2.43) was observed for the aflibercept arm and a mean decrease of - 14.35 (3.72) was observed for the laser arm (*Table 5.5.50*).

			Value at visit					Change from baseline of study 20090				
Treatment Group	Study	Visit	n	Mean (SD)	Median	Q1, Q3	Min, Max	n	Mean (SD)	Median	Q1, Q3	Min, Max
Aflibercept (N=60)	20090	BASELINE	116	15.62 (2.27)	14.00	14.00, 18.00	13.0, 19.0					
		WEEK 0, DAY 1	116	14.59 (3.10)	14.00	13.00, 17.00	7.0, 19.0	116	-1.03 (2.17)	0.00	0.00, 0.00	-7.0, 0.0
		WEEK 1	115	9.33 (5.83)	8.00	7.00, 13.00	0.0, 20.0	115	-6.30 (5.33)	-6.00	-8.00, 0.00	-19.0, 1.0
		WEEK 1, DAY 1	4	13.75 (7.23)	14.00	7.50, 20.00	7.0, 20.0	4	-2.75 (4.35)	-2.50	-6.50, 1.00	-7.0, 1.0
		WEEK 2	113	7.66 (6.24)	7.00	3.00, 12.00	0.0, 20.0	113	-8.02 (5.77)	-7.00	-14.00, -6.00	-19.0, 1.0
		WEEK 2, DAY 1	2	18.00 (0.00)	18.00	18.00, 18.00	18.0, 18.0	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0
		WEEK 3	114	6.30 (6.12)	7.00	0.00, 10.00	0.0, 20.0	114	-9.35 (5.69)	-10.00	-14.00, -6.00	-19.0, 1.0
		WEEK 4	114	5.08 (5.33)	3.00	0.00, 8.00	0.0, 20.0	114	-10.57 (4.90)	-11.00	-14.00, -7.00	-19.0, 1.0
		WEEK 4, DAY 1	2	5.50 (3.54)	5.50	3.00, 8.00	3.0, 8.0	2	-11.50 (3.54)	-11.50	-14.00, -9.00	-14.0, -9.0
		WEEK 5	6	8.33 (9.40)	5.00	0.00, 20.00	0.0, 20.0	6	-10.00 (9.17)	-12.00	-19.00, 1.00	-19.0, 1.0
		WEEK 6	112	4.53 (5.52)	3.00	0.00, 7.00	0.0, 20.0	112	-11.06 (4.91)	-13.00	-14.00, -8.00	-19.0, 1.0
		WEEK 6, DAY 1	2	9.50 (13.44)	9.50	0.00, 19.00	0.0, 19.0	2	-9.50 (13.44)	-9.50	-19.00, 0.00	-19.0, 0.0
		WEEK 7	2	3.00 (0.00)	3.00	3.00, 3.00	3.0, 3.0	2	-16.00 (0.00)	-16.00	-16.00, -16.00	-16.0, -16.0
		WEEK 8	112	3.89 (5.11)	3.00	0.00, 7.00	0.0, 20.0	112	-11.80 (4.94)	-14.00	-14.50, -8.00	-19.0, 1.0
		WEEK 8, DAY 1	2	13.00 (8.49)	13.00	7.00, 19.00	7.0, 19.0	2	-6.00 (8.49)	-6.00	-12.00, 0.00	-12.0, 0.0
		WEEK 10	110	3.08 (4.79)	1.00	0.00, 3.00	0.0, 20.0	110	-12.54 (4.87)	-14.00	-15.00, -11.00	-19.0, 1.0
		WEEK 10, DAY 1	4	4.75 (3.95)	5.50	1.50, 8.00	0.0, 8.0	4	-11.75 (6.75)	-11.00	-17.50, -6.00	-19.0, -6.0
		WEEK 11	6	9.33 (5.68)	13.00	2.00, 13.00	2.0, 13.0	6	-6.33 (4.41)	-4.00	-12.00, -3.00	-12.0, -3.0
		WEEK 11, DAY 1	4	13.00 (0.00)	13.00	13.00, 13.00	13.0, 13.0	4	-3.50 (0.58)	-3.50	-4.00, -3.00	-4.0, -3.0
		WEEK 12	114	2.66 (4.38)	0.50	0.00, 3.00	0.0, 20.0	114	-12.90 (4.49)	-14.00	-15.00, -12.00	-19.0, 1.0
		WEEK 14	4	2.75 (4.19)	1.00	0.50, 5.00	0.0, 9.0	4	-11.25 (4.19)	-13.00	-13.50, -9.00	-14.0, -5.0
		WEEK 14, DAY 1	2	4.50 (6.36)	4.50	0.00, 9.00	0.0, 9.0	2	-9.50 (6.36)	-9.50	-14.00, -5.00	-14.0, -5.0
		WEEK 15	6	9.17 (4.83)	10.00	9.00, 13.00	0.0, 13.0	6	-7.50 (5.82)	-5.00	-8.00, -4.00	-19.0, -4.0
		WEEK 15, DAY 1	2	9.00 (0.00)	9.00	9.00, 9.00	9.0, 9.0	2	-5.00 (0.00)	-5.00	-5.00, -5.00	-5.0, -5.0
		WEEK 16	111	2.52 (4.64)	0.00	0.00, 3.00	0.0, 20.0	111	-13.05 (4.46)	-14.00	-16.00, -12.00	-19.0, 1.0
		WEEK 16, DAY 1	8	8.63 (6.02)	8.00	3.00, 13.00	2.0, 19.0	8	-9.38 (6.19)	-10.00	-15.00, -4.00	-17.0, 0.0
		WEEK 17	8	7.50 (4.84)	6.50	3.00, 11.00	3.0, 16.0	8	-10.50 (4.93)	-12.00	-15.00, -6.00	-15.0, -3.0
		WEEK 20	104	1.95 (4.64)	0.00	0.00, 1.00	0.0, 21.0	104	-13.72 (4.55)	-14.00	-17.00, -13.00	-19.0, 3.0
		WEEK 24	112	1.34 (3.98)	0.00	0.00, 0.00	0.0, 21.0	112	-14.27 (4.38)	-14.00	-18.00, -14.00	-19.0, 5.0
		EARLY TERMINATION	2	20.00 (0.00)	20.00	20.00, 20.00	20.0, 20.0	2	1.00 (0.00)	1.00	1.00, 1.00	1.0, 1.0
	20275	Screening/Baseline	97	1.40 (4.40)	0.00	0.00, 0.00	0.0, 21.0	97	-14.06 (4.71)	-14.00	-18.00, -14.00	-19.0, 5.0
		40 weeks of age	46	1.30 (4.49)	0.00	0.00, 0.00	0.0, 22.0	46	-13.89 (4.86)	-14.00	-16.00, -14.00	-19.0, 6.0
		1 year of age	73	0.22 (1.16)	0.00	0.00, 0.00	0.0, 7.0	73	-14.67 (2.43)	-14.00	-15.00, -14.00	-19.0, -7.0
Laser (N=29)	20090	BASELINE	54	14.87 (2.32)	14.00	14.00, 17.00	7.0, 19.0					
		WEEK 0, DAY 1	53	13.83 (4.34)	14.00	13.00, 17.00	0.0, 19.0	53	-1.19 (3.57)	0.00	0.00, 0.00	-14.0, 0.0
		WEEK 1	54	9.72 (6.64)	13.00	3.00, 14.00	0.0, 19.0	54	-5.15 (6.17)	-1.50	-10.00, 0.00	-19.0, 0.0
		WEEK 1, DAY 1	2	18.00 (0.00)	18.00	18.00, 18.00	18.0, 18.0	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0
		WEEK 2	54	8.02 (6.44)	8.00	0.00, 13.00	0.0, 19.0	54	-6.85 (5.97)	-6.00	-13.00, 0.00	-19.0, 0.0
		WEEK 3	54	6.96 (6.62)	7.00	0.00, 13.00	0.0, 19.0	54	-7.91 (6.61)	-7.00	-14.00, 0.00	-19.0, 0.0
		WEEK 3, DAY 1	2	18.00 (0.00)	18.00	18.00, 18.00	18.0, 18.0	2	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0
		WEEK 4	53	5.60 (6.62)	3.00	0.00, 8.00	0.0, 20.0	53	-9.42 (6.38)	-11.00	-14.00, -6.00	-19.0, 2.0
		WEEK 6	52	5.33 (7.07)	1.00	0.00, 8.00	0.0, 20.0	52	-9.58 (6.24)	-11.50	-14.00, -6.00	-18.0, 2.0
		WEEK 6, DAY 1	4	16.25 (3.20)	16.50	13.50, 19.00	13.0, 19.0	4	0.25 (0.50)	0.00	0.00, 0.50	0.0, 1.0
		WEEK 7	2	7.00 (9.90)	7.00	0.00, 14.00	0.0, 14.0	2	-6.00 (9.90)	-6.00	-13.00, 1.00	-13.0, 1.0
		WEEK 8	47	2.23 (4.56)	0.00	0.00, 3.00	0.0, 20.0	47	-12.32 (4.37)	-14.00	-14.00, -11.00	-19.0, 2.0
		WEEK 10	46	1.28 (3.64)	0.00	0.00, 0.00	0.0, 21.0	46	-13.52 (3.68)	-14.00	-14.00, -13.00	-19.0, 3.0
		WEEK 10, DAY 1	2	8.00 (0.00)	8.00	8.00, 8.00	8.0, 8.0	2	-11.00 (0.00)	-11.00	-11.00, -11.00	-11.0, -11.0
		WEEK 12	44	1.50 (3.98)	0.00	0.00, 0.00	0.0, 21.0	44	-13.16 (3.93)	-14.00	-14.00, -13.00	-19.0, 3.0
		WEEK 16	48	0.85 (3.28)	0.00	0.00, 0.00	0.0, 21.0	48	-13.71 (3.55)	-14.00	-14.00, -13.00	-19.0, 3.0
		WEEK 20	45	0.60 (3.17)	0.00	0.00, 0.00	0.0, 21.0	45	-14.20 (3.24)	-14.00	-14.00, -14.00	-19.0, 3.0
		WEEK 24	53	0.62 (2.96)	0.00	0.00, 0.00	0.0, 21.0	53	-14.40 (3.33)	-14.00	-16.00, -14.00	-19.0, 3.0
	20275	Screening/Baseline	45	0.60 (3.17)	0.00	0.00, 0.00	0.0, 21.0	45	-14.20 (3.24)	-14.00	-14.00, -14.00	-19.0, 3.0
		40 weeks of age	20	0.00 (0.00)	0.00	0.00, 0.00	0.0, 0.0	20	-14.80 (1.94)	-14.00	-14.00, -14.00	-19.0, -13.0
		1 year of age	40	0.53 (3.32)	0.00	0.00, 0.00	0.0, 21.0	40	-14.35 (3.72)	-14.00	-15.00, -14.00	-19.0, 3.0

n refers to number of eyes
Study intervention as in previous study 20090

Table 5.5.50 - Summary statistics for Retinopathy of Prematurity Activity Scale from investigator assessment and changes from baseline of study 20090 by visit (all subjects entering extension)

Subjects with complete vascularization assessed by indirect ophthalmoscopy

Considering all subjects who completed the visit at 1 year of chronological age, 52 (45.2%) eyes had complete vascularization at week 24 (end of Study 20090) and 71 (61.7%) eyes had complete

vascularization at 1 year of chronological age. In the aflibercept arm, 35 (46.7%) eyes had complete vascularization at week 24 (end of Study 20090) and 52 (69.3%) eyes had complete vascularization at 1 year of chronological age; while in the laser arm, 17 (42.5%) eyes had complete vascularization at week 24 and 19 (47.5%) eyes had complete vascularization at 1 year of chronological age (*Table 5.5.51*).

	Aflibercept (N=39)	Laser (N=21)	Total (N=60)
Number of eyes	75 (100.0%)	40 (100.0%)	115 (100.0%)
Number of complete vascularized eyes at Week 24	35 (46.7%)	17 (42.5%)	52 (45.2%)
Number of complete vascularized eyes at 1 year of age	52 (69.3%)	19 (47.5%)	71 (61.7%)

Study intervention as in previous study 20090
Last observation carried forward (LOCF) approach is used for subjects who dropped out prior to their 1 year of age assessment.

Table 5.5.51 - Number of eyes with completion of vascularization of the peripheral retina according to investigator assessment to Week 24 and at 1 year of age (all subjects who completed visit at 1 year of chronological age)

Of all subjects who had entered the extension Study 20275, a total of 75 (44.1%) eyes had complete vascularization at week 24 and a total of 94 (55.3%) eyes had complete vascularization at 1 year of chronological age (considering last observation carried forward [LOCF] approach). In the aflibercept arm, 52 (44.8%) eyes had complete vascularization at week 24 and 71 (61.2%) eyes had complete vascularization at 1 year of chronological age, while in the laser arm, 23 (42.6%) eyes had complete vascularization at week 24, which was identical to the number of eyes that had complete vascularization at 1 year of chronological age (*Table 5.5.52*).

	Aflibercept (N= 60)	Laser (N= 29)	Total (N= 89)
Number of eyes	116 (100.0%)	54 (100.0%)	170 (100.0%)
Number of complete vascularized eyes at Week 24	52 (44.8%)	23 (42.6%)	75 (44.1%)
Number of complete vascularized eyes at 1 year of age	71 (61.2%)	23 (42.6%)	94 (55.3%)

Study intervention as in previous study 20090
Last observation carried forward (LOCF) approach is used for subjects who dropped out prior to their 1 year of age assessment.

Table 5.5.52 - Number of eyes with completion of vascularization of the peripheral retina according to investigator assessment to Week 24 and at 1 year of age (all subjects entering extension)

Considering the FAS of Study 20090, 88 (40.4%) eyes had complete vascularization at week 24 (end of Study 20090) and 107 (49.1%) eyes had complete vascularization at 1 year of chronological age (considering LOCF approach). In the aflibercept arm, 57 (39.0%) eyes had complete vascularization at week 24 and 76 (52.1%) eyes had complete vascularization at 1 year of chronological age, while in the laser arm, 31 (43.1%) eyes had complete vascularization at week 24 and at 1 year of chronological age (*Table 5.5.53*).

	Aflibercept (N= 75)	Laser (N= 38)	Total (N= 113)
Number of eyes	146 (100.0%)	72 (100.0%)	218 (100.0%)
Number of complete vascularized eyes at Week 24	57 (39.0%)	31 (43.1%)	88 (40.4%)
Number of complete vascularized eyes at 1 year of age	76 (52.1%)	31 (43.1%)	107 (49.1%)

Study intervention as in previous study 20090
Last observation carried forward (LOCF) approach is used for subjects who dropped out prior to their 1 year of age assessment.

Table 5.5.53 - Number of eyes with completion of vascularization of the peripheral retina according to investigator assessment to Week 24 and at 1 year of age (full analysis set of 20090)

In conclusion, the current data available on very few patients are still insufficient to conclude on long-term visual outcomes. The MAH was asked to provide the cut-off data at 2 year of chronological age for the extension study 20275. The applicant provided data of patient who underwent the 2nd year visit (54 infants: 36 aflibercept group and 18 laser group), wich tend to confirm long term efficacy of aflibercept.

Residual uncertainty is considered acceptable at this stage, and will be in the future further minimised by the submission of longer-term results as per RMP.

Assessment of the Summative Usability Evaluation

This study was intended to demonstrate that the pediatric dosing device can be used safely and effectively by the intended users, for the intended uses, and in the intended use environments – that is, without use errors that could lead to serious harm for which further mitigation would be practicable.

The summative usability evaluation involved simulated use testing of all critical tasks as well as hazard-related use scenarios that have been identified based on the use risk analysis.

Participants were scheduled t be at least 15 physicians who perform intravitreal injections to treat prematurely born patients with ROP. In setups where ophthalmic technicians, assistant physicians and/or nurses are taking over some of the tasks, they could also be included into summative usability evaluation. Training and familiarization will be representative for the real-world situation.

Any observed use errors or use difficulties was scheduled to be analyzed for their root cause, the severity of harm that could result from the observation and, if needed, the practicality of modification of the user interface to further mitigate use-related risks.

The human factors validation testing / summative usability evaluation was conducted in Germany (Berlin, Frankfurt), France (Paris) and Spain (Barcelona, Madrid) from 04 to 26 October 2021. A total of 30 participants (15 physicians, 15 nurses) experienced with intravitreal injections in prematurely born patients with ROP performed simulated procedures, including all critical tasks and hazard-related use scenarios for preparation and administration.

The human factors validation testing / summative usability evaluation provided objective evidence that the pediatric dosing device, when used in combination with the Aflibercept solution 40 mg/mL in prefilled syringe, can be used safely and effectively by the intended users. That is, without use errors or difficulties that did or could lead to serious harm when used in reality.

In particular, the study demonstrated the following:

1. The user interface of the PFS-with-PDD combination is adequate to support safe and effective execution of critical tasks.
2. The pediatric dosing device instructions for use is adequate to support safe and effective execution of critical tasks and to communicate information for safety.

Use errors and difficulties were observed related to the removal of air from the system (priming of PDD). Subsequent technical investigation provided evidence that the remaining air bubbles observed in the PDD during the human factors validation testing / summative usability evaluation would neither be ejected into the eye, nor lead to an underdose. Therefore, it is deemed improbable that these use errors and difficulties would lead to harm.

However, to minimize uncertainty during use in reality, the training materials developed as part of market access activities (out of scope of risk control) will provide additional guidance for the priming step.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

- Summary of Efficacy for trial FIREFLEYE

Title: FIREFLEYE - Open-label, Randomized, Two-Arm, Controlled Study to Assess the Efficacy, Safety, and Tolerability of Intravitreal (IVT) Aflibercept Compared to Laser Photocoagulation in Patients With Retinopathy of Prematurity (ROP)			
Study identifier	20090		
Design	Randomized, open-label, 2-arm, multicenter, controlled study, non-inferiority study evaluating the efficacy, safety and tolerability of IVT aflibercept 0.4 mg compared to laser photocoagulation for the treatment of ROP. Assessments to address the primary objective were performed on 24 weeks after starting investigational treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable until 5 years of age of the subjects
Hypothesis	Non-inferiority		
Treatments groups	Aflibercept 0.4 mg/0.01 mL		75
	Laser photocoagulation		43
Endpoints and definitions	Primary endpoint	Aflibercept 0.4 mg/0.01 mL Vs laser photocoagulation	absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting study treatment, as assessed by the Investigator
	Secondary endpoint	Aflibercept 0.4 mg/0.01 mL Vs laser photocoagulation	- Requirement for intervention with a second treatment modality from baseline to Week 24 - Recurrence of ROP from baseline to Week 24 - To explore new Retinopathy of Prematurity Activity Scale proposed by the International Neonatal Consortium - Number of aflibercept administrations from baseline to Week 24 - Number of laser treatments from baseline to Week 24 - Proportion of participants with ocular TEAEs and SAEs from baseline to Week 24 - Proportion of participants with systemic TEAEs and SAEs from baseline to Week 24 - Systemic exposure to free aflibercept (at expected maximum plasma concentration and during elimination period from plasma) determined by sparse sampling - Presence of anti-drug antibodies before and 12 weeks afteraflibercept injection

	other: endpoint	Aflibercept 0.4 mg/0.01 mL Vs laser photocoagulation	- Evaluation of visual function at Week 24 - Time required to perform treatment - Requirement for sedation or general anesthesia - Requirement for treatment with more than one aflibercept injection - Time to intervention with a second treatment modality for ROP or development of unfavorable structural outcomes - Time to recurrence of ROP - Regression of plus disease, regression of pre-retinal-vascularized ridge and progression of retinal vascularization beyond the ridge from baseline to Week 24 - Progression to Stage 4 or 5 ROP from baseline to Week 24 - Completion of vascularization of the peripheral retina to within one disc diameter of the ora serrata at Week 24 - Time to completion of vascularization - Number of visits required up to Week 24 - Systemic exposure to total aflibercept determined by sparse sampling - Various biomarkers (eg, diagnostic, safety, pharmacodynamics, monitoring, or potentially predictive biomarkers)
Database lock	Not applicable.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set, 24 weeks after the first study treatment.		
Descriptive statistics and estimate variability	Treatment group	Aflibercept 0.4 mg	Laser photocoagulation
	Number of subject	75	38
	Mean	0.852	0.816
	SD	0.041	0.062
Effect estimate per comparison	Primary endpoint	Comparison groups	Aflibercept 0.4 mg vs. laser therapy
		Mean difference	0.036
		SD	0.073
		90 % Credible Interval	(-0.080, 0.162)
		Probability for difference ≥-0.05%	0,884
Notes	The success criterion P(response probability for aflibercept > (response probability for laser -5%)) ⩾ 95% was not met.		
Analysis description	**Secondary analysis**		

	- Requirement for intervention with a second treatment modality from baseline to week (24 7.2% of subjects in the aflibercept arm and 9.6% subjects in the laser arm) - Recurrence of ROP from baseline to week 24 (16.1% of subjects in the aflibercept arm and 6.3% subjects in the laser arm)		
Analysis population and time point description	Full Analysis Set, 24 weeks after the first study treatment.		
Descriptive statistics and estimate variability	Treatment group	Aflibercept 0.4 mg	Laser photocoagulation
	Number of subject	75	38
	Mean	0.076	0.028
	SD	0.028	0.044
Effect estimate per comparison	Secondary endpoint Requirement for intervention with a second treatment modality from baseline to week	Comparison groups	Aflibercept 0.4 mg vs. laser therapy
		Mean difference	- 0.027
		SD	0.048
		90 % Credible Interval	(-0.110, 0.046)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Full Analysis Set, 24 weeks after the first study treatment.		
Descriptive statistics and estimate variability	Treatment group	Aflibercept 0.4 mg	Laser photocoagulation
	Number of subject	75	38
	Mean	0.165	0.068
	SD	0.041	0.033
Effect estimate per comparison	Secondary endpoint Recurrence of ROP from baseline to week 24	Comparison groups	Aflibercept 0.4 mg vs. laser therapy
		Mean difference	0.096
		SD	0.048
		90 % Credible Interval	(0.019, 0.175)

Supportive study

As agreed with the EMA's Pediatric Committee, an evidence synthesis study was conducted based on the data obtained from Study 20090 and considering historical efficacy data from literature (*Module 5.3.5.4 [ROP], Report PH-42120*). In particular, efficacy outcomes of subjects with ROP treated with aflibercept in Study 20090 were compared to outcomes of subjects treated with laser photocoagulation, including historic data for ROP laser treatment from the large randomized clinical trials, BEAT-ROP (Mintz-Hittner et al. 2011) and RAINBOW (Stahl et al. 2019). The endpoints evaluated were in line with the following primary and secondary efficacy endpoints investigated in Study 20090:

- Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment

- Recurrence of ROP requiring any post-baseline intervention until week 24

To allow for a comparison of recurrence rates in Study 20090 with those from the RAINBOW study (Stahl et al. 2019), which compared treatment effects of IVT ranibizumab with laser treatment, this endpoint was defined differently in the evidence synthesis study than in the statistical analysis plan of Study

20090. In line with what is reported for the RAINBOW study, a subject was considered to have had a recurrence of ROP if he/she received either a re-treatment with the randomized treatment or received a rescue treatment (laser for subjects in the aflibercept arm/aflibercept for subjects in the laser arm).

The data for the primary endpoint reported in RAINBOW (70.3%) and BEAT-ROP (73.9%) (*Module 5.3.5.4 [ROP], Evidence Synthesis Report, PH-42120, Section 7.2.1.1, Table 1*) were aggregated by a Bayesian meta-analytical prediction model to be used in the Bayesian analysis as prior information for the laser treatment effect in combination with the data collected in Study 20090. This prior information was centered at approximately 72% and is equivalent to approximately 47 additional subjects in the laser arm.

The primary analysis based on a Bayesian model resulted in an estimated response probability (median of the posterior distribution) in the aflibercept arm of 85.4% and 76.8% in the laser arm. The estimated difference between the treatment arms (median of posterior) was 8.5% with a 90% credible interval of (-1.7%, 18.6%). The primary success criterion "response probalilty of aflibercept is greater than the one for laser minus 5 percentage points with at least 95% probability" was met, as the respective posterior probability was 98.5% and therefore exceeded the threshold of 95%. The posterior probability of a treatment difference > 0, i.e. the probability that aflibercept is more efficacious than laser photocoagulation was 91.6% indicating that there is a high likelihood that aflibercept is superior to laser treatment (*Table 5.5.54*). The posterior distributions for response probabilities for the 2 treatment arms are visualized in Figure 5.5.6 and for the treatment difference (*Module 5.3.5.4 [ROP], PH-42120, Section 7.2.1.2*). Primary endpoint results for Study 20090 and the evidence synthesis study are summarized in Table *5.5.55*.

Treatment	Mean	SD	90% Credible interval [a]	Median	Mode [b]	Probability for difference ≥ -0.05	Probability for difference > 0
Aflibercept	0.851	0.041	(0.778 , 0.912)	0.854	0.858		
Laser	0.765	0.047	(0.685 , 0.838)	0.768	0.777		
Difference	0.085	0.062	(-0.017 , 0.186)	0.085	0.089	0.985	0.916

A subject is considered a responder in case of absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator assessment for both eyes, i.e. if a subject has 2 study eyes, both needed to respond.
Unfavorable structural outcome defined as retinal detachment, macular dragging, macular fold, or retrolental Opacity.
Response probability modeled as pi = p^2 + r*p*(1-p), with p response probability of an individual eye and r= correlation between two eyes.
For details on handling of missing data for primary endpoint, refer to study SAP.
a 90% Equal Tail credible intervals for posterior proportion are presented.
b Half-sample mode.

Table 5.5.54 - Bayesian model for proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment (FAS) - (beta(34.83, 13.87) distribution as prior for laser)

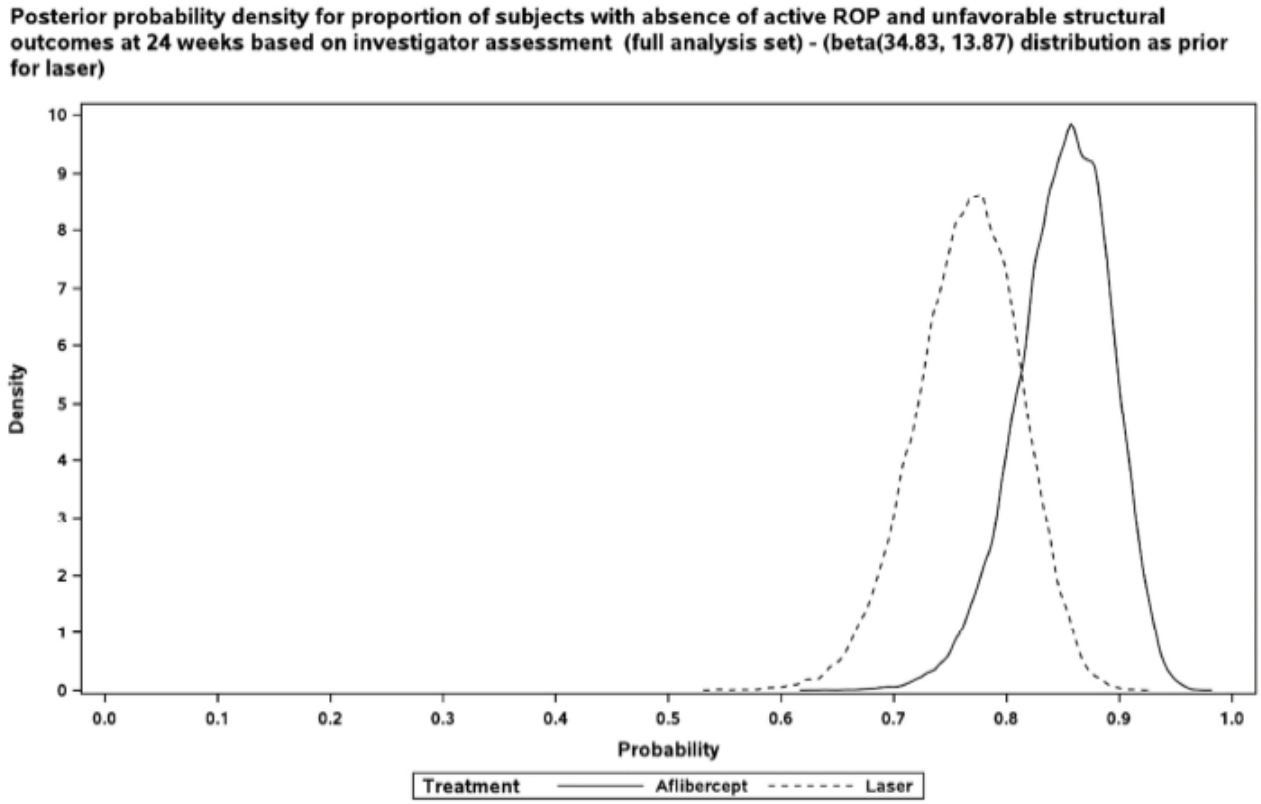


Figure 5.5.6 - Posterior probability density for proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks based on investigator assessment (FAS) – (beta(34.83, 13.87) distribution as prior distribution for laser)

	Treatment	Estimated response probabiltiy (median of posterior)	90% Credible interval (a)	P (diff ≥ -0.05)
Study 20090 only	Aflibercept	0.855	(0.780 , 0.913)	
	Laser	0.821	(0.705 , 0.908)	
	Difference	0.034	(-0.080 , 0.162)	0.884
Evidence Synthesis Study	Aflibercept	0.854	(0.778 , 0.912)	
	Laser	0.768	(0.685 , 0.838)	
	Difference	0.085	(-0.017 , 0.186)	0.985

(a) 90% Equal Tail credible intervals for posterior proportion are presented.

Table 5.5.55 - Primary endpoint results for Study 20090 and the Evidence Synthesis Study

Robustness of the results with respect to the impact of the prior distribution was confirmed in sensitivity analyses summarized in *Evidence Synthesis Report, Module 5.3.5.4 (ROP), PH-42120, Section 7.2.1.3*.

In the RAINBOW study (Stahl et al. 2019), 14/74 (18.9%) subjects randomized to laser treatment were reported to have received a re-treatment with laser or rescue treatment with ranibizumab, due to recurrence of ROP. Using this as prior information in the Bayesian analysis of recurrence, the estimated probability for a recurrence (median of posterior distribution) in at least one eye was 26.9% in the aflibercept group and 19.6% in the laser group, leading to an estimated difference of 7.2% in favor of laser treatment. Study 20090 reports 21.3% of subjects requiring a re-treatment with aflibercept and 6.7% requiring rescue treatment with laser (*Module 5.3.5.1 [ROP], Report PH-41617, Tables 14.1.7/1 and 14.1.7/2*), indicating that the recurrence rate for aflibercept is mainly driven by re-treatment. The sensitivity analysis showed no relevant difference in comparison to the main analysis (*Evidence Synthesis Report Module 5.3.5.4 [ROP], PH-42120, Sections 7.2.2.1 and 7.2.2.2*).

In conclusion, while in Study 20090 the estimated response rate in the aflibercept arm was numerically higher than the one for laser treatment, the formal success criterion was not met.

In the evidence synthesis study, clinical data from Study 20090 was complemented by historic data on laser treatment; and this integration of historical evidence increased the power for the formal statistical analysis. The success criterion (indicating non-inferiority of aflibercept versus laser treatment), that was pre-defined for both Study 20090 and the evidence synthesis study, was met. Further, the analysis showed a high (posterior) probability (above 90%) for aflibercept being superior to laser treatment. The various sensitivity analyses supported the robustness of the results of the evidence synthesis study; there was no indication of a prior data conflict.

Overall, - while the exercise is to be considered supportive and exploratory - positive ocular efficacy outcomes for IVT aflibercept in ROP patients reported in the literature (and as summarized in the evidence synthesis study report) were supported by the results obtained from the clinical Study 20090 and the additional integration of clinical relevant data from published literature as presented in the evidence synthesis study.

4.5.3. Discussion on clinical efficacy

The presented evidence supporting the clinical efficacy of aflibercept 0.4 mg for the treatment of ROP subjects was largely derived from studies whose methodology was agreed with PDCO. Indeed, following exchanges, the PDCO agreed with the proposed study design (in terms of indication, population, criteria of participation in the study, endpoints, number of patients and duration of the treatment).

Importantly, the agreed plan included a pivotal study with a relatively small number in the laser control group (2:1, aflibercept:laser), to be complemented with respective randomized controlled data from the literature in the framework of the evidence synthesis study. Hence, while a supportive exercise in some elements of its nature, this was a priori part of the strategy to demonstrate efficacy.

Accordingly, the fact that the formal non-inferiority criterion was not met in the pivotal study has to be seen in the context of the favourable point estimates, of the support provided by the evidence synthesis study, the consistency across endpoints (including the reassuring 2-year data submitted during the procedure) and the credibility of the mechanism of action.

The applicant has also committed (see RMP) to provide further data to minimise the residual uncertainties on the longer term outcomes.

4.5.4. Conclusions on the clinical efficacy

The efficacy in the target population is considered sufficiently demonstrated. Residual uncertainties are accepted and will be reduced by further data provision.

4.6. Clinical safety

Overview of clinical studies

The summary of clinical safety data presented is based on:

1. FIREFLEYE (20090) a completed phase 3 multicenter open label randomized, two arm, controlled 24-weeks study to assess the efficacy, safety and tolerability of IVT aflibercept compared to laser photocoagulation in patients with ROP;
2. FIREFLEYE NEXT (20275) an ongoing extension phase 3b multicenter 5-years study (expected end of study date July 2025) to assess the long term outcomes of subjects previously diagnosed with ROP who were treated in the completed study 20290.

Table 1: Studies included in the evaluation of clinical safety

Study / CSR /location	Study design	Study objectives	No. of Subjects: Dose regimens
FIREFLEYE Study 20090 Module 5.3.5.1 (ROP), Report PH- 41617	A phase 3, multicenter, open-label, randomized, two-arm, controlled study to assess the efficacy, safety, and tolerability of intravitreal (IVT) aflibercept compared to laser photocoagulation in patients with retinopathy of prematurity (ROP).	**Primary:** To assess the efficacy of aflibercept in subjects diagnosed with ROP in comparison to laser. **Secondary:** • To assess the safety and tolerability of aflibercept • To assess the treatment burden of aflibercept and laser • To describe the systemic exposure to aflibercept	Total randomized/treated: 118/113 **Aflibercept arm: 75** • 75 subjects: received a single dose of 0.4 mg (in 10 µL) per treatment-requiring eye at baseline • 16 subjects: received a second injection in at least one eye • 5 subjects: received laser photocoagulation as rescue treatment **Laser arm: 38** • 38 subjects: received laser treatments at baseline • 4 subjects: had retreatment with laser in at least one eye • 4 subjects: received aflibercept injection as rescue treatment

Study / CSR /location	Study design	Study objectives	No. of Subjects: Dose regimens
FIREFLEYE next Study 20275 Module 5.3.5.1 (ROP), Report PH- 41618	A phase 3b, multi-center study to assess the long-term outcomes of subjects previously diagnosed with ROP who were treated in the completed Study 20090 (after randomization in a 2:1 ratio to baseline treatment with aflibercept 0.4 mg or laser photocoagulation).	**Primary:** To evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for ROP. **Secondary:** To describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP.	Total subjects: 90 (**89** with data available at time of data cut-off) **Aflibercept arm:** 61 (**60** with data available at time of data cut-off) who had been randomized into the aflibercept arm and received study treatment in Study 20090. **Laser arm: 29** who had been randomized into the laser arm and received study treatment in Study 20090. No study treatment is administered in Study 20275. Study treatment (IVT aflibercept and/or laser) was administered in Study 20090. Any treatments for ROP are decided by the treating physician, according to local standards of care,

IVT = intravitreal; ROP = retinopathy of prematurity;

The criteria of inclusion for the study 20090 consisted of being preterm infants, treatment-naïve, with gestational age at birth ≤ 32 weeks or birth weight ≤ 1500 g, who weighed ≥ 800 g at baseline, with ROP classified in at least one eye as Zone I stage 1 plus, 2 plus, 3 non-plus or plus, or Zone II stage 2 plus or 3 plus, or AP-ROP according to the International Classification for ROP (ICROP 2005).

Eligible subjects were randomized in a 2:1 ratio to receive baseline treatment either with aflibercept or laser photocoagulation, respectively, per treatment-requiring eye, stratified by Japanese and non-Japanese sites as well as by ROP classification. Rescue treatment (laser for subjects in the aflibercept arm, aflibercept for subjects in the laser arm) was allowed in case rescue criteria were met.

The ongoing extension Study 20275 (FIREFLEYE next), a phase 3-b multi-center study, including 89 subjects (i.e.60 in aflibercept arm and 29 in laser arm) is to assess the long-term outcomes of subjects

previously diagnosed with ROP who were treated in the completed Study 20090 (end of study date 12 FEB 2021). The baseline visit was concomitant to the week 24 visit or the last follow up which was at the latest before the 13 month of chronological age. Overall, 60 subjects had completed their visit at 1 year of chronological age (i.e. 39 aflibercept arm and 21 laser arm) at the time of data-cut off for the interim analysis (01 MAR 2021) contributing to the interim ocular and systemic safety data until the chronological age of 1 year. The duration of 5 years for monitoring is acceptable.

Overall analysis plan (SAF)

Study 20090

Safety analysis for study 20090 included the safety analysis set (SAF) constituted of 113 subjects with ROP, among whom 75 were treated with 0.4 mg aflibercept per treatment-requiring eye at baseline, mostly bilaterally and on the same day.

Safety was monitored and evaluated continuously throughout the study, including a 30-day safety follow-up period after discontinuation of treatment. Safety evaluation consisted of AEs, ophthalmic and physical examinations, vital signs, clinical safety laboratory assessment and presence of anti-drug antibodies before and 12 weeks after baseline aflibercept injection.

Analysis	Age at assessment	Total of subject (SAF)	
Study 20090	6 month (e.q 24 weeks)	113 patients (75 aflibercept arm and 38 laser arm)	Last subject last visit 12 FEB 2021
Study 20275: Interim analysis	1 year	1. 89 patients who entered the study (60 aflibercept arm and 29 laser arm) at cut-off date 2. Including 60 patients at 1 year of chronological age at cut of date (39 aflibercept arm and 21 laser arm) at the cut-off date	Cut of date 01 Mar 2021
Study 20275: Final analysis	5 years	100 subjects overall (recruitment completed on 26 APRIL 2022)	Planned July 2025

Overall, of the randomized patients 104 subjects (68 in the aflibercept arm (90, 7%) and 36 in the laser arm (83, 7%)) completed study treatment and the study.

For more detail on the number of patient discontinued and the reasons associated *see clinical efficacy section (subject disposition).*

Study 20275

For the study 20275, the population for the safety analysis was the SAF (n=89) which included all subjects who had entered the extension ongoing study) i.e 60 subjects in the aflibercept arm and 29 subjects in the laser arm including 60 patients (39 aflibercept arm and 21 laser arm) who had safety data available until 1 year of chronological age as of 01 MAR 2021 (cut of date for the interim analysis).

Safety evaluations for the ongoing extension Study 20275 include an annual visit until the 5 year of chronological age of the patient with an evaluation of AEs, physical examinations, vital signs, neurodevelopment scales (BSID-III at screening, mandatory at 2 year but recommended at screening, 1 and 2 year/VABS-II at 2 year and 5 year/WPSSI-IV at 3,4 and 5 year) and hearing test (BAER at visit 1 and 6). No treatment was administered in the ongoing extension study.

Table 2: Schedules of procedure

	Visit Number	Screening/ baseline Visit 1a	1b	2	3	4	5	6 EOS
	Visit Window		**-7d/ +14d**	**±1mo**	**-1mo/ +3mo**	**-1mo/ +3mo**	**-1mo/ +3mo**	**-1mo/ +3mo**
	Chronological Age		**40 w**	**1 yr**	**2 yrs**	**3 yrs**	**4 yrs**	**5 yrs**
Procedure	Informed consent	X						
	In/exclusion criteria	X						
	Medical history	X						
	Prior/concomitant meds	X	X	X	X	X	X	X
	Physical examination	XX	X	X	X	X	X	X
	Vital signs	XX	X	X	X	X	X	X
	Body weight	XX	X	X	X	X	X	X
	Height	XX	X	X	X	X	X	X
	Head circumference	XX	X	X	X	X		
	Hearing test	X						X
	Adverse events	XX	X	X	X	X	X	X
Developmental Assessment	BSID-III	(X)		(X)	X			
	VABS-II				X	(X)	(X)	X
	WPPSI-IV or DAS-II					(X)	(X)	X
Ophthalmological Assessments	Visual function/acuity [a]	XX	X	X	X	X	X	X
	Refraction		X	X	X	X	X	X
	Ocular extrinsic motility		X	X	X	X	X	X
	Stereopsis							X
	Visual fields							X
	Binocular indirect ophthalmoscopy	XX	X	X	X	X	X	X
	Anterior segment exam	XX	X	X	X	X	X	X

X= mandatory; (X)= recommended; XX = if visit 1 is conducted concomitantly with the EOS visit of Study 20090, these assessments were performed as part of Study 20090.

[a] Visual acuity evaluated at visits 4, 5, and 6.

BSID = Bayley Scales of Infant Development; d = day; DAS-II = Differential Ability Scales® II; EOS = end of study; meds = medications; mo = month; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; WPPSI-IV= Wechsler Preschool and Primary Scale of Intelligence™, Fourth Edition, DAS-II= Differential Ability Scales® II, w = week, yr = year.

Upon request, the Applicant has committed to not only provide 2-years and final 5-years data but also interim results at 3 and 4 years.

Patient exposure

1. Exposure to treatment

Study 20090

Subjects randomized to aflibercept received a single IVT injection of aflibercept 0.4 mg/10 µL per eligible eye at baseline. The injection was to be performed in both eyes on the same day, if applicable.

Up to 2 additional IVT injections of aflibercept 0.4 mg/10 µL may have been administered in each eye if retreatment criteria were met. Patients were treated up to 23 weeks (including retreatment and rescue treatment), and had a final visit at week 24 (up to week 27 for subjects treated after week 21).

Study duration was planned for at least 24 weeks in the study protocol.

The 75 subjects (146 eyes) in the aflibercept arm were treated with a total of 172 aflibercept injections. Of the 146 eyes treated in the aflibercept arm, 120 (82.2%) received 1 aflibercept injection, and 26 (17.8%) received 2 injections.

The 38 subjects (72 eyes) in the laser arm were treated with a total of 89 laser treatments, among which 71 eyes were eligible and received laser treatments at baseline. Of the 72 treated eyes in the laser arm, 65 (90.3%) received 1 laser treatment, 5 (6.9%) received 2 laser treatments, and 2 (2.8%) received 3 laser treatments.

Treatment duration ranged from 1 to 121 days in the aflibercept arm and 1 to 75 days in the laser arm. For subjects with only a single treatment day at baseline, the treatment duration was 1 day.

Study 20275

No study treatment is administered in the ongoing Study 20275 as study treatment (IVT aflibercept and/or laser) was given in Study 20090.

Re-treatment and rescue treatment

Study 20090

In the FIREFLEYE study, of the 75 subjects in the aflibercept arm, 5 subjects had a total of 7 laser treatments as rescue treatment in a total of 7 eyes (1 treatment per eye).

Of the 38 subjects in the laser arm, 4 subjects (8 eyes) were treated with a total of 9 aflibercept injections as rescue treatment. On the 8 treated eyes, 7 received 1 aflibercept injection and 1 received 2 injections.

Overall, in the aflibercept arm rescue treatment with laser was necessary for 4.8% of eyes (6.7% of subjects) while in the laser arm rescue treatment, aflibercept was required for 8 eyes (11.1%) for a total of 4 subjects (10.5%) with one eye which required two rescue injections. One of the subjects in the aflibercept arm received rescue treatment, i.e. laser treatment, for the first eye on the same day when aflibercept was initialized for the second eye. Two subjects in the aflibercept arm and 1 subject in the laser arm initialized treatments for the second eye after baseline.

Study 20275

No study treatment is administered in the ongoing Study 20275 as study treatment (IVT aflibercept and/or laser) was given in Study 20090

2. Demographic and other characteristics of study population

Study 20090

A demographic graph of the population included in the study 20090 is available in the *clinical efficacy section*.

Overall, the SAF analysis population consisted of a majority of male (53.1% versus 46.9%), white subjects (73.5%), not originated from Japan (85.8%) and with the majority of subjects in the <28 week category (83.2% subjects overall). Patient's birth weight was for the majority of subjects (68.1%) in the 500 to <1000 gram category and nearly half of them had an Apgar score of 4 to 7, inclusive, at both 1 and 5 minutes after birth. The majority of subjects in the SAF were classified by the investigators as having Zone II ROP (excluding AP-ROP) (63.7%), followed by Zone I ROP (excluding AP-ROP) (19.5%),

and AP-ROP (16.8%) based on the assessment of the more severe eye in case that both eyes were eligible.

The subjects in the aflibercept arm weighted more on average, with 19 (25.3%) subjects weighting ≥ 2500 grams versus 2 (5.3%) subjects in the laser arm. The mean (SD) weight at time of baseline treatment in the aflibercept arm was 2027.8 grams (675.69) and 1842.1 grams (554.18) in the laser arm. As per protocol, the minimum body weight at time of baseline treatment was 800 grams.

Most subjects had oxygen supplementation at baseline at a similar rate across both treatment arms, 45 subjects (60.0%) in the aflibercept arm and 23 subjects (60.5%) in the laser arm.

Histories of sepsis and necrotizing enterocolitis were present in 47 (41.6%) and 20 (17.7%) subjects overall, respectively, with similar proportions of subjects in each treatment arm. A history of intraventricular hemorrhage was present in 19 (25.3%) subjects in the aflibercept arm and 16 subjects (42.1%) in the laser arm.

Overall, the population of the SAF is consistent with the characteristics of the premature infant population affected by ROP condition. Indeed, most patients were born at gestational age below 32 weeks and with very low birth weight, i.e. ⩽1500g.

Study 20275

In the extension study for all 89 subjects who entered the study at the cut-off date, there were slightly more male than female subjects (53.9% versus 46.1%) The majority of subjects were White (76.4%) and not from Japan (87.6%), the gestational age at birth ranged from 23 weeks to 31 weeks (median 26 weeks, 0 day), with the majority of subjects in the ≥24 to <27 weeks category (60.7% subjects overall).

Birth weight ranged from 410 to 1780 grams (median 825.0 grams), with the majority of subjects in the ≥500 gram to <1000 gram category (65.2%). The mean weight at birth was slightly higher for the aflibercept arm (907.0 grams, SD = 309.9) than for the laser arm (820.4 grams, SD = 252.9). Approximately half of the subjects had an Apgar score of 4 to 7, inclusive, at 1 and 5 minutes after birth.

Mean chronological age at baseline in Study 20090 was 10.3 weeks for both arms, and the mean baseline weight was slightly higher for the aflibercept arm (2055.0 grams, SD = 683.78) than for the laser arm (1882.4 grams, SD = 579.96).

At time of entry into the follow-up Study 20275, mean chronological age was 8.8 months across both arms and the mean baseline weight was similar between the aflibercept (6.59 kg, SD = 1.13) and laser (6.45 kg, SD = 1.21) arms.

For the 60 subjects at 1 year of chronological age, the majority of eyes at baseline in Study 20090 presented with ROP Zone II (72.2%, n = 83), with 54 (72.0%) eyes in the aflibercept arm and 29 (72.5%) eyes in the laser arm. The greatest proportion of eyes with ROP Zone II were stage 3 plus (55.7%, n=64), with 42 (56.0%) eyes in the aflibercept arm and 22 (55.0%) eyes in the laser arm.

A total of 18 (15.7%) eyes presented with AP-ROP, with 12 (16.0%) eyes in the aflibercept arm and 6 (15.0%) eyes in the laser arm. A total of 14 (12.2%) eyes presented with ROP Zone I, with 9 (12.05%) in the aflibercept arm and 5 (12.5%) in the laser arm.

Overall, for the study 20275 there is no indication that the 89 subjects included in the study 20275 relevantly differed from the overall population in Study 20090.

3. Medical history, prior and concomitant medication or treatments

Study 20090

All SAF subjects (100%) had medical history findings (excluding ROP) that started before the start of study intervention and were considered relevant to the study. The most frequent PT in both arms were neonatal respiratory distress syndrome, bronchopulmonary dysplasia, and anaemia neonatal (in 66.7%, 64.0%, and 58.7% of subjects in the aflibercept arm and 68.4%, 76.3%, and 73.7% of subjects in the laser arm, respectively).

Overall, there were no considerable differences between treatment arms (using a difference of >10%) in medical history findings by primary SOC, with the exception of blood and lymphatic system disorders (84.0% of aflibercept arm subjects versus 97.4% of laser arm subjects), cardiac disorders (13.3% of aflibercept arm subjects versus 26.3% of laser arm subjects), gastrointestinal disorders (57.3% of aflibercept arm subjects versus 34.2% of laser arm subjects), and metabolism and nutrition disorders (41.3% of aflibercept arm subjects versus 55.3% of laser arm subjects).

In total, 75 (66.4%) subjects had mothers with medical history findings; 54 (72.0%) subjects in the aflibercept arm and 21 (55.3%) subjects in the laser arm. All maternal medical history findings by preferred term were reported in $\leqslant$10.5% of subjects in either treatment arm.

For the prior medication ended before study intervention, in both arms the most frequent PT were ophthalmologicals, stomatological preparations, and other respiratory system products (in 98.7%, 97.3%, and 96.0% of subjects in the aflibercept arm, respectively, and in 100% of subjects in the laser arm for all 3 classes). With the exception of antineoplastic and immunomodulating agents (12.0% of aflibercept arm subjects versus no laser arm subjects) and systemic hormonal preparations excluding sex hormones and insulins (52.0% of aflibercept arm subjects versus 71.1% of laser arm subjects), there were no considerable differences between treatment arms in prior medications by ATC class.

Overall, all 113 (100%) subjects took at least one concomitant medication during the study. There were no considerable differences between treatment arms in concomitant medications by ATC class, with the exception of anti-infectives for systemic use (97.3% of aflibercept arm subjects and 81.6% of laser arm subjects), antineoplastic and immunomodulating agents (33.3% of aflibercept arm subjects versus 13.2% of laser arm subjects), and genitourinary system and sex hormones (73.3% of aflibercept arm subjects versus 55.3% of laser arm subjects).

At baseline, 43 aflibercept arm subjects (57.3%) and 25 laser arm subjects (67.6%) had oxygen supplementation. At the week 24 visit, 11 aflibercept arm subjects (16.2%) and 8 laser arm subjects (22.2%) had oxygen supplementation since the previous visit.

Study 20275

There is no indication that the 89 subjects included in the interim analysis relevantly differed from the overall population in Study 20090.

Adverse events

1. Common adverse event

Treatment-emergent AE (TEAE) were defined as AE observed or reported after the first and not later than 30 days after the last administration of study treatment.

Study 20090

In the study 20090, TEAE were reported for a total of 84 subjects (74.3%) with ocular TEAE in treated eyes for 43 subjects (38.1%) and systemic TEAE for 63 (55.8%) subjects. The proportions of subjects with TEAE was similar between the two treatment arms (aflibercept 74.7% vs laser 73.7%). Moreover, ocular TEAE in the non-treated eye were reported for one subject.

Ocular TEAE in treated eyes were balanced in the two treatment arms (aflibercept 38.7% vs laser 36.8%) while systemic TEAE were more pronounced in the laser arm (aflibercept 52.0% vs laser 63.2%).

Overall, SAE were reported for 40 subjects (35.4%). In the cross-treatment arm comparison, the proportion of subjects reported with ocular SAE was slightly higher in the aflibercept arm (aflibercept 13.3% vs laser 7.9%) whereas the proportion of subjects reported with systemic SAE was higher in the laser arm (aflibercept 24.0% vs laser 36.8%).

TESAE were reported for 19 subjects (16.8%). TEAE with fatal outcome was reported in 1 subject (0.9%). The overall summary of TEAE were similar between treatment arms, with the exception that the proportion of subjects reported with TESAE was higher in the laser arm (aflibercept 12.0% vs laser 26.3%) and the difference was mainly driven by systemic TESAE (aflibercept 6.7% vs laser 18.4%). Most of the TEAE were mild or moderate in intensity, and severe TEAE were reported in 8 (10.7%) subjects in the aflibercept arm and 5 (13.2%) in the laser arm.

Table 3: Adverse events: overall summary (SAF)

	Aflibercept N=75 (100%)	Laser N=38 (100%)	Total N=113 (100%)
Any TEAE	56 (74.7%)	28 (73.7%)	84 (74.3%)
Any ocular TEAE in treated eye	29 (38.7%)	14 (36.8%)	43 (38.1%)
Any ocular TEAE in non treated eye	1 (1.3%)	0	1 (0.9%)
Any systemic TEAE	39 (52.0%)	24 (63.2%)	63 (55.8%)
Any aflibercept-related TEAE	3 (4.0%)	1 (2.6%)	4 (3.5%)
Any photocoagulation-related TEAE	1 (1.3%)	8 (21.1%)	9 (8.0%)
Any TEAE related to injection procedure	15 (20.0%)	0	15 (13.3%)
Any TEAE related to procedures required by the protocol	8 (10.7%)	7 (18.4%)	15 (13.3%)
Any TEAE leading to discontinuation of study intervention	3 (4.0%)	1 (2.6%)	4 (3.5%)
Any SAE	24 (32.0%)	16 (42.1%)	40 (35.4%)
Any ocular SAE	10 (13.3%)	3 (7.9%)	13 (11.5%)
Any systemic SAE	18 (24.0%)	14 (36.8%)	32 (28.3%)
Any aflibercept-related SAE	1 (1.3%)	1 (2.6%)	2 (1.8%)
Any photocoagulation-related SAE	0	0	0
Any SAE related to injection procedure	1 (1.3%)	0	1 (0.9%)
Any SAE related to procedures required by the protocol	0	0	0
Any SAE leading to discontinuation of study intervention	2 (2.7%)	1 (2.6%)	3 (2.7%)
Any TESAE	9 (12.0%)	10 (26.3%)	19 (16.8%)
Any ocular TESAE	6 (8.0%)	3 (7.9%)	9 (8.0%)
Any systemic TESAE	5 (6.7%)	7 (18.4%)	12 (10.6%)
Any aflibercept-related TESAE	0	1 (2.6%)	1 (0.9%)
Any photocoagulation-related TESAE	0	0	0
Any TESAE related to injection procedure	1 (1.3%)	0	1 (0.9%)
Any TESAE related to procedures required by the protocol	0	0	0
Any TESAE leading to discontinuation of study intervention	2 (2.7%)	1 (2.6%)	3 (2.7%)
TEAE with outcome death	1 (1.3%)	0	1 (0.9%)

Source: Module 5.3.5.1 (ROP), Report PH-41617, Table 14.3.1 / 2, Table 14.3.1 / 5
End of table
SAF = safety analysis set; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent-emergent serious adverse event.

Study 20275

In Study 20275, there were no TEAEs by definition, as no study treatment is administered. AE causality in Study 20275 was assessed based on relationship to treatment or procedure in Study 20090.

All subjects

For the 89 subjects who entered the extension Study 20275, the number of events that occurred between start of study treatment in Study 20090 and 1 year of chronological age are summarized below.

Table 4: Overall summary of number of subjects with any adverse events until 1 year of chronological age (Unilaterally & bilaterally treated subjects in 20090) (all subjects who entered the extension Study 20275)

	Aflibercept N=60 (100%)	Laser N=29 (100%)	Total N=89 (100%)
Any AE	56 (93.3)	26 (89.7)	82 (92.1)
Any ocular AE	35 (58.3)	16 (55.2)	51 (57.3)
Any ocular AE on treated eye	34 (56.7)	16 (55.2)	50 (56.2)
Any ocular AE on non treated eye	2 (3.3)	0	2 (2.2)
Any non ocular AE	48 (80.0)	24 (82.8)	72 (80.9)
Maximum intensity for any AE			
MILD	27 (45.0)	11 (37.9)	38 (42.7)
MODERATE	20 (33.3)	8 (27.6)	28 (31.5)
SEVERE	9 (15.0)	7 (24.1)	16 (18.0)
Any aflibercept-related AE	3 (5.0)	1 (3.4)	4 (4.5)
Maximum intensity for aflibercept-related AE			
MILD	2 (3.3)	0	2 (2.2)
MODERATE	0	1 (3.4)	1 (1.1)
SEVERE	1 (1.7)	0	1 (1.1)
Any photocoagulation-related AE	2 (3.3)	9 (31.0)	11 (12.4)
Maximum intensity for photocoagulation-related AE			
MILD	2 (3.3)	4 (13.8)	6 (6.7)
MODERATE	0	5 (17.2)	5 (5.6)
Any AE related to injection procedure	12 (20.0)	0	12 (13.5)
Any AE related to procedures required by the protocol	5 (8.3)	4 (13.8)	9 (10.1)
Any AE leading to discontinuation of study intervention	1 (1.7)	0	1 (1.1)
Any SAE	15 (25.0)	14 (48.3)	29 (32.6)
Any aflibercept-related SAE	1 (1.7)	1 (3.4)	2 (2.2)
Any photocoagulation-related SAE	0	0	0
Any SAE related to injection procedure	1 (1.7)	0	1 (1.1)
Any SAE related to procedures required by the protocol	0	0	0
Any SAE leading to discontinuation of study intervention	0	0	0
AE with outcome death	0	0	0

Study intervention was in previous Study 20090
Rescue treatment for aflibercept was laser, rescue treatment for laser was aflibercept
AE = adverse event; SAE = serious adverse event

Overall, AE were reported for a total of 82 (92.1%) subjects; 50 (56.2%) subjects for the treated eye and 2 (2.2%) subjects for the non-treated eye. Non-ocular systemic AE were reported for 72 (80.9%) subjects.

The proportion of subjects with overall AE was slightly higher in the aflibercept arm compared to the laser arm (93.3% vs. 89.7%), while the proportion of subjects with overall SAE was lower in the aflibercept arm compared to the laser arm (25.0% vs 48.3%).

Patients who completed the 1-year visit and 2-years visit

For the 60 subjects who completed the visits until 1 year of chronological age, 37 (94.9%) subjects treated at baseline with aflibercept in the Study 20090 presented with at least 1 AE, compared to 20 (95.2%) subjects treated with laser at baseline in Study 20090.

Table 5: Overall summary of number of subjects with any adverse events until 1 year of chronological age (Unilaterally & bilaterally treated subjects in 20090) (all subjects who completed 1 year of chronological age)

	Aflibercept N=39 (100%)	Laser N=21 (100%)	Total N=60 (100%)
Number (%) of subjects with adverse events			
Any ocular AE	23 (59.0)	12 (57.1)	35 (58.3)
Any ocular AE on treated eye	22 (56.4)	12 (57.1)	34 (56.7)
Any ocular AE on non treated eye	2 (5.1)	0	2 (3.3)
Any systemic AE	33 (84.6)	18 (85.7)	51 (85.0)
Any AE	37 (94.9)	20 (95.2)	57 (95.0)
Maximum intensity for any AE			
MILD	20 (51.3)	10 (47.6)	30 (50.0)
MODERATE	12 (30.8)	4 (19.0)	16 (26.7)
SEVERE	5 (12.8)	6 (28.6)	11 (18.3)
Any aflibercept-related AE	1 (2.6)	1 (4.8)	2 (3.3)
Maximum intensity for aflibercept-related AE			
MILD	1 (2.6)	0	1 (1.7)
MODERATE	0	1 (4.8)	1 (1.7)
Any photocoagulation-related AE	0	6 (28.6)	6 (10.0)
Maximum intensity for photocoagulation-related AE			
MILD	0	3 (14.3)	3 (5.0)
MODERATE	0	3 (14.3)	3 (5.0)
Any AE related to injection procedure	7 (17.9)	0	7 (11.7)
Any AE related to procedures required by the protocol	2 (5.1)	3 (14.3)	5 (8.3)
Any AE leading to discontinuation of study intervention*	0	0	0
Any SAE	7 (17.9)	10 (47.6)	17 (28.3)
Any aflibercept-related SAE	0	1 (4.8)	1 (1.7)
Any photocoagulation-related SAE	0	0	0
Any SAE related to injection procedure	0	0	0
Any SAE related to procedures required by the protocol	0	0	0
Any SAE leading to discontinuation of study intervention	0	0	0
AE with outcome death	0	0	0

All events with start date on birth date + 365 days are included.
AEs in treated eye refers to study treatment in study 20090.
*The subject who discontinued in Table 14.3.1/1 is from FIREFLEYE study who did not reach the 1 year visit and is therefore not showing in this Table (by definition, FIREFLEYE next did not include any study intervention during the study).
Study intervention was in previous study 20090.
AE = adverse event; SAE = serious adverse event

Regarding long-term safety of study 20275, the MAH submitted a first interim analysis of the data at 2 years of chronological age for more than half of the patient during the procedure and completed data at 2 years of chronological age for all patients will be submitted in June 2023.

The Applicant also committed to the yearly provision of longer-term data.

2. Ocular adverse events

Study 20090

The most frequently affected primary SOC were eye disorders in 30 (26.5%) subjects in total (aflibercept 20 [26.7%] vs laser 10 [26.3%]), followed by infections and infestations in 7 (6.2%) subjects (aflibercept 3 [4.0%] subjects vs laser 4 [10.5%]). All other primary SOC were reported in ⩽5% of subjects in total.

The most frequent ocular TEAE by Preferred term (PT) in treated eyes (with the incidence > 5% in either treatment arm) were retinal hemorrhage (aflibercept 6.7% vs laser 13.2%), retinal detachment (aflibercept 5.3% vs laser 5.3%), conjunctival hemorrhage (aflibercept 5.3% vs laser 0%), and eyelid oedema (aflibercept 2.7% vs laser 7.9%) in the eye disorders SOC; and conjunctivitis (aflibercept 4.0% vs laser 10.5%) in the infections and infestations SOC.

All other ocular TEAE in treated eyes were reported in less than 3% of subjects in total.

Table 6: Number of subjects with ocular treatment-emergent adverse events in treated eyes (unilaterally & bilaterally treated subjects) by Preferred Term (SAF)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept N=75 (100%)	Laser N=38 (100%)	Total N=113 (100%)
Number (%) of subjects with at least one such adverse event	29 (38.7%)	14 (36.8%)	43 (38.1%)
Eye disorders	20 (26.7%)	10 (26.3%)	30 (26.5%)
Retinal haemorrhage	5 (6.7%)	5 (13.2%)	10 (8.8%)
Eyelid oedema	2 (2.7%)	3 (7.9%)	5 (4.4%)
Retinal detachment	4 (5.3%)	2 (5.3%)	6 (5.3%)
Conjunctival haemorrhage	4 (5.3%)	0	4 (3.5%)
Retinopathy of prematurity	2 (2.7%)	1 (2.6%)	3 (2.7%)
Conjunctival oedema	2 (2.7%)	0	2 (1.8%)
Corneal oedema	1 (1.3%)	1 (2.6%)	2 (1.8%)
Keratitis	1 (1.3%)	0	1 (0.9%)
Lenticular opacities	1 (1.3%)	0	1 (0.9%)
Retinal artery occlusion	1 (1.3%)	0	1 (0.9%)
Retinal vascular disorder	1 (1.3%)	0	1 (0.9%)
Swelling of eyelid	1 (1.3%)	0	1 (0.9%)
Vitreoretinal traction syndrome	1 (1.3%)	0	1 (0.9%)
Vitreous haemorrhage	1 (1.3%)	1 (2.6%)	2 (1.8%)
Vitreous opacities	1 (1.3%)	0	1 (0.9%)
Iris adhesions	0	1 (2.6%)	1 (0.9%)
Macular fibrosis	1 (1.3%)	0	1 (0.9%)
General disorders and administration site conditions	5 (6.7%)	0	5 (4.4%)
Injection site haemorrhage	3 (4.0%)	0	3 (2.7%)
Injection site reaction	1 (1.3%)	0	1 (0.9%)
Crying	1 (1.3%)	0	1 (0.9%)
Infections and infestations	3 (4.0%)	4 (10.5%)	7 (6.2%)
Conjunctivitis	3 (4.0%)	4 (10.5%)	7 (6.2%)
Injury, poisoning and procedural complications	2 (2.7%)	1 (2.6%)	3 (2.7%)
Post procedural oedema	0	1 (2.6%)	1 (0.9%)
Multiple use of single-use product	1 (1.3%)	0	1 (0.9%)
Overdose	1 (1.3%)	0	1 (0.9%)
Investigations	3 (4.0%)	0	3 (2.7%)
Intraocular pressure increased	3 (4.0%)	0	3 (2.7%)

SAF: safety analysis set; N: number of subjects; MedDRA: Medical Dictionary for Regulatory Activities.
Source: Module 5.3.5.1 PH-41617, Table 14.3.1.1/13

Severity

Most ocular TEAEs in treated eyes were either mild or moderate in intensity. Severe ocular TEAEs were reported in 2 (2.7%) subjects in the aflibercept arm and 1 (2.6%) in the laser arm.

Relation to study treatment/procedure

Aflibercept-related ocular TEAEs were reported in treated eyes of 3 subjects (4.0%), one event of retinal artery occlusion, retinal vascular disorder, and vitreous opacities in each subject, in the aflibercept arm and retinal detachment in 1 subject (2.6%) in the laser arm.

The event retinal artery occlusion was reported for 1 subject in the aflibercept arm in 2 eyes. Both events were non-serious and were mild in intensity. The action taken with aflibercept did not change and the outcome was resolved for both events. The case of retinal artery occlusion is nonetheless of concern considering that this topic is closely monitored in PSUR in adult population and its causality to aflibercept is still unknown. The event occurred in the two eyes for one subject, was non-serious and severity was mild. Based on this single case, no sufficient information are available to associate this case with a thromboembolic or a local vasoconstriction cause nor of IOP increase related to anti-VEGF treatment

with aflibercept. Overall, this topic will be further monitored in post-marketing surveillance through the PSUR and in the follow-up study 20275 up to 5 years of chronological age.

The event retinal vascular disorder was reported for 1 subject in the aflibercept arm in 2 eyes. Both events were non-serious and were moderate in intensity. The action taken with aflibercept did not change and the outcome was resolved for both events.

The event vitreous opacities was reported for 1 subject in the aflibercept arm in 2 eyes. Both events were non-serious and were mild in intensity. The action taken with aflibercept did not change and the outcome was resolved for both events.

The event retinal detachment was reported for 1 subject in the laser arm in the right eye twice. The subject first experienced stage 4a of ROP and then the event progressed to stage 4b. Both events were serious and were moderate in intensity. Action taken with aflibercept did not change. The outcome was not resolved for the first event and was considered as resolving for the second event.

Injection procedure-related ocular TEAE in treated eyes were reported for 14 (18.7%) subjects in the aflibercept arm; the most common were conjunctival haemorrhage in 4 (5.3%) subjects, followed by retinal haemorrhage, injection site haemorrhage, and intraocular pressure increased (each in 3 [4.0%] subjects).

Regarding ocular infections, a total of 7 subjects presented the event conjonctivitis with a higher proportion in the laser arm than in the aflibercept arm (10.5% vs 4,0%). Considering that premature infants are more prone to infections, endophtalmitis, a known risk of anti-VEGF drugs by IVT route is of concern but no case was reported in study 20090. Additional warnings have been proposed by the Applicant in sections 4.2 and 4.4 of the SmPC for ROP patients which are endorsed.

Study 20275

All subjects

For the 89 subjects who entered the extension study 20275, the proportion of subjects at the cut-off date of 01 MAR 2021 with ocular AE was similar in the 2 treatment arms (aflibercept 34 [56.7%] vs laser 16 [55.2%]).

The most frequently affected primary SOC were *eye disorders* in 42 (47.2%) subjects in total (aflibercept 28 [46.7%] vs laser 14 [48.3%]), followed by *infections and infestations* in 6 (6.7%) subjects (aflibercept 3 [5.0%] subjects vs laser 3 [10.3%]). All other primary SOCs were reported in ⩽5% of subjects in total.

The most frequent ocular AEs by PT in treated eyes, occurring in more than 10% of the subjects in either arm, were myopia (aflibercept 15.0% vs laser 17.2%), astigmatism (aflibercept 8.3% vs laser 20.7%), retinal haemorrhage (aflibercept 8.3% vs laser 17.2%), conjunctivitis (aflibercept 5.0% vs laser 10.3%), and strabismus (aflibercept 3.3% vs laser 10.3%). All other ocular AE in treated eyes were reported in less than 10% of subjects in total.

Table 7: Number of subjects with ocular adverse events until 1 year of chronological age in treated eyes in previous study 20090 by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects in 20090) (all subjects entering extension)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	Aflibercept N=60 (100%)	Laser Events	Laser N=29 (100%)	Total Events	Total N=89 (100%)
Number (%) of subjects with at least one adverse event	114	34 (56.7%)	62	16 (55.2%)	176	50 (56.2%)
Congenital, familial and genetic disorders	0	0	1	1 (3.4%)	1	1 (1.1%)
Congenital myopia	0	0	1	1 (3.4%)	1	1 (1.1%)
Eye disorders	93	28 (46.7%)	50	14 (48.3%)	143	42 (47.2%)
Amblyopia	0	0	4	2 (6.9%)	4	2 (2.2%)
Astigmatism	8	5 (8.3%)	12	6 (20.7%)	20	11 (12.4%)
Cataract	0	0	1	1 (3.4%)	1	1 (1.1%)
Conjunctival haemorrhage	4	3 (5.0%)	0	0	4	3 (3.4%)
Conjunctival oedema	4	2 (3.3%)	0	0	4	2 (2.2%)
Conjunctivitis allergic	1	1 (1.7%)	0	0	1	1 (1.1%)
Corneal oedema	1	1 (1.7%)	2	1 (3.4%)	3	2 (2.2%)
Eye movement disorder	1	1 (1.7%)	0	0	1	1 (1.1%)
Eyelid oedema	4	2 (3.3%)	2	1 (3.4%)	6	3 (3.4%)
Hypermetropia	1	1 (1.7%)	0	0	1	1 (1.1%)
Iris adhesions	0	0	1	1 (3.4%)	1	1 (1.1%)
Keratitis	2	1 (1.7%)	0	0	2	1 (1.1%)
Lenticular opacities	2	1 (1.7%)	0	0	2	1 (1.1%)
Macular degeneration	1	1 (1.7%)	0	0	1	1 (1.1%)
Macular fibrosis	5	3 (5.0%)	0	0	5	3 (3.4%)
Myopia	16	9 (15.0%)	9	5 (17.2%)	25	14 (15.7%)
Retinal artery occlusion	2	1 (1.7%)	0	0	2	1 (1.1%)
Retinal detachment	11	3 (5.0%)	2	1 (3.4%)	13	4 (4.5%)
Retinal haemorrhage	6	5 (8.3%)	7	5 (17.2%)	13	10 (11.2%)
Retinal neovascularisation	3	3 (5.0%)	0	0	3	3 (3.4%)
Retinal vascular disorder	4	2 (3.3%)	0	0	4	2 (2.2%)
Retinopathy of prematurity	4	2 (3.3%)	2	1 (3.4%)	6	3 (3.4%)
Saccadic eye movement	1	1 (1.7%)	0	0	1	1 (1.1%)
Strabismus	3	2 (3.3%)	7	3 (10.3%)	10	5 (5.6%)
Swelling of eyelid	2	1 (1.7%)	0	0	2	1 (1.1%)
Vitreoretinal traction syndrome	2	1 (1.7%)	0	0	2	1 (1.1%)
Vitreous haemorrhage	2	2 (3.3%)	1	1 (3.4%)	3	3 (3.4%)
Vitreous opacities	3	2 (3.3%)	0	0	3	2 (2.2%)
General disorders and administration site conditions	4	3 (5.0%)	0	0	4	3 (3.4%)
Injection site haemorrhage	2	2 (3.3%)	0	0	2	2 (2.2%)
Injection site reaction	2	1 (1.7%)	0	0	2	1 (1.1%)
Infections and infestations	6	3 (5.0%)	5	3 (10.3%)	11	6 (6.7%)
Conjunctivitis	6	3 (5.0%)	5	3 (10.3%)	11	6 (6.7%)
Injury, poisoning and procedural complications	2	2 (3.3%)	2	1 (3.4%)	4	3 (3.4%)
Multiple use of single-use product	1	1 (1.7%)	0	0	1	1 (1.1%)
Overdose	1	1 (1.7%)	0	0	1	1 (1.1%)
Post procedural oedema	0	0	2	1 (3.4%)	2	1 (1.1%)
Investigations	4	3 (5.0%)	0	0	4	3 (3.4%)
Intraocular pressure increased	4	3 (5.0%)	0	0	4	3 (3.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	1 (1.7%)	0	0	4	1 (1.1%)
Retinoblastoma	4	1 (1.7%)	0	0	4	1 (1.1%)
Nervous system disorders	0	0	4	2 (6.9%)	4	2 (2.2%)
Nystagmus	0	0	4	2 (6.9%)	4	2 (2.2%)
Vascular disorders	1	1 (1.7%)	0	0	1	1 (1.1%)
Vasodilatation	1	1 (1.7%)	0	0	1	1 (1.1%)

Adverse events are sorted in alphabetical order by primary SOC and preferred term.
A subject is counted only once within each preferred term or any primary SOC.
All events with start date on birth date + 365 days are included.
Study intervention as in previous study 20090.
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From all 89 subjects who entered the extension Study 20275, a total of 8 eyes (from 4 subjects in each arm) were not treated in Study 20090; 2 (25.0%) subjects in the aflibercept arm experienced events, no subjects in the laser arm experienced events, one (25.0%) subject was reported with events (retinal haemorrhage, ROP, and vitreoretinal traction syndrome) in the SOC eye disorders and 1 (25.0%) subject was reported with an event (conjunctivitis) in the SOC infections and infestations.

Overall, ocular AE until the visit at 1 year of chronological age in eyes treated previously in Study 20090 were reported for a total of 50 (56.2%) subjects. These results were similar to those described above for all subjects who entered the extension Study 20275

Severity

For the 89 subjects who entered the extension study 20275, most of the ocular AE in treated eyes were mild or moderate in intensity.

In the treated eye, four (6.7%) subjects in the aflibercept arm and no subjects in the laser arm were reported with ocular events of severe intensity. All severe events occurred for the SOC Eye disorders; the PTs for the severe events were as follows: 1 (1.7%) subject each was reported with AE of severe intensity for macular fibrosis (in a subject with retinal detachment), myopia, retinal neovascularization, and vitreous opacities; 3 (5.0%) subjects were reported with AE of severe intensity for retinal detachment.

For all 60 subjects who completed the visit at 1 year of chronological age, in the non-treated eye AEs were mild in intensity for the majority. One (33.3%) subject in the aflibercept arm was reported with the PT retinopathy of prematurity of severe intensity.

Relation to study treatment/procedure

For the 89 subjects who entered the extension study 20275, ocular AE until the visit at 1 year of chronological age in eyes treated previously in Study 20090, in the treated eyes, 3 subjects (5.0%) in the aflibercept arm and 1 (3.4%) subject in the laser arm experienced aflibercept-related ocular AEs, 2 (3.3%) and 9 (31.0%) subjects experienced laser-related ocular AEs, and 11 (18.3%) and 0 subjects experienced injection-related ocular AEs, respectively. Retinal detachment was reported for 1 (3.4%) subject in the laser arm. In the aflibercept arm events of retinal detachment, macular fibrosis, retinal vascular disorder, retinal haemorrhage, and retinal neovascularisation were reported in 1 subject, and retinal artery occlusion and vitreous opacity were each reported in 1 subject.

Table 8: Number of subjects with ocular aflibercept-related adverse events until 1 year of chronological age in treated eyes in previous study 20090 by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects in 20090) (all subjects entering extension)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept		Laser		Total	
	Events	N=60 (100%)	Events	N=29 (100%)	Events	N=89 (100%)
Number (%) of subjects with at least one adverse event	14	3 (5.0%)	2	1 (3.4%)	16	4 (4.5%)
Eye disorders	14	3 (5.0%)	2	1 (3.4%)	16	4 (4.5%)
Macular fibrosis	2	1 (1.7%)	0	0	2	1 (1.1%)
Retinal artery occlusion	2	1 (1.7%)	0	0	2	1 (1.1%)
Retinal detachment	4	1 (1.7%)	2	1 (3.4%)	6	2 (2.2%)
Retinal haemorrhage	1	1 (1.7%)	0	0	1	1 (1.1%)
Retinal neovascularisation	1	1 (1.7%)	0	0	1	1 (1.1%)
Retinal vascular disorder	2	1 (1.7%)	0	0	2	1 (1.1%)
Vitreous opacities	2	1 (1.7%)	0	0	2	1 (1.1%)

Adverse events are sorted in alphabetical order by primary SOC and preferred term.
A subject is counted only once within each preferred term or any primary SOC.
All events with start date on birth date + 365 days are included.
Study intervention as in previous study 20090.
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Concerning the laser-related ocular AE in treated eye, the most reported events were myopia (4AE, 13.8%) and retinal haemorrhage (4AE, 13.8%).

Concerning the injection procedure-related AE in treated eye, the event consisted as follow:

Table 9: Number of subjects with ocular injection procedure related adverse events in treated eyes in previous study 20090 by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects in 20090) (all subjects entering extension)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	 N=60 (100%)	Laser Events	 N=29 (100%)	Total Events	 N=89 (100%)
Number (%) of subjects with at least one adverse event	18	11 (18.3%)	0	0	18	11 (12.4%)
Eye disorders	10	6 (10.0%)	0	0	10	6 (6.7%)
Conjunctival haemorrhage	4	3 (5.0%)	0	0	4	3 (3.4%)
Corneal oedema	1	1 (1.7%)	0	0	1	1 (1.1%)
Retinal haemorrhage	3	2 (3.3%)	0	0	3	2 (2.2%)
Vitreous opacities	2	1 (1.7%)	0	0	2	1 (1.1%)
General disorders and administration site conditions	4	3 (5.0%)	0	0	4	3 (3.4%)
Injection site haemorrhage	2	2 (3.3%)	0	0	2	2 (2.2%)
Injection site reaction	2	1 (1.7%)	0	0	2	1 (1.1%)
Investigations	4	3 (5.0%)	0	0	4	3 (3.4%)
Intraocular pressure increased	4	3 (5.0%)	0	0	4	3 (3.4%)

Adverse events are sorted in alphabetical order by primary SOC and preferred term.
A subject is counted only once within each preferred term or any primary SOC.
Study intervention as in previous study 20090.
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Patients who completed the 1-year visit and 2-years visit

For the 60 subjects who had completed the visit at 1 year of chronological age, among unilaterally and bilaterally-treated subjects, the aflibercept arm had no subjects with retinal detachment and 1 (2.6%) subject with retinal artery occlusion, as compared to 1 (4.8%) subject with retinal detachment in the laser arm.

Injection related event consisted of the three SOC *Eye disorder, General disorder and administration site conditions* and *Investigations* with the PT conjunctival haemorrhage (5,1%), retinal haemorrhage (2,6%), injection site haemorrhage (2,6%), injection site reaction (2,6%) and intraocular pressure increased (5,1%). No injection related event was reported in the laser arm.

Laser related event consisted of in the laser arm; congenital myopia (4,8%), astigmatism (4,8%), corneal oedema (4,8%), myopia (9,5%), retinal haemorrhage (19%) and post-procedural oedema (4,8%).

Overall, AE causality in Study 20275 was assessed based on relationship to treatment or procedure in Study 20090.

Regarding long-term safety of study 20275, the MAH submitted an interim analysis of the data at 2 years of chronological age for more than half of the patient during the procedure and completed data at 2 years of chronological for all patients will be submitted in June 2023.

Overall, data leave residual uncertainties regarding long-term safety that can be accepted at time of opinion but will be reduced through data provision.

3. Systemic adverse events

Study 20090

The proportion of subjects with any systemic TEAE was higher in the laser arm compared to the aflibercept arm (aflibercept 52.0% vs laser laser 63.2%).

For subjects with systemic TEAE, the most frequent systemic TEAE by PTs, occurring in more than 5% of the subjects in either arm, were apnoea (aflibercept 2.7% vs laser 7.9%), umbilical hernia (aflibercept 1.3% vs laser 7.9%), haemorrhage subcutaneous (aflibercept 0.0% vs laser 7.9%), anaemia (aflibercept 1.3% vs laser 5.3%), and anaemia neonatal, bacterial disease carrier, and infantile apnoea (each in 5.3% subjects in the laser arm only). All other systemic TEAEs in treated eyes were reported in ≤2.7 % of subjects in total.

Table 10: Overall summary of number of subjects with systemic treatment emergent adverse events by PT (Unilaterally & bilaterally treated subjects) (safety analysis set)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	Aflibercept N=75 (100%)	Laser Events	Laser N=38 (100%)	Total Events	Total N=113 (100%)
Number (%) of subjects with at least one such adverse event	90	39 (52.0%)	47	24 (63.2%)	137	63 (55.8%)
Blood and lymphatic system disorders	2	1 (1.3%)	5	4 (10.5%)	7	5 (4.4%)
Anaemia	1	1 (1.3%)	3	2 (5.3%)	4	3 (2.7%)
Anaemia neonatal	0	0	2	2 (5.3%)	2	2 (1.8%)
Splenomegaly	1	1 (1.3%)	0	0	1	1 (0.9%)
Cardiac disorders	4	4 (5.3%)	1	1 (2.6%)	5	5 (4.4%)
Bradycardia	2	2 (2.7%)	0	0	2	2 (1.8%)
Pulmonary valve stenosis	0	0	1	1 (2.6%)	1	1 (0.9%)
Sinus tachycardia	1	1 (1.3%)	0	0	1	1 (0.9%)
Tachycardia	1	1 (1.3%)	0	0	1	1 (0.9%)
Congenital, familial and genetic disorders	3	3 (4.0%)	1	1 (2.6%)	4	4 (3.5%)
Ankyloglossia congenital	1	1 (1.3%)	0	0	1	1 (0.9%)
Congenital arterial malformation	1	1 (1.3%)	0	0	1	1 (0.9%)
Cryptorchism	1	1 (1.3%)	0	0	1	1 (0.9%)
Laryngomalacia	0	0	1	1 (2.6%)	1	1 (0.9%)
Ear and labyrinth disorders	0	0	1	1 (2.6%)	1	1 (0.9%)
Auditory disorder	0	0	1	1 (2.6%)	1	1 (0.9%)
Endocrine disorders	2	2 (2.7%)	0	0	2	2 (1.8%)
Adrenomegaly	1	1 (1.3%)	0	0	1	1 (0.9%)
Cushingoid	1	1 (1.3%)	0	0	1	1 (0.9%)
Gastrointestinal disorders	11	9 (12.0%)	10	8 (21.1%)	21	17 (15.0%)
Umbilical hernia	1	1 (1.3%)	3	3 (7.9%)	4	4 (3.5%)
Inguinal hernia	3	2 (2.7%)	1	1 (2.6%)	4	3 (2.7%)
Diarrhoea	1	1 (1.3%)	1	1 (2.6%)	2	2 (1.8%)
Gastrooesophageal reflux disease	1	1 (1.3%)	1	1 (2.6%)	2	2 (1.8%)
Abdominal distension	1	1 (1.3%)	0	0	1	1 (0.9%)
Abdominal pain	0	0	1	1 (2.6%)	1	1 (0.9%)
Cheilitis	1	1 (1.3%)	0	0	1	1 (0.9%)
Dysphagia	1	1 (1.3%)	0	0	1	1 (0.9%)
Enterocolitis	0	0	1	1 (2.6%)	1	1 (0.9%)
Flatulence	0	0	1	1 (2.6%)	1	1 (0.9%)
Gastric haemorrhage	1	1 (1.3%)	0	0	1	1 (0.9%)
Necrotising colitis	0	0	1	1 (2.6%)	1	1 (0.9%)
Vomiting	1	1 (1.3%)	0	0	1	1 (0.9%)
General disorders and administration site conditions	4	4 (5.3%)	0	0	4	4 (3.5%)
Pyrexia	3	3 (4.0%)	0	0	3	3 (2.7%)
Pain	1	1 (1.3%)	0	0	1	1 (0.9%)
Hepatobiliary disorders	2	1 (1.3%)	0	0	2	1 (0.9%)
Cholestasis	1	1 (1.3%)	0	0	1	1 (0.9%)
Hepatic lesion	1	1 (1.3%)	0	0	1	1 (0.9%)
Infections and infestations	12	9 (12.0%)	12	11 (28.9%)	24	20 (17.7%)
Bronchiolitis	3	2 (2.7%)	1	1 (2.6%)	4	3 (2.7%)
Rhinitis	2	2 (2.7%)	1	1 (2.6%)	3	3 (2.7%)
Bacterial disease carrier	0	0	2	2 (5.3%)	2	2 (1.8%)
Oral fungal infection	1	1 (1.3%)	1	1 (2.6%)	2	2 (1.8%)
Bacteriuria	0	0	1	1 (2.6%)	1	1 (0.9%)
COVID-19	1	1 (1.3%)	0	0	1	1 (0.9%)
Cytomegalovirus infection	0	0	1	1 (2.6%)	1	1 (0.9%)
Ear infection	1	1 (1.3%)	0	0	1	1 (0.9%)
Infection	1	1 (1.3%)	0	0	1	1 (0.9%)
Nasopharyngitis	1	1 (1.3%)	0	0	1	1 (0.9%)
Pneumonia	1	1 (1.3%)	0	0	1	1 (0.9%)
Respiratory tract infection	0	0	1	1 (2.6%)	1	1 (0.9%)
Rhinovirus infection	0	0	1	1 (2.6%)	1	1 (0.9%)
Sepsis	0	0	2	1 (2.6%)	2	1 (0.9%)
Upper respiratory tract infection	1	1 (1.3%)	0	0	1	1 (0.9%)
Urinary tract infection	0	0	1	1 (2.6%)	1	1 (0.9%)

Injury, poisoning and procedural complications	1	1 (1.3%)	0	0	1	1 (0.9%)
Contusion	1	1 (1.3%)	0	0	1	1 (0.9%)
Investigations	11	6 (8.0%)	1	1 (2.6%)	12	7 (6.2%)
Oxygen saturation decreased	4	3 (4.0%)	0	0	4	3 (2.7%)
Brain stem auditory evoked response abnormal	3	2 (2.7%)	0	0	3	2 (1.8%)
Otoacoustic emissions test abnormal	3	2 (2.7%)	0	0	3	2 (1.8%)
C-reactive protein increased	0	0	1	1 (2.6%)	1	1 (0.9%)
Cardiac murmur	1	1 (1.3%)	0	0	1	1 (0.9%)
Metabolism and nutrition disorders	6	5 (6.7%)	0	0	6	5 (4.4%)
Alkalosis	2	1 (1.3%)	0	0	2	1 (0.9%)
Hypoglycaemia	1	1 (1.3%)	0	0	1	1 (0.9%)
Hypokalaemia	1	1 (1.3%)	0	0	1	1 (0.9%)
Hypomagnesaemia	1	1 (1.3%)	0	0	1	1 (0.9%)
Metabolic acidosis	1	1 (1.3%)	0	0	1	1 (0.9%)
Musculoskeletal and connective tissue disorders	3	3 (4.0%)	0	0	3	3 (2.7%)
Osteopenia	2	2 (2.7%)	0	0	2	2 (1.8%)
Extremity contracture	1	1 (1.3%)	0	0	1	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2 (2.7%)	0	0	2	2 (1.8%)
Haemangioma	1	1 (1.3%)	0	0	1	1 (0.9%)
Haemangioma of liver	1	1 (1.3%)	0	0	1	1 (0.9%)
Nervous system disorders	7	7 (9.3%)	1	1 (2.6%)	8	8 (7.1%)
Hypoxic-ischaemic encephalopathy	2	2 (2.7%)	0	0	2	2 (1.8%)
Intraventricular haemorrhage neonatal	1	1 (1.3%)	1	1 (2.6%)	2	2 (1.8%)
Developmental coordination disorder	1	1 (1.3%)	0	0	1	1 (0.9%)
Intraventricular haemorrhage	1	1 (1.3%)	0	0	1	1 (0.9%)
Neonatal seizure	1	1 (1.3%)	0	0	1	1 (0.9%)
Thalamus haemorrhage	1	1 (1.3%)	0	0	1	1 (0.9%)
Renal and urinary disorders	2	2 (2.7%)	3	1 (2.6%)	5	3 (2.7%)
Proteinuria	1	1 (1.3%)	1	1 (2.6%)	2	2 (1.8%)
Glycosuria	1	1 (1.3%)	0	0	1	1 (0.9%)
Haematuria	0	0	1	1 (2.6%)	1	1 (0.9%)
Leukocyturia	0	0	1	1 (2.6%)	1	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	13	11 (14.7%)	8	8 (21.1%)	21	19 (16.8%)
Apnoea	2	2 (2.7%)	3	3 (7.9%)	5	5 (4.4%)
Bronchopulmonary dysplasia	2	2 (2.7%)	0	0	2	2 (1.8%)
Infantile apnoea	0	0	2	2 (5.3%)	2	2 (1.8%)
Chronic respiratory disease	1	1 (1.3%)	0	0	1	1 (0.9%)
Cough	1	1 (1.3%)	0	0	1	1 (0.9%)
Laryngeal stenosis	0	0	1	1 (2.6%)	1	1 (0.9%)
Nasal obstruction	1	1 (1.3%)	0	0	1	1 (0.9%)
Oropharyngeal pain	1	1 (1.3%)	0	0	1	1 (0.9%)
Pneumonia aspiration	1	1 (1.3%)	0	0	1	1 (0.9%)
Pulmonary hypertension	1	1 (1.3%)	0	0	1	1 (0.9%)
Respiratory arrest	0	0	1	1 (2.6%)	1	1 (0.9%)
Respiratory distress	1	1 (1.3%)	0	0	1	1 (0.9%)
Rhonchi	1	1 (1.3%)	0	0	1	1 (0.9%)
Stridor	0	0	1	1 (2.6%)	1	1 (0.9%)
Tachypnoea	1	1 (1.3%)	0	0	1	1 (0.9%)
Skin and subcutaneous tissue disorders	5	4 (5.3%)	4	4 (10.5%)	9	8 (7.1%)
Dermatitis diaper	2	2 (2.7%)	1	1 (2.6%)	3	3 (2.7%)
Haemorrhage subcutaneous	0	0	3	3 (7.9%)	3	3 (2.7%)
Dermatitis	1	1 (1.3%)	0	0	1	1 (0.9%)
Eczema infantile	1	1 (1.3%)	0	0	1	1 (0.9%)
Intertrigo	1	1 (1.3%)	0	0	1	1 (0.9%)

Adverse events are sorted by frequency within primary SOC.
A subject is counted only once within each preferred term or any primary SOC.
Treatment emergent is defined as an AE that is observed or reported after the first and not later than 30 days after the last administration of study treat ment.
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The most reported SOC were Infections and infestations, Respiratory, thoracic and mediastinal disorders and Gastrointestinal disorders with higher rates reported in the laser arm (respectively 28.9% vs 12.0%; 21.1% vs 14.7% and 21.1% vs 12.0%).

The most reported events were apnoea (aflibercept 2.7% vs laser 7.9%), umbilical hernia (aflibercept 1.3% vs laser 7.9%), haemorrhage subcutaneous (aflibercept 0.0% vs laser 7.9%), anaemia (aflibercept 1.3% vs laser 5.3%), anaemia neonatal and infantile apnoea (each in 5.3% subjects in the laser arm vs 0% in aflibercept arm). These events are possible complications of premature infants.

However, two SOC are of concern considering higher rates reported in aflibercept arm and known mechanism of action of anti-VEGF such as Cardiac disorders (5.3% vs 2.6%) and Nervous system disorders (9.3% vs 2.6%). In Cardiac disorders SOC, two cases of bradycardia were reported in aflibercept arm. In addition, one event of developmental coordination disorders reported in aflibercept group were of concern considering existing clinical data with bevacizumab in ROP as highlighted in the PIP.

Considering uncertainties of systemic exposure in this vulnerable population including higher exposure reported from PK data compared to adult patients, and known effects of VEGF on cardiovascular systems, the MAH was requested to further discuss these imbalances of these two SOCs.

For the SOC "Cardiac disorders", 7 events were reported in total (5 in the aflibercept group and 2 events in the laser group) but the incidences at 2 years of chronological age were similar when comparing the aflibercept group to the laser group, respectively 7,6% vs 5,9%. The events occurring in the aflibercept group were all non-serious and consisted of bradycardia (n=2, 1 day and 23 days after the first dose of aflibercept, recovered), cardiac failure (n=1, 72 days after the first dose of aflibercept, not recovered), sinus tachycardia (n=1, 2 days after the first dose of aflibercept, recovered) and tachycardia (n=1, 99 days after the first dose of aflibercept, recovered). All events were assessed by the investigators as unrelated to aflibercept treatment due to plausible alternative explanations such as underlying comorbidities and/or as unlikely due to the mechanism of action of anti-VEGF. For the two events of transient tachycardia, one occurred in a context of fever and the other occurred 2 days after the first administration of aflibercept in a patient with underlying bronchopulmonary dysplasia (BPD) and pulmonary hypertension. The event of cardiac failure occurred in a patient with atrial septal defect 72 days after the first administration of aflibercept.

For the SOC "Nervous disorder", 30 events were reported in total (21 in aflibercept group and 9 in laser group) but the incidences at 2 years of chronological age were similar between both groups, respectively 19,7% vs 17,6%. The events occurring in the aflibercept group were all non-serious apart from two events, a syndrome of west occurring 7 months after the first administration of aflibercept in a patient with congenital cerebrovascular anomaly recovering after treatment and a cerebellar atrophy of the lower part pointing out to a congenital disorder and occurring 7 months after the first dose of aflibercept. In the aflibercept group, two non-serious cases of transient posthypoxic encephalo-pathy assessed as due to stress related to protocol-procedure, occurred directly after the first administration of aflibercept and recovered after treatment. All events reported in the aflibercept group consisted of arachnoid cyst (n=1), cerebral/cerebellar atrophy (n=2) cerebral ventricular dilatation (n=1), Developmental coordination disorder (n=1), Epilepsy (n=1), Febrile convulsion (n=2), Focal dyscognitive seizures (n=1), Hypotonia (n=1), Infantile spasms (n=3), Motor developmental delay (n=1), Motor dysfunction (n=1), Neonatal seizure (n=1), Speech disorder developmental (n=1) and Tremor (n=1). All events were assessed as not related to study treatment by the treating physician due to underling comorbidities or as unlikely in a context of non-chronic exposition of anti-VEGF. Three cases of non-serious intracerebral hemorrhage events were reported in the aflibercept arm: intraventricular haemorrhage neonatal at 18 days after first dose of aflibercept in a premature patient with low weight and predisposing risk factors of respiratory distress syndrome and infection, intraventricular haemorrhage at 37 days after first dose of aflibercept in a premature patient with low weight and predisposing risk factors of BPD, anaemia and apnoea, thalamus haemorrhage at 20 days after the first dose of aflibercept in a patient with patent ductus arteriosus and disturbance in cerebral blood flow due to underlying respiratory distress syndrome. The events of delayed motor development and of syndrome movement's disturbance occurred in two patients with medical history of perinatal brain damage and/or pyramidal tract syndrome and cerebral haemorrhage which are plausible alternative explanations.

Overall, at this stage, available data is not in favour of a causal relationship between aflibercept IVT and nervous and cardiac disorders. Nonetheless, these uncertainties will be further reduced by provision of data in the context of the longer term follow-up and in the PSURs.

Renal disorders were also highlighted by non-clinical data but similar rates were reported between arms (2.7% vs 2.6%). One proteinuria event was reported in each arm. In the aflibercept group, the event of (transient and spontaneously recovered) proteinuria occurred in one patient presenting proteinuria at baseline. The causal relationship to aflibercept was assessed as unlikely. No further cases have been reported until 2 years of chronological age among the 54 patients who completed the visit. This potential issue will also be followed in the further post-approval data submissions.

Severity

Most of the systemic TEAE were mild or moderate in intensity, and severe TEAE were in higher proportion in laser arm (18, 4%) than in aflibercept (6,7%).

Relation to study treatment/procedure

There were no aflibercept-related systemic TEAE in the study while injection-related systemic TEAE (PT, pain) was reported for 1 subject (1.3%) in the aflibercept arm. The event was non-serious and mild in intensity. The action taken with aflibercept did not change, and the outcome was resolved.

Laser-related systemic TEAE occurred in 2 (5.3%) subjects in the laser arm, and the reported events were anemia neonatal and apnea.

Study 20275

All subjects

For all 89 subjects who entered the extension Study 20275, the proportion of subjects with at least one systemic AE was similar between the 2 arms (aflibercept 48 [80.0%] vs laser 24 [82.8%]).

Table 11: Number of subjects with systemic adverse events until 1 year of chronological age by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects in 20090) (all subjects entering extension)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	 N=60 (100%)	Laser Events	 N=29 (100%)	Total Events	 N=89 (100%)
Number (%) of subjects with at least one such adverse event	190	48 (80.0%)	73	24 (82.8%)	263	72 (80.9%)
Blood and lymphatic system disorders	4	2 (3.3%)	5	2 (6.9%)	9	4 (4.5%)
Anaemia	1	1 (1.7%)	4	2 (6.9%)	5	3 (3.4%)
Iron deficiency anaemia	1	1 (1.7%)	0	0	1	1 (1.1%)
Leukopenia	1	1 (1.7%)	0	0	1	1 (1.1%)
Splenomegaly	1	1 (1.7%)	0	0	1	1 (1.1%)
Thymus enlargement	0	0	1	1 (3.4%)	1	1 (1.1%)
Cardiac disorders	4	4 (6.7%)	1	1 (3.4%)	5	5 (5.6%)
Bradycardia	2	2 (3.3%)	0	0	2	2 (2.2%)
Cardiac failure	1	1 (1.7%)	0	0	1	1 (1.1%)
Pulmonary valve stenosis	0	0	1	1 (3.4%)	1	1 (1.1%)
Tachycardia	1	1 (1.7%)	0	0	1	1 (1.1%)
Congenital, familial and genetic disorders	8	6 (10.0%)	5	4 (13.8%)	13	10 (11.2%)
Ankyloglossia congenital	1	1 (1.7%)	0	0	1	1 (1.1%)
Atrial septal defect	1	1 (1.7%)	0	0	1	1 (1.1%)
Cerebral palsy	0	0	1	1 (3.4%)	1	1 (1.1%)
Congenital arterial malformation	1	1 (1.7%)	0	0	1	1 (1.1%)
Craniotabes	0	0	1	1 (3.4%)	1	1 (1.1%)
Cryptorchism	1	1 (1.7%)	0	0	1	1 (1.1%)
Deafness congenital	1	1 (1.7%)	0	0	1	1 (1.1%)
Developmental hip dysplasia	0	0	1	1 (3.4%)	1	1 (1.1%)
Hydrocele	2	1 (1.7%)	1	1 (3.4%)	3	2 (2.2%)
Laryngomalacia	0	0	1	1 (3.4%)	1	1 (1.1%)
Patent ductus arteriosus	1	1 (1.7%)	0	0	1	1 (1.1%)
Ear and labyrinth disorders	2	2 (3.3%)	4	3 (10.3%)	6	5 (5.6%)
Auditory disorder	0	0	1	1 (3.4%)	1	1 (1.1%)
Deafness neurosensory	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
Deafness unilateral	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
Hypoacusis	0	0	1	1 (3.4%)	1	1 (1.1%)
Endocrine disorders	1	1 (1.7%)	0	0	1	1 (1.1%)
Adrenomegaly	1	1 (1.7%)	0	0	1	1 (1.1%)
Gastrointestinal disorders	22	15 (25.0%)	13	8 (27.6%)	35	23 (25.8%)
Abdominal adhesions	0	0	1	1 (3.4%)	1	1 (1.1%)
Abdominal pain	0	0	1	1 (3.4%)	1	1 (1.1%)
Cheilitis	1	1 (1.7%)	0	0	1	1 (1.1%)
Constipation	2	2 (3.3%)	0	0	2	2 (2.2%)
Diarrhoea	4	4 (6.7%)	1	1 (3.4%)	5	5 (5.6%)
Enterocolitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Flatulence	0	0	1	1 (3.4%)	1	1 (1.1%)
Gastric haemorrhage	1	1 (1.7%)	0	0	1	1 (1.1%)
Gastrooesophageal reflux disease	2	2 (3.3%)	0	0	2	2 (2.2%)
Haematochezia	0	0	1	1 (3.4%)	1	1 (1.1%)
Inguinal hernia	4	3 (5.0%)	2	2 (6.9%)	6	5 (5.6%)
Intestinal prolapse	0	0	1	1 (3.4%)	1	1 (1.1%)
Mechanical ileus	1	1 (1.7%)	0	0	1	1 (1.1%)
Necrotising colitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Umbilical hernia	1	1 (1.7%)	3	3 (10.3%)	4	4 (4.5%)
Vomiting	6	5 (8.3%)	0	0	6	5 (5.6%)
General disorders and administration site conditions	13	10 (16.7%)	3	3 (10.3%)	16	13 (14.6%)
Developmental delay	0	0	1	1 (3.4%)	1	1 (1.1%)
Pain	1	1 (1.7%)	0	0	1	1 (1.1%)
Pyrexia	12	10 (16.7%)	2	2 (6.9%)	14	12 (13.5%)
Hepatobiliary disorders	2	1 (1.7%)	1	1 (3.4%)	3	2 (2.2%)
Cholestasis	1	1 (1.7%)	0	0	1	1 (1.1%)
Gallbladder disorder	0	0	1	1 (3.4%)	1	1 (1.1%)
Hepatic lesion	1	1 (1.7%)	0	0	1	1 (1.1%)
Immune system disorders	1	1 (1.7%)	0	0	1	1 (1.1%)
Secondary immunodeficiency	1	1 (1.7%)	0	0	1	1 (1.1%)

Infections and infestations	48	28 (46.7%)	13	11 (37.9%)	61	39 (43.8%)
Abdominal wall infection	1	1 (1.7%)	0	0	1	1 (1.1%)
Asymptomatic COVID-19	1	1 (1.7%)	0	0	1	1 (1.1%)
Bacterial disease carrier	0	0	1	1 (3.4%)	1	1 (1.1%)
Bacteriuria	0	0	1	1 (3.4%)	1	1 (1.1%)
Bronchiolitis	8	4 (6.7%)	1	1 (3.4%)	9	5 (5.6%)
Bronchitis	3	3 (5.0%)	0	0	3	3 (3.4%)
COVID-19	1	1 (1.7%)	0	0	1	1 (1.1%)
Cytomegalovirus infection	0	0	1	1 (3.4%)	1	1 (1.1%)
Ear infection	2	2 (3.3%)	0	0	2	2 (2.2%)
Gastroenteritis	2	1 (1.7%)	0	0	2	1 (1.1%)
Gastroenteritis salmonella	1	1 (1.7%)	0	0	1	1 (1.1%)
Gastroenteritis viral	1	1 (1.7%)	0	0	1	1 (1.1%)
Gastrointestinal candidiasis	1	1 (1.7%)	0	0	1	1 (1.1%)
Infection	1	1 (1.7%)	0	0	1	1 (1.1%)
Laryngitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Nail infection	1	1 (1.7%)	0	0	1	1 (1.1%)
Nasopharyngitis	7	5 (8.3%)	0	0	7	5 (5.6%)
Neonatal infection	1	1 (1.7%)	0	0	1	1 (1.1%)
Oral candidiasis	2	2 (3.3%)	0	0	2	2 (2.2%)
Oral fungal infection	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
Otitis media	1	1 (1.7%)	0	0	1	1 (1.1%)
Otitis media acute	1	1 (1.7%)	0	0	1	1 (1.1%)
Otosalpingitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Pharyngitis	1	1 (1.7%)	0	0	1	1 (1.1%)
Pneumonia	2	2 (3.3%)	0	0	2	2 (2.2%)
Respiratory tract infection	1	1 (1.7%)	0	0	1	1 (1.1%)
Rhinitis	3	3 (5.0%)	2	2 (6.9%)	5	5 (5.6%)
Rhinovirus infection	0	0	1	1 (3.4%)	1	1 (1.1%)
Sepsis	1	1 (1.7%)	2	1 (3.4%)	3	2 (2.2%)
Upper respiratory tract infection	3	3 (5.0%)	1	1 (3.4%)	4	4 (4.5%)
Viral sepsis	1	1 (1.7%)	0	0	1	1 (1.1%)
Injury, poisoning and procedural complications	3	3 (5.0%)	0	0	3	3 (3.4%)
Postoperative adhesion	1	1 (1.7%)	0	0	1	1 (1.1%)
Procedural pain	1	1 (1.7%)	0	0	1	1 (1.1%)
Vaccination complication	1	1 (1.7%)	0	0	1	1 (1.1%)
Investigations	13	7 (11.7%)	1	1 (3.4%)	14	8 (9.0%)
Body temperature increased	1	1 (1.7%)	0	0	1	1 (1.1%)
Brain stem auditory evoked response abnormal	4	2 (3.3%)	0	0	4	2 (2.2%)
C-reactive protein increased	0	0	1	1 (3.4%)	1	1 (1.1%)
Cardiac murmur	1	1 (1.7%)	0	0	1	1 (1.1%)
Otoacoustic emissions test abnormal	3	2 (3.3%)	0	0	3	2 (2.2%)
Oxygen saturation decreased	4	3 (5.0%)	0	0	4	3 (3.4%)
Metabolism and nutrition disorders	8	7 (11.7%)	2	2 (6.9%)	10	9 (10.1%)
Hypoglycaemia	1	1 (1.7%)	0	0	1	1 (1.1%)
Hypokalaemia	1	1 (1.7%)	0	0	1	1 (1.1%)
Hypomagnesaemia	1	1 (1.7%)	0	0	1	1 (1.1%)
Hypophagia	1	1 (1.7%)	0	0	1	1 (1.1%)
Lactose intolerance	0	0	1	1 (3.4%)	1	1 (1.1%)
Malnutrition	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
Metabolic acidosis	1	1 (1.7%)	0	0	1	1 (1.1%)
Metabolic alkalosis	1	1 (1.7%)	0	0	1	1 (1.1%)
Vitamin B12 deficiency	1	1 (1.7%)	0	0	1	1 (1.1%)
Musculoskeletal and connective tissue disorders	5	4 (6.7%)	1	1 (3.4%)	6	5 (5.6%)
Extremity contracture	1	1 (1.7%)	0	0	1	1 (1.1%)
Osteopenia	2	2 (3.3%)	0	0	2	2 (2.2%)
Pathological fracture	1	1 (1.7%)	0	0	1	1 (1.1%)
Rickets	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	2 (3.3%)	1	1 (3.4%)	4	3 (3.4%)
Cerebral haemangioma	1	1 (1.7%)	0	0	1	1 (1.1%)
Haemangioma	1	1 (1.7%)	0	0	1	1 (1.1%)
Haemangioma of liver	1	1 (1.7%)	0	0	1	1 (1.1%)
Spinal cord lipoma	0	0	1	1 (3.4%)	1	1 (1.1%)
Nervous system disorders	12	9 (15.0%)	3	2 (6.9%)	15	11 (12.4%)
Arachnoid cyst	1	1 (1.7%)	0	0	1	1 (1.1%)
Cerebellar atrophy	1	1 (1.7%)	0	0	1	1 (1.1%)
Cerebral atrophy	1	1 (1.7%)	0	0	1	1 (1.1%)
Hypoxic-ischaemic encephalopathy	2	2 (3.3%)	0	0	2	2 (2.2%)
Infantile spasms	3	1 (1.7%)	0	0	3	1 (1.1%)
Intraventricular haemorrhage neonatal	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
Motor developmental delay	1	1 (1.7%)	0	0	1	1 (1.1%)
Movement disorder	0	0	1	1 (3.4%)	1	1 (1.1%)
Neonatal seizure	1	1 (1.7%)	0	0	1	1 (1.1%)
Tethered cord syndrome	0	0	1	1 (3.4%)	1	1 (1.1%)
Tremor	1	1 (1.7%)	0	0	1	1 (1.1%)
Psychiatric disorders	2	2 (3.3%)	1	1 (3.4%)	3	3 (3.4%)
Neurodevelopmental disorder	2	2 (3.3%)	0	0	2	2 (2.2%)
Psychomotor retardation	0	0	1	1 (3.4%)	1	1 (1.1%)
Renal and urinary disorders	2	2 (3.3%)	4	2 (6.9%)	6	4 (4.5%)
Glycosuria	1	1 (1.7%)	0	0	1	1 (1.1%)
Haematuria	0	0	1	1 (3.4%)	1	1 (1.1%)
Leukocyturia	0	0	1	1 (3.4%)	1	1 (1.1%)
Nephrocalcinosis	1	1 (1.7%)	0	0	1	1 (1.1%)
Proteinuria	0	0	1	1 (3.4%)	1	1 (1.1%)
Pyelocaliectasis	0	0	1	1 (3.4%)	1	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	14	9 (15.0%)	10	7 (24.1%)	24	16 (18.0%)
Apnoea	3	3 (5.0%)	2	2 (6.9%)	5	5 (5.6%)
Bronchopulmonary disease	1	1 (1.7%)	0	0	1	1 (1.1%)
Bronchopulmonary dysplasia	1	1 (1.7%)	0	0	1	1 (1.1%)
Catarrh	0	0	1	1 (3.4%)	1	1 (1.1%)
Cough	2	2 (3.3%)	0	0	2	2 (2.2%)
Infantile apnoea	0	0	2	2 (6.9%)	2	2 (2.2%)
Nasal obstruction	1	1 (1.7%)	0	0	1	1 (1.1%)
Oropharyngeal pain	1	1 (1.7%)	0	0	1	1 (1.1%)
Pneumonia aspiration	1	1 (1.7%)	0	0	1	1 (1.1%)
Pulmonary hypertension	1	1 (1.7%)	0	0	1	1 (1.1%)
Respiratory arrest	0	0	1	1 (3.4%)	1	1 (1.1%)
Respiratory distress	0	0	1	1 (3.4%)	1	1 (1.1%)
Rhonchi	1	1 (1.7%)	0	0	1	1 (1.1%)
Stridor	0	0	1	1 (3.4%)	1	1 (1.1%)
Tachypnoea	1	1 (1.7%)	0	0	1	1 (1.1%)
Upper respiratory tract inflammation	1	1 (1.7%)	2	1 (3.4%)	3	2 (2.2%)
Skin and subcutaneous tissue disorders	20	13 (21.7%)	4	3 (10.3%)	24	16 (18.0%)
Decubitus ulcer	0	0	1	1 (3.4%)	1	1 (1.1%)
Dermatitis	2	2 (3.3%)	0	0	2	2 (2.2%)
Dermatitis atopic	1	1 (1.7%)	0	0	1	1 (1.1%)
Dermatitis diaper	5	3 (5.0%)	1	1 (3.4%)	6	4 (4.5%)
Eczema	2	2 (3.3%)	1	1 (3.4%)	3	3 (3.4%)
Eczema asteatotic	2	2 (3.3%)	0	0	2	2 (2.2%)
Eczema infantile	1	1 (1.7%)	0	0	1	1 (1.1%)
Haemorrhage subcutaneous	0	0	1	1 (3.4%)	1	1 (1.1%)
Intertrigo	2	2 (3.3%)	0	0	2	2 (2.2%)
Miliaria	1	1 (1.7%)	0	0	1	1 (1.1%)
Rash	2	2 (3.3%)	0	0	2	2 (2.2%)
Rash macular	1	1 (1.7%)	0	0	1	1 (1.1%)
Urticaria	1	1 (1.7%)	0	0	1	1 (1.1%)
Surgical and medical procedures	1	1 (1.7%)	0	0	1	1 (1.1%)
Inguinal hernia repair	1	1 (1.7%)	0	0	1	1 (1.1%)
Uncoded	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
CEREBRAL VENTRICLE DILATATION	1	1 (1.7%)	0	0	1	1 (1.1%)
CRANEO-SYNOSTOSIS	0	0	1	1 (3.4%)	1	1 (1.1%)
Vascular disorders	1	1 (1.7%)	0	0	1	1 (1.1%)
Cyanosis	1	1 (1.7%)	0	0	1	1 (1.1%)

Adverse events are sorted in alphabetical order by primary SOC and preferred term.
A subject is counted only once within each preferred term or any primary SOC.
All events with start date on birth date + 365 days are included.
Study intervention as in previous study 20090.
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The most frequent systemic AE by PT, occurring in more than 10% of the subjects in either arm were pyrexia (aflibercept 16.7% vs laser 6.9%) and umbilical hernia (aflibercept 1.7% vs laser 10.3%). All other systemic AE were reported in less than 10% of subjects in total.

Systemic AE are considered compatible with the underlying prematurity and reflect no clinically meaningful differences across both treatment arms.

Severity

Most of the systemic TEAEs were mild or moderate in intensity, and severe TEAEs were reported in 5 (6.7%) subjects in the aflibercept arm and 4 (10.5%) in the laser arm.

For all 89 subjects who entered the extension Study 20275, most of the systemic AEs were mild or moderate in intensity, and severe AEs were reported by 6 (10.0%) subjects in the aflibercept arm and 7 (24.1%) in the laser arm.

Relation to study treatment/procedure

For all 89 subjects who entered the extension Study 20275, for 1 (1.7%) subject in the aflibercept arm an injection procedure-related systemic AE was reported (pain of mild intensity, as reported in Study 20090). No systemic AEs with a fatal outcome were reported for either arm.

Patients who completed the 1 year visit and the 2 year visit

For the 60 subjects who completed the visit at 1 year of chronological age, the results were similar to those described above for all subjects.

For all 60 subjects who completed the visit at 1 year of chronological age, among unilaterally and bilaterally-treated subjects at 1 year of chronological age, there were no aflibercept-related systemic AEs reported for any population included in these analyses. Moreover, there were no laser-related systemic AEs reported for any population included in these analyses.

Regarding long-term safety of study 20275, the MAH submitted a first interim analysis of the data at 2 years of chronological age for more than half of the patient (see Annex 2 and 4) and completed data will be submitted in June 2023.

Deaths/Serious adverse event/other significant events

1. Deaths

Study 20090

Three subjects in the aflibercept arm died during Study 20090, at approximately 4 to 9 weeks after the last treatment. All 3 deaths were assessed as associated with complications of underlying prematurity, and as causally unrelated to the drug.

The summarized death are as follow:

1. a 71-day-old Asian female with a gestational age at birth of 23 weeks and 6 days, the cause of death was reported as bronchopulmonary dysplasia and pneumothorax. Her death occurred 144 days after the start of the study treatment and 59 days after the last study treatment.
2. a 61-day-old white female with a gestational age at birth of 2 weeks and 1 day, the cause of death was reported as bronchiolitis. Her death occurred 57 days after the start of the study treatment and 56 days after the last study treatment.
3. a 90-day-old white male with a gestational age at birth of 2 weeks, the cause of death was reported as bronchopulmonary dysplasia. His death occurred 61 days after the start of the study treatment and 28 days after the last study treatment.

None of the deaths were assessed as related to aflibercept but as complications of the underlying prematurity. All deaths occurred at more than a month after last study treatment.

Study 20275

No deaths were reported during the ongoing extension Study 20275 (FIREFLEYE NEXT).

4. SAE/TESAE

In study 20090, overall SAE occurred in 40 (35.4%) subjects overall, and the proportion of subjects with SAE was higher in the laser arm compared to the aflibercept arm (aflibercept 24 [32.0%] vs laser 16 [42.1%]). Treatment-emergent SAE occurred in 19 (16.8%) subjects overall, and the proportion of

subjects with TESAE was higher in the laser arm compared to the aflibercept arm (aflibercept 9 [12.0%] vs laser 10 [26.3%]).

In study 20275, serious AE were reported for 29 (32.6%) subjects, and the proportion of subjects with overall SAE was lower in the aflibercept arm compared to the laser arm (25.0% vs 48.3%).

OCULAR SAE/TESAE

Study 20090

Thirteen (11.5%) subjects had an ocular SAE in the treated eye, which occurred in slightly higher proportion of subjects in the aflibercept arm (aflibercept 10 [13.3%] vs laser 3 [7.9%]). The events recorded for more than 1 subject were retinal detachment (aflibercept 5 [6.7%] vs laser 2 [5.3%]) and retinal haemorrhage (2 [2.7%] subjects in the aflibercept arm).

Nine (8.0%) subjects had an ocular TESAE in the treated eye, which occurred in similar proportion of subjects in both treatment arms (aflibercept 6 [8.0%] vs laser 3 [7.9%]).

The events recorded for more than 1 subject were retinal detachment (aflibercept 3 [4.0%] vs laser 2 [5.3%]) and retinal haemorrhage (2 [2.7%] subjects in the aflibercept arm).

Table 12: Number of subjects with ocular treatment-emergent serious adverse events in treated eyes by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects) (safety analysis set)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	Aflibercept N=75 (100%)	Laser Events	Laser N=38 (100%)	Total Events	Total N=113 (100%)
Number (%) of subjects with at least one such adverse event	10	6 (8.0%)	3	3 (7.9%)	13	9 (8.0%)
Eye disorders	8	6 (8.0%)	2	2 (5.3%)	10	8 (7.1%)
Retinal detachment	3	3 (4.0%)	2	2 (5.3%)	5	5 (4.4%)
Retinal haemorrhage	2	2 (2.7%)	0	0	2	2 (1.8%)
Corneal oedema	1	1 (1.3%)	0	0	1	1 (0.9%)
Retinopathy of prematurity	1	1 (1.3%)	0	0	1	1 (0.9%)
Vitreous haemorrhage	1	1 (1.3%)	0	0	1	1 (0.9%)
Infections and infestations	0	0	1	1 (2.6%)	1	1 (0.9%)
Conjunctivitis	0	0	1	1 (2.6%)	1	1 (0.9%)
Injury, poisoning and procedural complications	1	1 (1.3%)	0	0	1	1 (0.9%)
Overdose	1	1 (1.3%)	0	0	1	1 (0.9%)
Investigations	1	1 (1.3%)	0	0	1	1 (0.9%)
Intraocular pressure increased	1	1 (1.3%)	0	0	1	1 (0.9%)

Adverse events are sorted by frequency within primary SOC.
A subject is counted only once within each preferred term or any primary SOC.
Treatment emergent is defined as an AE that is observed or reported after the first and not later than 30 days after the last administration of study treatment.
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There was no laser-related TESAE. One (2.6%) subject in the laser arm had aflibercept-related TESAE, and 1 (1.3%) subject in the aflibercept arm had injection-procedure-related TESAE. For one subject in the aflibercept arm, transient, spontaneously resolved ocular events of corneal oedema and intraocular pressure increased were reported for the inadvertently overdosed (right) eye (with 4.0 mg, while the left received the intended dose of 0.4 mg). For a subject in the laser arm, the ocular event of retinal detachment in the treated eye was reported.

Study 20275

For all 89 subjects who entered the extension study, the most frequent ocular SAE by PTs in treated eyes, occurring in more than 3% of the subjects in either arm, were retinal detachment (aflibercept 5.0% vs laser 3.4%), retinal haemorrhage (aflibercept 3.3% vs laser 0%) and conjunctivitis (no subjects

in aflibercept vs 3.4% in laser). All other ocular SAEs in treated eyes were reported in less than 2% of subjects in total.

Table 13: Number of subjects with ocular serious adverse events until 1 year of chronological age in treated eyes in previous study 20090 by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects in 20090) (all subjects entering extension)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	Aflibercept N=60 (100%)	Laser Events	Laser N=29 (100%)	Total Events	Total N=89 (100%)
Number (%) of subjects with at least one adverse event	23	7 (11.7%)	3	2 (6.9%)	26	9 (10.1%)
Eye disorders	17	6 (10.0%)	2	1 (3.4%)	19	7 (7.9%)
Corneal oedema	1	1 (1.7%)	0	0	1	1 (1.1%)
Macular degeneration	1	1 (1.7%)	0	0	1	1 (1.1%)
Retinal detachment	8	3 (5.0%)	2	1 (3.4%)	10	4 (4.5%)
Retinal haemorrhage	2	2 (3.3%)	0	0	2	2 (2.2%)
Retinal neovascularisation	1	1 (1.7%)	0	0	1	1 (1.1%)
Retinopathy of prematurity	2	1 (1.7%)	0	0	2	1 (1.1%)
Vitreous haemorrhage	1	1 (1.7%)	0	0	1	1 (1.1%)
Vitreous opacities	1	1 (1.7%)	0	0	1	1 (1.1%)
Infections and infestations	0	0	1	1 (3.4%)	1	1 (1.1%)
Conjunctivitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Injury, poisoning and procedural complications	1	1 (1.7%)	0	0	1	1 (1.1%)
Overdose	1	1 (1.7%)	0	0	1	1 (1.1%)
Investigations	1	1 (1.7%)	0	0	1	1 (1.1%)
Intraocular pressure increased	1	1 (1.7%)	0	0	1	1 (1.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	1 (1.7%)	0	0	4	1 (1.1%)
Retinoblastoma	4	1 (1.7%)	0	0	4	1 (1.1%)

Adverse events are sorted in alphabetical order by primary SOC and preferred term.
A subject is counted only once within each preferred term or any primary SOC.
All events with start date on birth date + 365 days are included.
Study intervention as in previous study 20090.
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The greatest proportion of subjects had events that were considered moderate in intensity (5 [5.6%)]. Three (5.0%) subjects in the aflibercept arm were reported with events of severe intensity; 3 (5.0%) subjects were reported with retinal detachment of severe intensity, 1 (1.7%) subject was reported with retinal neovascularization of severe intensity, and 1 (1.7%) subject was reported with vitreous opacities of severe intensity.

There were no subjects with ocular SAEs in non-treated eyes.

SYSTEMIC SAE/TESAE

Study 20090

Thirty-two subjects (28.3%) had a systemic SAE, which occurred in higher proportion of subjects in the laser arm compared to the aflibercept arm (aflibercept 18 [24.0%] vs laser 14 [36.8%]). The events recorded for more than 1 subject was bronchiolitis (aflibercept 5 [6.7%] vs laser 2 [5.3%]), bronchopulmonary dysplasia in 3 (4.0%) subjects in the aflibercept arm, infantile apnoea in 2 (5.3%) subjects in the laser arm, and upper respiratory tract infection and apnoea (in 1 subject in each treatment arm, respectively).

For TESAE, twelve subjects (10.6%) had a systemic TESAE, which occurred in a higher proportion of subjects in the laser arm compared to the aflibercept arm (aflibercept 5 [6.7%] vs laser 7 [18.4%]). The events recorded for more than 1 subject was bronchiolitis (aflibercept 2 [2.7%] vs laser 1 [2.6%]) and infantile apnoea (2 [5.3%] subjects in the laser arm).

Table 14: Number of subjects with systemic treatment-emergent serious adverse events by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects) (safety analysis set)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	 N=75 (100%)	Laser Events	 N=38 (100%)	Total Events	 N=113 (100%)
Number (%) of subjects with at least one such adverse event	7	5 (6.7%)	9	7 (18.4%)	16	12 (10.6%)
Cardiac disorders	0	0	1	1 (2.6%)	1	1 (0.9%)
Pulmonary valve stenosis	0	0	1	1 (2.6%)	1	1 (0.9%)
Gastrointestinal disorders	0	0	1	1 (2.6%)	1	1 (0.9%)
Necrotising colitis	0	0	1	1 (2.6%)	1	1 (0.9%)
Infections and infestations	5	4 (5.3%)	2	2 (5.3%)	7	6 (5.3%)
Bronchiolitis	2	2 (2.7%)	1	1 (2.6%)	3	3 (2.7%)
COVID-19	1	1 (1.3%)	0	0	1	1 (0.9%)
Pneumonia	1	1 (1.3%)	0	0	1	1 (0.9%)
Rhinitis	0	0	1	1 (2.6%)	1	1 (0.9%)
Upper respiratory tract infection	1	1 (1.3%)	0	0	1	1 (0.9%)
Investigations	0	0	1	1 (2.6%)	1	1 (0.9%)
C-reactive protein increased	0	0	1	1 (2.6%)	1	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	2	2 (2.7%)	4	4 (10.5%)	6	6 (5.3%)
Infantile apnoea	0	0	2	2 (5.3%)	2	2 (1.8%)
Apnoea	0	0	1	1 (2.6%)	1	1 (0.9%)
Bronchopulmonary dysplasia	1	1 (1.3%)	0	0	1	1 (0.9%)
Pneumonia aspiration	1	1 (1.3%)	0	0	1	1 (0.9%)
Respiratory arrest	0	0	1	1 (2.6%)	1	1 (0.9%)

Adverse events are sorted by frequency within primary SOC.
A subject is counted only once within each preferred term or any primary SOC.
Treatment emergent is defined as an AE that is observed or reported after the first and not later than 30 days after the last administration of study treatment.
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Overall, systemic SAE and TESAE occurred in a higher proportion of subjects in the laser arm compared to the aflibercept arm (respectively 36.8% vs 24.0% and 18.4% vs 6.7%). The events reported for more than one subject are infantile apnoea and bronchiolitis and are possible complications of premature conditions.

Study 20275

For all 89 subjects who entered the extension study 20725, systemic SAE were reported in 11 (18.3%) subjects in the aflibercept arm and 13 (44.8%) subjects in the laser arm. the majority of subjects had events that were considered severe in intensity (10 [11.2%]).

The most frequently reported PT for systemic SAE was infantile apnoea (no subjects in the aflibercept arm vs laser 2 [6.9%]).

Table 15: Number of subjects with systemic serious adverse events until 1 year of chronological age by primary system organ class, preferred term (Unilaterally & bilaterally treated subjects in 20090) (all subjects entering extension)

Primary system organ class Preferred term MedDRA version 23.1	Aflibercept Events	 N=60 (100%)	Laser Events	 N=29 (100%)	Total Events	 N=89 (100%)
Number (%) of subjects with at least one such adverse event	19	11 (18.3%)	17	13 (44.8%)	36	24 (27.0%)
Cardiac disorders	0	0	1	1 (3.4%)	1	1 (1.1%)
Pulmonary valve stenosis	0	0	1	1 (3.4%)	1	1 (1.1%)
Ear and labyrinth disorders	0	0	1	1 (3.4%)	1	1 (1.1%)
Deafness neurosensory	0	0	1	1 (3.4%)	1	1 (1.1%)
Gastrointestinal disorders	3	3 (5.0%)	4	3 (10.3%)	7	6 (6.7%)
Abdominal adhesions	0	0	1	1 (3.4%)	1	1 (1.1%)
Gastrooesophageal reflux disease	1	1 (1.7%)	0	0	1	1 (1.1%)
Inguinal hernia	0	0	1	1 (3.4%)	1	1 (1.1%)
Intestinal prolapse	0	0	1	1 (3.4%)	1	1 (1.1%)
Mechanical ileus	1	1 (1.7%)	0	0	1	1 (1.1%)
Necrotising colitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Vomiting	1	1 (1.7%)	0	0	1	1 (1.1%)
Infections and infestations	8	5 (8.3%)	4	4 (13.8%)	12	9 (10.1%)
Bronchiolitis	3	2 (3.3%)	1	1 (3.4%)	4	3 (3.4%)
COVID-19	1	1 (1.7%)	0	0	1	1 (1.1%)
Gastroenteritis	1	1 (1.7%)	0	0	1	1 (1.1%)
Gastroenteritis salmonella	1	1 (1.7%)	0	0	1	1 (1.1%)
Laryngitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Pneumonia	1	1 (1.7%)	0	0	1	1 (1.1%)
Respiratory tract infection	1	1 (1.7%)	0	0	1	1 (1.1%)
Rhinitis	0	0	1	1 (3.4%)	1	1 (1.1%)
Upper respiratory tract infection	0	0	1	1 (3.4%)	1	1 (1.1%)
Injury, poisoning and procedural complications	1	1 (1.7%)	0	0	1	1 (1.1%)
Postoperative adhesion	1	1 (1.7%)	0	0	1	1 (1.1%)
Investigations	0	0	1	1 (3.4%)	1	1 (1.1%)
C-reactive protein increased	0	0	1	1 (3.4%)	1	1 (1.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1	1 (3.4%)	1	1 (1.1%)
Spinal cord lipoma	0	0	1	1 (3.4%)	1	1 (1.1%)
Nervous system disorders	2	2 (3.3%)	0	0	2	2 (2.2%)
Cerebellar atrophy	1	1 (1.7%)	0	0	1	1 (1.1%)
Infantile spasms	1	1 (1.7%)	0	0	1	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	3	3 (5.0%)	5	5 (17.2%)	8	8 (9.0%)
Apnoea	1	1 (1.7%)	1	1 (3.4%)	2	2 (2.2%)
Bronchopulmonary disease	1	1 (1.7%)	0	0	1	1 (1.1%)
Infantile apnoea	0	0	2	2 (6.9%)	2	2 (2.2%)
Pneumonia aspiration	1	1 (1.7%)	0	0	1	1 (1.1%)
Respiratory arrest	0	0	1	1 (3.4%)	1	1 (1.1%)
Respiratory distress	0	0	1	1 (3.4%)	1	1 (1.1%)
Surgical and medical procedures	1	1 (1.7%)	0	0	1	1 (1.1%)
Inguinal hernia repair	1	1 (1.7%)	0	0	1	1 (1.1%)
Vascular disorders	1	1 (1.7%)	0	0	1	1 (1.1%)
Cyanosis	1	1 (1.7%)	0	0	1	1 (1.1%)

Adverse events are sorted in alphabetical order by primary SOC and preferred term.
A subject is counted only once within each preferred term or any primary SOC.
All events with start date on birth date + 365 days are included.
Study intervention as in previous study 20090.
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Other significant events

1. Overdose

One subject in the aflibercept arm injected bilaterally on the same day, was overdosed on the right eye i.e. overdose on the right eye with 4.0 mg (100 µL), while the left received the intended dose of 0.4 mg (10 µL) a few minutes later. The patient presented transient corneal oedema and intraocular pressure (corneal odema lasted for 5 minutes and increased intraocular pressure from 6.3mmHg pre-injection to 35mmHg 15 mn post-injection which returned to 17.4mmHg within 60mn). The events were transient and resolved spontaneously.

Mandatory use of the PDD with the PFS allows the administration of a single dose of 10 µL/0.4 mg of aflibercept (range of 10.9 µL to 12.6 µL) and afterward the dose button will be blocked. Thus the risk of overdose would be limited.

2. Multiple use of single use product

For one patient, the event multiple use of single use product was reported. Extraction of multiple doses from a vial or a PFS is of concern considering risk of contamination and infection. Use of the PDD would allow to limit this risk since it cannot be reused without a major manipulation.

The single use of the PFS is well mentioned in section 4.2 and 6.6 of the SmPc and in the Instruction for use (IFU) of the PDD.

COVID-19 related adverse events

For 2 subjects in the aflibercept arm, COVID-19 related AEs were reported. One of the events was a TESAE, and required remedial drug therapy. The action taken with aflibercept did not change, and the outcome was resolved.

Medical device incident

Overall, no medical device incidents were reported.

Analysis of adverse events by organ system or syndrome

There are no AE in the Studies 20090 and 20275, reported to have occurred in the context of any organ system or syndrome. No adverse events of special interest were defined in Study 20090 or Study 20275.

Discontinuation due to adverse events

Study 20090

Overall, 4 subjects (3.5%) discontinued the study intervention due to AE, three (4.0%) in the aflibercept arm and 1 (2.6%) in the laser arm discontinued study intervention because of ocular TEAEs in treated eyes. Furthermore, none of the systemic TEAE and AE led to discontinuation of study intervention.

The 3 subjects in the aflibercept arm discontinued aflibercept and the events were retinal detachment for 2 subjects and retinopathy of prematurity for 1. The subject in the laser arm discontinued laser due to event retinal detachment.

Furthermore, SAE leading to discontinuation of study intervention occurred in 2 (2.7%) subjects (ROP and retinal detachment, respectively) in the aflibercept arm and 1 (2.6%) subject (retinal detachment) in the laser arm.

Laboratory findings

Clinical laboratory evaluations

Laboratory (hematology, chemistry, and urinalysis) analyses were performed and reviewed at screening (Visit 1). No further lab tests were mandated by study protocol other than urine protein test.

Clinically significant findings during the course of the study was reported as AEs. Systemic TEAE proteinuria was reported in 1 subject in each of the treatment arms. Both events were non-serious, overall in the aflibercept arm proteinuria occurred 12 days after the start of the study treatment was

transient, asymptomatic and mild in intensity while in the laser arm proteinuria was moderate in intensity and occurred 22 days after the start of the study treatment in context of a urinary tract infection.

Both events were assessed by the investigators as unrelated to aflibercept, laser or injection procedure and were resolved in 18 days for the aflibercept arm and 10 days for the laser arm.

In total, no association of aflibercept treatment and development of proteinuria was identified.

No clinical laboratory data were collected in Study 20275.

Vital signs, physical findings, and other observations related to safety

Clinically significant abnormal findings in physical examinations and vital signs were reported as AEs. The following analyses of these routinely assessed variables provide complementary safety information.

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) were analysed in the SAF.

Mean values for the vital signs were similar in the treatment arms at baseline and stayed almost unchanged or considered as not clinically relevant over time. No AE of hypertension was reported.

Regarding physical examinations (body length, head circumference and weight), the mean values at baseline and the increasing trend with increasing age were similar between treatment arms for the physical examination parameters, with the exception that subjects were slightly heavier in the aflibercept arm compared to the laser arm at baseline as well as at week 24.

Concerning surgical procedures, four (5.3%) subjects in the aflibercept arm and 1 (2.6%) in the laser arm underwent ocular surgical procedures after study start. Laser coagulation therapy was performed in 3 subjects (all in aflibercept arm) and other ocular surgical procedure was performed in 2 subjects, 1 in each arm (reported term lensvitrshvartectomy LVSHE which refers to extracapsular lens extraction and vitrectomy that were performed simultaneously) for the subject in the aflibercept arm and vitrectomy for the subject in the laser arm).

Furthermore, a total of 23 (20.4%) subjects underwent at least one non-ocular surgical procedure after study start, and the proportion was similar between the treatment arms (aflibercept 15 [20.0%] vs laser 8 [21.1%]). The most common surgical procedure was abdominal surgery, which was performed in 3 (4.0%) subjects in the aflibercept arm and 2 (5.3%) in the laser arm. The second most common surgical procedure was tracheostomy, which was performed in 3 (2.7%) subjects in total (aflibercept 2 [2.7%] vs laser 1[2.6%]). All other surgical procedures were performed in 2 or less subjects.

For the extension study 20275, the mean values at baseline and the increasing trend with increasing age were similar between treatment arms for the physical examination parameters.

Ophthalmologic examinations

At baseline, the proportion of eyes with abnormal findings in the posterior segment was low but relatively higher in the aflibercept arm compared to the laser arm (aflibercept 6.2% vs laser 1.4%). From week 0, day 1 onwards, the proportion of eyes with abnormal findings was generally comparable between the treatment arms at any assessment time point.

In parallel, the proportions of subjects with abnormal findings in the anterior segment and clinically significant abnormal findings were low at any assessment time point, and generally decreased during the course of the study from week 1 onwards. Overall, few subjects transitioned from “normal” towards

"abnormal" or "clinically significant abnormal" in either treatment arm. There was no subject transitioned from "abnormal" towards "clinically significant abnormal" in either arm.

Concerning intra-ocular pressure (IOP), any episode of clinically significant IOP were reported as an ocular AE. As expected for intravitreal injections, IOP was slightly higher in the aflibercept arm compared to the laser arm, but the changes from preinjection to postinjection were comparable between the treatment arms.

Presence of anti-drug antibodies before and 12 weeks after aflibercept injection

Immunogenicity to aflibercept in Study 20090 was very low. ADA was reported in 1 subject in the aflibercept arm at week 12. It was a treatment-emergent ADA response, and the ADA titer was low (1:30). Neutralizing antibodies were not detected in this subject.

Safety in special populations

Intrinsec factors

Extensive safety analyses were performed for aflibercept use across multiple indications in adult patients using ethnic factors, defined as relating to intrinsic (genetic [gender, race, genetics] and physiologic [height, body weight, absorption, distribution, metabolism, and excretion {ADME}, age, history of diseases]) characteristics of a population which concluded that the data from all pivotal aflibercept trials in adult patients provided no evidence of an impact by intrinsic factors.

As far as the target pediatric population of preterm infants with ROP is concerned, pharmacokinetic data in the Study 20090 did not reveal any relevant and consistent differences among Japanese and non-Japanese subjects. Subgroups were investigated by body weight and gestational age at baseline, sex, and region (Japan vs outside Japan) which did not appear to influence free (pharmacologically active) aflibercept concentrations in plasma.

Overall, plasma aflibercept concentrations measured in 75 subjects in the aflibercept arm were not correlated with arterial hypertension or any other adverse clinical findings. Among the 75 subjects, 69 subjects were treated bilaterally on the same day at baseline, 2 subjects had the 2nd eye treated with aflibercept after baseline, and 4 subjects were treated unilaterally throughout Study 20090.

In conclusion, mean free aflibercept concentrations all declined from week 0/day 1 onwards independent of the baseline body weight. Mean adjusted bound aflibercept concentrations increased from week 0/day 1 until week 4 and declined thereafter. Exploratory subpopulation analysis revealed no clinically relevant differences in free or adjusted bound aflibercept concentrations in plasma with respect to baseline body weight, gender, race, gestational age, oxygen supplementation at baseline, history of sepsis, or intraventricular hemorrhage.

No specific studies in patients with hepatic and/or renal impairment have been conducted and is to be expected with aflibercept as the available data does not suggest a need for a dose adjustment with aflibercept in these patients.

Extrinsec factors

No extrinsic factors were analyzed in Study 20090.

Use in pregnancy

Concerning the use in pregnancy and during lactation, overall there are data on the use of aflibercept in pregnant women however reproductive toxicity after systemic administration has been shown in preclinical studies. In the same way, as it is unknown whether aflibercept is excreted in human milk; a risk cannot be excluded.

As such, preterm infants with previous exposure to any intravitreal anti-VEGF agents, including maternal exposure during pregnancy and/or during breastfeeding were excluded from the pivotal Study 20090.

Withdrawal and rebound

Tolerance, withdrawal or rebound effects were not evaluated. 73.3% of subjects in the aflibercept 0.4 mg group in the pivotal study required initial treatment only Administration of IVT aflibercept to subjects with treatment-requiring ROP is a non-chronic treatment option. Typically, the drug is administered timely after diagnosis, usually bilaterally on the same day in a single treatment session. Usually, in the majority of cases, a single injection per eye appears sufficient, and if needed one re-injection after a minimum interval of 28 days may be required. The underlying disease of ROP may respond to treatment, reoccur or progress despite treatment.

Abuse and Overdose

No drug abuse is to be expected with Eylea (Aflibercept), solution for injection.

As 73.3% of subjects in the aflibercept 0.4 mg group in the pivotal study required initial treatment only, tolerance, withdrawal or rebound effects were not evaluated.

Typically, the drug is administered timely after diagnosis, usually bilaterally on the same day in a single treatment session. Usually, in the majority of cases, a single injection per eye appears sufficient, and if needed one re-injection after a minimum interval of 28 days may be required.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been analyzed or performed in study 20090.

Post marketing experience

As of 31 May 2021, 46 post-marketing cases (194 events) reported the use of aflibercept administered off-label in patients with ROP at doses of 0.4 mg to 2 mg corresponding to 31 were spontaneous reports, 13 derived from observational study reports and 2 from literature.

Of the 46 cases in total, 35 were non-serious and 11 serious. In the vast majority of cases the event outcome was not reported; there were 6 cases with a fatal outcome considered causally unrelated to aflibercept treatment by the reporter but related to complications of preterm birth.

Based on the review of these cases from cumulative post-marketing reporting, no new safety concern was identified.

MedDRA PT	Events Total
Off label use	49
Product use in unapproved indication	31
Product administered to patient of inappropriate age	18
Product use issue	15
Drug effective for unapproved indication	7
Therapeutic response unexpected	5
Iris vascular disorder	4
Pupil fixed	4
Retinal neovascularisation	4
Bronchopulmonary dysplasia	4
Patent ductus arteriosus	3
Necrotising colitis	2
Pre-existing condition improved	2
Neonatal candida infection	2
Pneumonia	2
Brain injury	2
Central nervous system haemorrhage	2
Intraventricular haemorrhage	2
Posthaemorrhagic hydrocephalus	2
Anaemia neonatal	1
Thrombocytopenia	1
Cardiovascular insufficiency	1
Congenital pneumonia	1
Trisomy 21	1
Ventricular septal defect	1
Conjunctival haemorrhage	1
Corneal oedema	1
Eyelid oedema	1
Retinal haemorrhage	1
Retinopathy of prematurity	1
Vitreous haemorrhage	1
Ascites	1
Gastrointestinal disorder	1
Inguinal hernia	1
General physical health deterioration	1
Hepatitis	1
CNS ventriculitis	1
Encephalitis	1
Endophthalmitis	1
Meningitis	1
Sepsis neonatal	1
Wrong technique in product usage process	1
Intraocular pressure increased	1
Foot deformity	1
Cerebral ischaemia	1
Hydrocephalus	1
Ischaemic stroke	1
Neonatal disorder	1
Somatic symptom disorder	1
Pulmonary artery stenosis	1
Hypertensive crisis	1
Total	**192**

MedDRA = medical dictionary of regulatory activities; PT = preferred term; ROP = retinopathy of prematurity; CNS = central nervous system

In post marketing, 46 cases off-label use were reported in premature infants for ROP. Few information was available including outcomes but conditions of administration such as dose, number of injections, and schedule of administration could be different from the one assessed in study 20090.

Among events reported, one AE of endophtalmitis was reported. Considering that premature infants are more prone to infections, this important identified risk for aflibercept is of concern. No case was reported in study 20090 and conditions of off-label use could be different from the authorized ones. Warnings have been implemented in the product information for the premature indication and this topic will be closely monitored in post-marketing surveillance in this population through PSUR.

4.6.1. Discussion on clinical safety

The clinical safety analysis is based on one phase III study of 6 months (FIREFLEYE, study 20090) which assessed administration of one or two intravitreal injections of aflibercept 0.4mg in premature infants diagnosed with ROP in comparison to laser photocoagulation. An extension study of a duration of 5 years (FIREFLEYE NEXT, study 20275) is also ongoing and evaluates long-term safety data of patients who completed the study 20090 including neurodevelopment assessment at 2 years, physical examination and ophthalmologic assessment. Submission of 5-year data is planned in Q1 2026 and interim analysis were submitted up to 2 years of chronological age as requested.

Patient exposure

Study 20090 enrolled 113 patients including 75 treated with aflibercept and 38 treated with laser. The extension study 20275 included 89 patients for a 5-year period with submitted data at a mean chronological age of 8.8 months and data at 1 year of chronological age for only 60 patients (39 in the aflibercept arm and in 21 in the laser arm).

Considering the vulnerable population of preterm infants for which long-term safety is crucial, non-clinical data which reported bone and renal risks, and neurodevelopment impairment reported with bevacizumab -another anti-VEGF- in ROP indication, submitted 1-year data for slightly more than half of patients were not considered sufficient. As requested in the first request of supplementary information, the MAH submitted the data available at 2 years of chronological age for more than half of the patients and the complete interim analysis will be submitted in June 2023. Furthermore, further discussion and available data on growth parameters and neurodevelopment test were submitted. In terms of exposure to be reported in future submissions to further reduce the uncertainties, a submission of only final results of the 5-year extension study in Q1 2026 was considered as not sufficient and interim analysis at 3 and 4 years are awaited in 2024 and 2025 as requested.

The majority of patients (>83%) completed the study 20090 at week 24 (90,7% in the aflibercept arm and 83,7% in the laser arm).

On the 75 patients in the aflibercept arm (146 eyes), 94,7% were bilaterally treated and a total of 120 eyes (82.2%) received a single IVT administration of 0,4 mg of aflibercept with a mean volume of 10,5 µL while 26 eyes (17.8%) received 2 injections. Rescue treatment was allowed with a higher proportion in the laser arm retreated by aflibercept (4 patients among 38) than in the aflibercept arm retreated by laser (5 patients among 75).

Patient demographics and baseline characteristics were consistent across treatment groups except for birth weight and reflect the ROP population with a majority of patients born at gestational age below 32 weeks and with very low birth weight, i.e. ≤1500g.

Adverse event (AE)

Ocular AE

In study 20090, incidences of ocular TEAE were well balanced between aflibercept and laser groups (38.7% vs 36.8%). The most reported ocular TEAE in treated eyes consisted of retinal haemorrhage (6,7% in aflibercept arm vs 13,2 % in the laser arm), retinal detachment (5,3% in both arms), conjunctival haemorrhage (5,3 % vs 0%), conjonctivitis (4,0% vs 10,5%) and eyelid oedema (2,7 % vs 7,9%). Severity was mainly mild to moderate. Despite low number of patients and AE reported which made challenging the comparison between arms, several PT were reported with a slightly higher rate in

aflibercept group such as conjunctival haemorrhage (5,3% vs 0%), conjunctival oedema (2,7% vs 0%), injection site haemorrhage and intraocular pressure increased (4,0% vs 0% both). Most of them are known complications of IVT administration which are listed in sections 4.4 and 4.8 of the SmPC.

Ocular SAE were reported in slightly higher proportions in the aflibercept arm in study 20090 (13.3% vs 7.9%) while the proportion of subjects with ocular TESAE was similar in both arms (8.0% vs 7.9%). The most reported TEAE were retinal detachment and retinal haemorrhage.

Otherwise, one case of retinal artery occlusion in both eyes reported in the aflibercept arm and assessed as related to aflibercept is of concern considering this sight-threatening AE and a close monitoring of this topic in PSUR in adult population and its causality to aflibercept is still unknown. The event occurred in the two eyes for one subject, was non-serious and severity was mild. Based on this single case, no sufficient information are available to associate this case with a thromboembolic or a local vasoconstriction cause nor of IOP increase related to anti-VEGF treatment with aflibercept. Overall, in case of a positive issue of the MAH, this topic will be further monitored in post-marketing surveillance through the PSUR and in the follow-up study 20275 up to 5 years of chronological age.

Regarding ocular infections, a topic of concern considering that premature infants are more prone to develop such events, a total of 7 subjects presented conjonctivitis with a higher proportion in the laser arm (10.5% vs 4,0%). No case of endophtalmitis, a known risk of anti-VEGF drugs by IVT route, was reported. Additional warnings have been proposed for endophtalmitis by the Applicant in sections 4.2 and 4.4 of the SmPC for ROP patients which are endorsed.

In addition, one case of overdose was reported with a dose 10 times higher than the recommended one. The medication error resulted in IOP increased and corneal oedema which were transient and of favourable outcome without any corrective treatment. More information about this case were requested during the procedure. Mandatory use of the PDD with the PFS allows the administration of a single dose of 10 µL/0.4 mg of aflibercept (range of 10.9 µL to 12.6 µL) and afterward the dose button will be blocked. Thus the risk of overdose would be limited.

Furthermore, one case of multiple-use of a single use product was also reported and more information about this case was requested. Extraction of multiple doses from a vial or a PFS is of concern considering risk of contamination and infection. Use of the PDD would allow to limit this risk since it cannot be reused without a major manipulation. The single use of the PFS is well mentioned in section 4.2 and 6.6 of the SmPc and in the Instruction for use (IFU) of the PDD.

Similar tendency was retrieved in study 20275 at 8.8 months and at 1 year for the 60 patients with similar proportions of subject presenting ocular TEAE (56.7% vs 55.2%; 56.4% vs 57.1%). Among the most reported events, myopia, astigmatism, retinal haemorrhage, conjunctivitis and strabismus were retrieved which are events compatible to possible consequences of the ROP evolution. Other known AE of aflibercept in adult population were also observed such as conjunctival haemorrhage (3 patients), vitreous haemorrhage (2 patients), corneal oedema (1 patient), intraocular pressure increased (3 patients) and retinal detachment (3 patients). For the last event, ROP evolution limits causal interpretability.

Further long term safety results (up to 2 years of chronological age) are discussed in above and completed data up to 2 years of age will be submitted in June 2023. Overall, an analysis of adverse events until 1 year of chronological age (in Studies 20090 and 20275) from 89 subjects who entered the extension Study 20275 demonstrated a similar proportion of ocular AEs between both groups (aflibercept 56.7% vs laser 55.2%) and showed lower rate of strabismus (96% aflibercept vs 84.6% laser), higher proportion of myopia was reported in the aflibercept arm (19.7%, vs 17.6%), but less pronounced myopia (2 out 13 for aflibercept and 2 out of 6 for laser), absence of cataract and age appropriate visual function.

Systemic AE

In study 20090, higher incidences of systemic TEAE were reported in the laser arm (63,2% vs 52,0%). The most reported SOC were Infections and infestations (17.7%), Respiratory, thoracic and mediastinal disorders (16.8%) and Gastrointestinal disorders (15.0%) with higher rates reported in the laser arm (respectively 28.9% vs 12.0%; 21.1% vs 14.7% and 21.1% vs 12.0%). The most reported events such as apnoea, umbilical hernia, haemorrhage subcutaneous, anaemia, and infantile apnoea are possible complications of premature infants.

Systemic SAE and TESAE occurred in a higher proportion of subjects in the laser arm compared to the aflibercept arm in study 20090 (respectively 36.8% vs 24.0% and 18.4% vs 6.7%). The events reported for more than one subject are infantile apnoea and bronchiolitis.

However, two SOC were of concern considering higher rates reported in aflibercept arm and known mechanism of action of anti-VEGF such as Cardiac disorders (5.3% vs 2.6%) and Nervous system disorders (9.3% vs 2.6%). Similar tendency was reported in study 20275 at 8.8 months arm (respectively 6.7% vs 3.4% and 15.0% vs 6.9%). Considering uncertainties on systemic exposure in this vulnerable population including higher exposure reported from PK data compared to adult patients, and known effects of VEGF on cardiovascular systems, a discussion on these imbalances was requested (see above). In addition, in study 20090 one event of developmental coordination disorders reported in aflibercept group is of concern considering existing data on bevacizumab in ROP as highlighted in the PIP. In study 20275, one event of movement disorders and one of motor development delay were reported in aflibercept arm. In the extension study 20275, incidences of systemic adverse events until 2 years of chronological age were similar between aflibercept and laser group (respectively 57,6% vs 55,0%). Overall, at this stage, available data is not in favour of a causal relationship between aflibercept IVT and nervous and cardiac disorders. Nonetheless, these uncertainties will be further reduced by provision of data in the context of the longer term follow-up and in the PSURs.

During the procedure, the MAH was requested to provide data on neurodevelopmental testing which was available for nearly half of the patient who had completed their 2 years of chronological age visit and considering a potential risk on the neurodevelopment of premature infants. Overall, at this stage the submitted data remains limited but the results for more than half of the patients up to 2 years on neurodevelopmental test as well as the previously submitted data on the SOC Nervous system disorders are reassuring and does not seems in favour of a risk of neurodevelopemental impairment in premature patients with ROP treated by aflibercept IVT.

Furthermore, the available data on the growth parameters on the 54 patients who had completed their 2 years of chronological age were requested considering the plausible risk and the limited data available on the topic. Overall, the change from baseline at visit for the weight, height and head circumference does not seems to differ between the aflibercept group and the laser group.

Overall, these topics will be closely monitored in post-marketing through PSUR and in the follow up study 20275 up to 5 years of chronological age. Interim analysis at 3 and 4 year of age are awaited in 2024 and 2025.

Renal disorders were also highlighted by non-clinical data but similar rates were reported between arms (2.7% vs 2.6%) in study 20090. One proteinuria event was reported in each arm. In study 20275, higher rates were reported in laser arm (6.9% vs 3.3%). Considering non-clinical data, known proteinuria AE of anti-VEGF by IV route and uncertainties on systemic exposure in this vulnerable population including higher exposure reported from PK data compared to adult patients, a discussion on renal monitoring in the extension study 20275 until 5 years of chronological age was requested. Overall, in regards of the mechanism of action of anti-VEGF, systemic AE including renal disorders need to be closely monitored

in the follow up study 20275 up to 5 years of chronological age and in post-marketing surveillance through PSUR.

Overall, three deaths were reported in study 20090 (bronchopulmonary dysplasia and pneumothorax; bronchiolitis; and bronchopulmonary dysplasia) at approximately 4 to 9 weeks after the last treatment and which were assessed as related to complications of underlying prematurity. No deaths were reported during the ongoing extension Study 20275.

No significant findings emerged from laboratory evaluations and ophthalmologic assessment in study 20090. In the extension study, no safety findings emerged from vital signs and physical examination at 8.8 months and at 1 year of chronological age for the 60 patients.

4.6.2. Conclusions on clinical safety

Overall, the safety profile for aflibercept in ROP patients appears similar to the one already described in adult population. In the initial submission data at 1 year of chronological age were provided for slightly more than half of patients and major concerns remained on the long-term safety profile considering the vulnerable population and the mechanism of action of aflibercept. These concerns were answered with a thoroughtt discussion on long-term safety which was provided by the MAH with the submission of an interim analysis at 2 years for more than half of the patients. The full interim analysis at 2 years is expected for June 2023 and the Applicant will also submit annual interims analysis (in 2024 and 2025) up to 5 years of chronological age to monitor premature patient's safety althrough the follow-up study 20275. Furthermore, the safety profile of alfibercept in the ROP population will be further monitored in pot-marketing-surveillance through PSUR.

4.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

5. Risk management plan

The MAH submitted an updated RMP version with this application. The main proposed RMP changes were the following:

1. **Part I: Product Overview**

This part was updated to add detail information on new indication ROP and dosage in preterm infants.

2. Part II

1. SI: Epidemiology

New indication ROP added, epidemiology of the disease, concomitant medications in the target population, and important co-morbidities found in the target population updated.

2. SII: **Non clinical part**

Update based on ROP specific considerations

3. SIII: **Clinical trial exposure**

Development in the indication ROP, brief description of ROP studies (FIREFLEYE study # 20090 and Phase IIIb study FIREFLEYE NEXT study # 20275), and clinical trial exposure in ROP studies added.

4. SIV: Populations not studied

Update to include key exclusion criteria of study 20090

5. SVII : Identified and potential risks

Whole section updated with information from Phase III study FIREFLEYE (Study # 20090) and Phase IIIb study FIREFLEYE NEXT (Study #20275); new safety concern added missing information regarding long-term safety of aflibercept in preterm infants with ROP.

Changes proposed in Part I and in Part II SI to SVII are acceptable.

6. SVIII Summary of safety concern

Table SVIII.1: Summary of safety concerns

Important identified risks	1.	Endophthalmitis (likely infectious origin)
	2.	Intraocular inflammation
	3.	Transient intraocular pressure increase
	4.	Retinal pigment epithelial tears
	5.	Cataract (especially of traumatic origin)
Important potential risks		
	6.	Medication errors
	7.	Off-label use and misuse
	8.	Embryo-fetotoxicity
Missing information	9.	Long-term safety of aflibercept in preterm infants with ROP

Long-term safety of aflibercept in preterm infants with ROP is considered as a missing information. The current knowledge about potential long-term effects of aflibercept IVT treatment in preterm infants with ROP is lacking and current safety profile is based on the 6-months pivotal study FIREFLEYE. Considering renal and growth disorders highlighted from non-clinical data, neurodevelopment impairment retrieved from clinical data with other anti-VEGF drugs and uncertainties on systemic aflibercept exposure including higher exposure retrieved compared to adult population in the vulnerable population of premature infants, monitoring of long-term safety is deemed necessary. An extension study FIREFLEYE NEXT (20275) has been set-up to evaluate the long-term outcomes up to 5 years of chronological age of patients who received treatment for ROP in study FIREFLEYE (20090). This study is ongoing and follows up on ocular, neurodevelopmental and overall clinical outcomes until 5 years of age when detailed assessment of visual function and overall development becomes more feasible.

10. Part III: PV Plan

Additional pharmacovigilance activities

Study FIREFLEYE NEXT (Study # 20275) was added as additional PV activity.

Table Part III.2: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).				

Table Part III.2: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Review safety outcomes of FIREFLEYE NEXT study **BAY 86-5321/20275**: An extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in Study 20090 Status: Ongoing	• Primary study objective: To evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for retinopathy of prematurity (ROP) • Secondary study objective: To describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP	• The purpose of the current study is to collect the missing data of the potential long-term effects after treatment with aflibercept and laser. Subjects will be followed up to 5 years of chronological age, which will enable a detailed assessment of visual function and overall development.	Protocol finalized (27 NOV 2019) LPLV: planned for OCT 2025	Interim study reports: • 2-year of age data in Q2 2023, • 3-year of age data in 2024, • 4-year of age data in 2025 Final study report 2026

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).

The MAH proposed to monitor safety data in ROP patients through the extension study 20275 until the 5 years of patients initially included in study 20090. A category 3 is proposed and final results are expected in Q1 2026.

Taking into account uncertainties on premature infants development after administration of anti-VEGF drug products, the Applicat was asked – and committed to - submit Interim analyses of study 20275 at 3 and 4 years of chronological age in 2024 and 2025.

- **Part V: Risk minimisation measures**

Routine risk minimisation measures

Table V.1 has been updated with addition of routine risk communication from the updated product information, i.e. additional warnings and statements proposed for paediatric population in sections 4.2, 4.4 and 4.8 of the SmPC and the corresponding sections of the PIL. For the treatment of babies born prematurely with ROP, a separate package leaflet instruction is provided (Information for guardians of babies born prematurely).

Additional risk minimisation measures

One set of educational material for Eylea will be used for both adult and pediatric populations. The key elements have been updated to reflect the need to use the paediatric dosing device and prime it properly in ROP.

- **Part VI: Summary of the RMP**

Updated in line with the changes above.

5.1. Overall conclusion on the RMP

☒ The changes to the RMP (vesion 32.3) are acceptable.

6. Changes to the Product Information

As a result of this group of variations, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

6.1.1. User consultation

This readability test result illustrates a positive assessment of the Eylea package leaflet. The package leaflet is laid out clearly, comprehensibly and fulfils the readability guideline recommendations relating to layout and design.

It must be stated that the participants in the final package leaflet survey located all information as requested with ease, thus comprehending and acting appropriately. Difficulties experienced in locating and comprehending information contained in the first tested package leaflet were reduced during the readability test; however, some additional optimisations are recommended.

Nevertheless, a positive acceptance was observed amongst the participants.

In conclusion, the Eylea package leaflet fulfils the requirements of articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

Retinopathy of prematurity (ROP) is a disorder of the blood vessels of the retina that affects extremely premature infants. ROP is a biphasic disease: phase 1 (~22 to 30 weeks postmenstrual age) is presented with hyperoxia and decreased VEGF levels that lead to interruption of normal vascularization and later ischemia of the retina and a phase 2 (~31 to 44 weeks postmenstrual age) with hypoxia and increased VEGF levels resulting in proliferation of new blood vessels. In preterm infants with disrupted angiogenesis, the abnormal neovascularisation and the leaky new blood vessels formed in this environment result in intraocular fibrosis, leading to retinal distortion, detachment, and at the end visual disability. In this context, the treatment by suppressing VEGF has a clear rationale.

According to the International Classification of Retinopathy of Prematurity (IC-ROP 2005), the main features for the classification of ROP are: the location of retinal involvement (Zone I, II or III), the extent of circumferential disease, the stage of severity (stage 1 to 5) and the vascular dilatation and tortuosity (plus disease. Additionally, a subtype called aggressive posterior ROP (AP-ROP) is an uncommon severe form of ROP, characterized by posterior location, prominence of plus disease, with extremely intense vascular.

The benefit-risk evaluation is conducted for patients with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.

Available therapies and unmet medical need

The current treatment strategy for ROP involves laser photocoagulation, anti-VEGF therapy (Lucentis) and surgery (vitrectomy or scleral buckle surgery for stage 4 or 5 ROP).

The treatment of ROP is initiated as soon as diagnosed. The laser photocoagulation consists in the ablation of the peripheral retina and result in a significant improvement in long-term visual function. However, laser treatment requires sedation or general anesthesia. It is also associated with loss of peripheral visual field, intraocular bleeding, myopia, macular dragging, cataract formation, and/or retinal detachment.

Since 2019, Lucentis (ranibizumab) is approved for the treatment of ROP with Zone I (stage 1+, 2+, 3 or 3+), Zone II (stage 3+) or AP-ROP (aggressive posterior ROP). The anti-VEGF therapy consist in one IVT injections and up to three per eye within six months of treatment initiation if there are signs of disease activity under local anesthesia. It is also associated with ocular (increase in IOP, vitritis, vitreous detachment, retinal haemorrhage,...) and systemic complications.

7.1.2. Main clinical studies

The efficacy of aflibercept in the treatment of infants born prematurely with retinopathy of prematurity was evaluated in one pivotal trial, its extension study, and a synthesis of available other studies used to contextualise results from the pivotal study.

- **Study 20090 (FIREFLEYE, Core study)** Open-label, Randomized, Two-Arm, Controlled Study to Assess the Efficacy, Safety, and Tolerability of Intravitreal (IVT) Aflibercept 0.4 mg Compared to Laser Photocoagulation in Patients With Retinopathy of Prematurity (ROP).

- **Study 20275 (FIREFLEYE extension)** is a currently ongoing Extension Study evaluating the Long-term Outcomes of Subjects Who Received Treatment for Retinopathy of Prematurity in Study 20090. The Last subject last visit for the Extension Study is planned for Jul 2025. Interim analysis were conducted to provide long term 1 year and 2 years of chronological age in the subset of patients for which these data were available.

- **Historical/published evidence synthesis study**: In the completed evidence synthesis study, no new data was collected, however, clinical data collected in Study 20090 was complemented by historical evidence for laser efficacy from the published randomized clinical trials BEAT-ROP and RAINBOW (Mintz-Hittner et al. 2011, Stahl et al. 2019), using a Bayesian statistical model.

The development was in accordance with the European Medicines Agency Paediatric Investigation Plan for aflibercept.

7.1.3. Favourable effects

In the pivotal study, treatment success (primary efficacy variable) was defined as the absence of active ROP and absence of unfavourable structural outcomes (retinal detachment, macular dragging, macular fold, or retrolental opacity) at 24 weeks after start of study treatment. At the primary endpoint (24 weeks), treatment success was numerically slightly higher with aflibercept IVT injection (85.5%) compared to laser photocoagulation (82.1%) with absence of active ROP and unfavorable structural outcomes.

Regarding the secondary endpoints results, the requirement for intervention with a second treatment modality from baseline to week 24 where the estimated median probability for subjects requiring an intervention with a second treatment modality from baseline until week 24 was numerically in favour of

the aflibercept arm: 7.2% (90% Credible Interval: 3.6, 12.7) in the aflibercept arm and 9.6% (90% Credible Interval: 4.2, 18.4) in the laser arm.

At 2 years of chronological age, efficacy data are available for 54 patients (36 in the aflibercept group and 18 in the laser group). Regarding the primary efficacy variable, the number of patients with active ROP numerically decrease from 9 eyes (6,2%) at 24 weeks to 7 eyes (4,8%) at 1 year and 0 at 2 years in the aflibercept group compared to 2 eyes (3,1%) at 24 weeks and 1 eye (2,9%) at 2 years in laser group. Severity of the disease decrease in both group and appear to stabilize at 2 years. Regarding the second primary outcome, namely the presence of unfavourable structural outcomes: the number of patients without any decreased from 4 eyes (3,1%) at 1 year to 0 eye at 2 years in the aflibercept group compared to 1 eye (1,6%) at 1 year and 1 eye (3%) at 2 years in the laser group.

A positive effect was also noted at all timepoints on a functional endpoint such as the ability to fix and follow a 5 cm toy. This ability continuedly improved over time through 2 years of chronological age in the aflibercept group, from 117 (94.4%) eyes at week 24 of Study 20090, to 124 (96.9%) eyes at 1 year and 68 (100%) eyes at 2 years of chronological age. The respective rates of eyes in the laser group were 88.9% at week 24, 98.4% at 1 year and 94.3% at 2 years of chronological age.

7.2. Uncertainties and limitations about favourable effects

The pivotal study FIREFLEYE (20090) did not demonstrate statistical relevance of the success criterion (non-inferiority of IVT aflibercept therapy to conventional laser therapy), although treatment success was numerically slightly higher with IVT aflibercept (85.5%) compared to laser (82.1%) at Week 24 and despite the study type I error being more relaxed than typically expected for a confirmatory study (lower limit of the one-sided 95% credible interval for the treatment difference (aflibercept – laser) was greater than -5%). However, the development plan was such that an uncertainty in the primary analysis could be anticipated, and the evaluation of all the available evidence (including with the context provided by the data synthesis exercise) allows to conclude that there is clinically meaningful efficacy for aflibercept in the target population.

Additionally, there is potential uncertainty about long-term efficacy beyond 2 years. This will be addressed by the submission of longer-term data.

7.3. Unfavourable effects

The safety profile of aflibercept 0,4 mg in premature infants diagnosed with ROP appears overall similar to the one described in adult population.

In study 20090, among the 75 patients treated with aflibercept, the proportions of subjects with ocular events were well balanced. The most reported ocular AE for aflibercept were retinal haemorrhage, retinal detachment, conjunctival haemorrhage and conjunctivitis which were mostly mild to moderate in intensity. Despite challenging comparison of arms due to low number of patients included, some AE were more reported in aflibercept group and could be related to IVT administration such as conjunctival haemorrhage, injection site haemorrhage and intraocular pressure increased.

7.4. Uncertainties and limitations about unfavourable effects

Considering the duration of the observations available at time of approval, long-term safety is considered sufficiently but not fully characterised in this vulnerable population.

Considering uncertainties on systemic exposure and the mechanism of action of aflibercept, the imbalances reported in the SOC Cardiac disorders and Nervous system disorders between arms in study

20090 and also at 8.8 months in study 20275 were of concern. The updated data at 1 year for all treated patients are at reassuring since no disparity was seen for the SOC "Nervous disorders" and "Cardiac disorders".

The above uncertainties are overall acceptable at this stage and will be further reduced with provision of further follow-up data as per RMP and in post-marketing surveillance through PSUR.

7.5. Effects Table

- **Effects Table for EYLEA in pre-term infant with ROP (data cut-off: 01 MARCH 2021)**

Effect	Short description	Unit	Aflibercept	Laser	Uncertainties / Strength of evidence	References
Favourable Effects						
ROP	Treatment success: absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting study treatment.	Descriptive	Core study 85.5 % success with aflibercept 0.4 mg	Core study 82.1 % success with laser ablation therapy	Core study result not statistically significant.	
	Unfavorable structural outcome at 1 year of chronological age	Descriptive	Extension study 10 eyes (6.8%)	Extension study 4 eyes (5.6%)	Long term follow-up missing.	
	Absence of active ROP at 1 year of chronological age	Descriptive	Extension study 7 eyes (4.8%) in the aflibercept group showed recurrence of ROP	Extension study 2 eyes (2.8%) in the laser group showed recurrence of ROP	Long term follow-up missing.	
Unfavourable Effects						
Ocular AE	Retinal haemorrhage	N (%)	5 (6.7%)	5 (13.2%)	Most reported AE	(1)
	Retinal detachment	N (%)	4 (5,3 %)	2 (5,3%)	Most reported AE	(1)
	Conjunctival haemorrhage	N (%)	4 (5,3 %)	0	Most reported AE	(1)

Effect	Short description	Unit	Aflibercept	Laser	Uncertainties / Strength of evidence	References
	Intraocular pressure increase	N (%)	3 (4,0 %)	0	AE related to injection procedure	(1)
	Retinal artery occlusion	N (%)	1 (1,3 %)	0	Sight-threatening AE closely monitored in adult population	(1)
Non ocular AE	SOC Cardiac disorders		5.3% 7.6%	2.6% 5.9%	Topic of concern considering mechanism of action of anti-VEGF and uncertainties on systemic exposure	(1) (2)
	SOC Nervous system disorders		9.3% 19.7%	2.6% 17.6%		(1) (2)

1. Study 20090
2. Study 20275 at 1 year

7.6. Benefit-risk assessment and discussion

7.6.1. Importance of favourable and unfavourable effects

The primary endpoint was the proportion of patients with absence of active ROP (i.e. ROP requiring treatment) and unfavorable structural outcomes (retinal detachment, macular fold, macular dragging, retrolental opacity) at 24 weeks after start of study treatment, based on the investigator's assessment for both eyes.

The clinical relevance of the efficacy demonstrated is supported by the endpoint measuring the ability to fix and follow a 5 cm toy, an age-appropriate technique to evaluate visual function, established in medical practice, and considered of high clinical relevance.

The ocular safety profile of aflibercept in this population comprised mainly injection procedure-related AEs, known from the use of aflibercept in adult patients and considered manageable.

7.6.2. Balance of benefits and risks

The totality of evidence supports that a clinically relevant level of efficacy for aflibercept has been demonstrated in the target population. The safety profile appears manageable. The uncertainties are acceptable at time of opinion, and will be further reduced by post-approval provision of data.

The benefit/risk balance is positive.

7.7. Conclusions

The overall B/R of EYLEA is positive.