EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Eylea

aflibercept

Procedure no: EMEA/H/C/002392/P46/020

Note

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

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1. Introduction

On 04th August 2021, the MAH submitted a completed paediatric study for EYLEA, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the Paediatric Investigation Plan (EMEA-000236-PIP05-18; P/0115/2019).

The study submitted as part of this P46 variation will be part of an upcoming Type II variation to reflect the clinical data of this study in the product information. The MAHs current estimated submission date is in November 2021.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Aflibercept (EYLEA) is a 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. In Europe, aflibercept (EYLEA) is approved for the following therapeutic indications:

"Eylea is indicated for adults for the treatment of :

• *neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),*

• *visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),*

• *visual impairment due to diabetic macular oedema (DME) (see section 5.1),*

• *visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1)."*

Following the agreed PIP following study have been conducted:

The FIREFLEYE paediatric study in PAH subjects was conducted as part of the PIP: EMEA-000236-PIP05-18 (EMA P/0115/2019)

- FIREFLEYE (BAY86-5321/20090): 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).

The 6-month core study was followed by a 5-years extension study, which was not part of the PIP:

- FIREFLEYE next (20275): An Extension Study to Evaluate the Long-term Outcomes of Subjects Who Received Treatment for Retinopathy of Prematurity in Study 20090

The purpose of the clinical overview (BAY 86-5321, dated 29 July 2021), is to assess the cumulative safety data for these 113 paediatric participants (23 to 31 weeks), from the start of aflibercept treatment in the FIREFLEYE study up to the end in 27 coutries. The present submission complies with Article 46 of Regulation (EC) No. 1901/2006 (the 'Paediatric Regulation').

2.2. Information on the pharmaceutical formulation used in the study

Aflibercept is formulated as a sterile solution for intravitreal injection, aseptically filled in a sterile glass vial at a concentration of 40 mg/mL. The currently marketed formulation in the EU was used.

During review of PIP [EMA P/0115/2019], the PDCO Formulation Working Group concluded that as the formulation is already optimised there is no concern for its intravitreal injection to the paediatric population.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Title of Study: 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 Name: FIREFLEYE (aFlIbeRcEpt For ROP - IVT injection versus Laser therapy[E])

2.3.2. Clinical study

Description

Methods

Study participants

FIREFLEYE was an open-label, randomize, double-arm controlled Phase 3 study, which enrolled male and female preterm infants with treatment-naïve ROP classified according to the International Classification for ROP (IC-ROP 2005) as Zone I Stage 1 plus, 2 plus, 3 non-plus or plus, or Zone II Stage 2 plus or 3 plus or aggressive posterior retinopathy of prematurity (AP-ROP) in at least one eye.

Further key inclusion criteria were:

- gestational age at birth ≤ 32 weeks or birth weight ≤ 1500 g

- body weight at baseline (day of treatment) ≥ 800 g

Key exclusion criteria

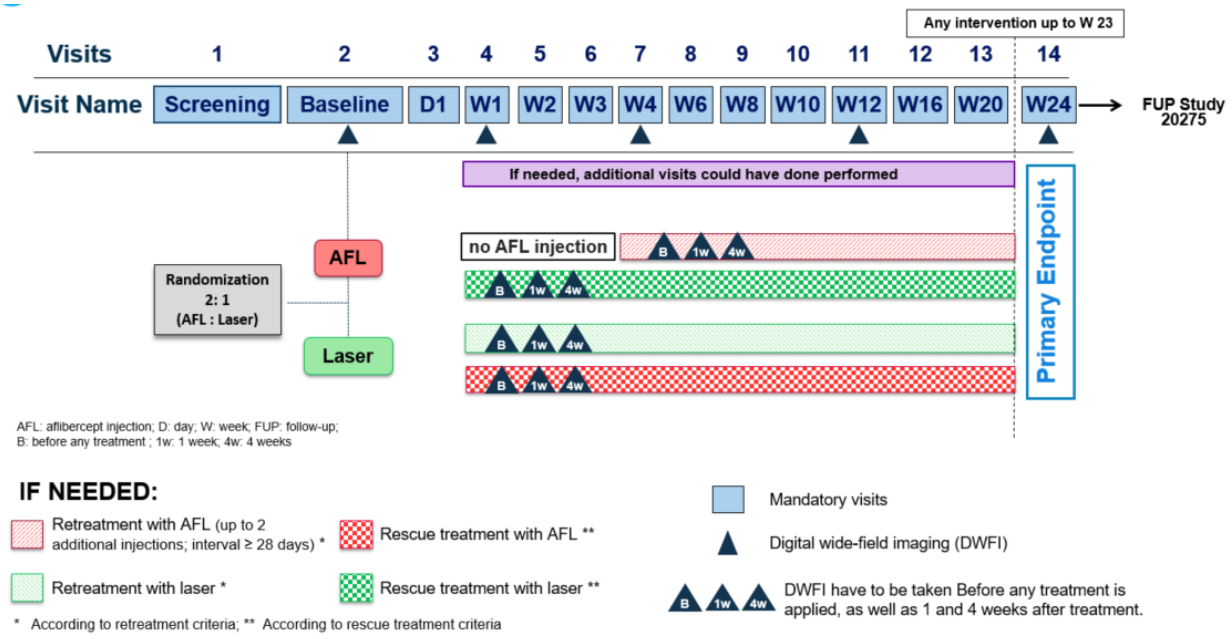
Subjects or their potential treated eye/s were excluded from the study if any of the criteria outlined in Module 5.3.5.1, Report PH-41617, Section 7.2.2 were met.

Treatments / Randomisation and blinding (masking)

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.



Objectives

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:

- Assess the safety and tolerability of aflibercept
- Assess the treatment burden of aflibercept and laser
- Describe the systemic exposure to aflibercept

Other prespecified objectives were to:

- Characterize further aspects of the effect of aflibercept in the treatment of ROP
- 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

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

Outcomes/endpoints /Statistical Methods

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 investigator assessment. Unfavorable structural outcomes were pre-specified in the protocol as retinal detachment, macular dragging, macular fold, and or retrolental opacity. Active ROP was defined (according to the inclusion criteria) as ROP requiring treatment.

Secondary efficacy variables included:

- 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

Safety was assessed based on SAEs, TEAEs and presence of anti-drug antibodies.

A Bayesian statistical model was used for the primary analysis. The success criterion was defined as "response probability for aflibercept is greater than 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 can be interpreted as non-inferiority hypothesis with a non-inferiority margin of 5 percentage points. A sensitivity analysis was also performed where the central reading center data was used instead of the investigators' assessments of ROP at week 24. Key secondary efficacy endpoints addressing the primary objective were "requirement for intervention with a second treatment modality from baseline to week 24" and as well as "recurrence of ROP from baseline to week 24", which were also analysed using Bayesian statistical models. Safety analyses included variables such as ocular and non-ocular (systemic) adverse events (AEs), treatment-emergent adverse events (TEAEs, defined as AEs reported after the first treatment and no later than 30 days after the last treatment administration), serious adverse events (SAEs), device events, clinical laboratory parameters, and other safety evaluations as outlined in the 20090 CSR.

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. 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:

- 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.

- 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).

The primary analysis of the primary efficacy variable used the full analysis set (FAS). The FAS included all subjects who received any study treatment and had a baseline and at least one post-baseline assessment of efficacy. Safety variables were analysed based on the safety analysis set (SAF). The SAF included all subjects who received any type of study treatment. Both FAS and the SAF included a total of 113 subjects treated at baseline, 75 in the aflibercept arm and 38 in the laser arm.

Results

Recruitment / Number analysed

FIREFLEYE study was conducted at 64 centers 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. 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.

Baseline data

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, 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 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 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%).

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%]) (Module 5.3.5.1 Report PH-41617, Table 14.1.4 / 8).

All subjects took at least one concomitant medication during the study. The most frequent medications in the aflibercept arm were: ophthalmologicals, vitamins, and antibacterials for systemic use in 100%, 93.3%, and 92.0% of subjects, respectively. In the laser arm, the most frequent medications were: ophthalmologicals, all other therapeutic products, and vitamins in 100%, 94.7%, and 92.1% of subjects, respectively. There were no considerable differences between treatment arms in concomitant medications by ATC class, with the exception of antiinfectives for systemic use (97.3% of aflibercept subjects and 81.6% of laser subjects), antineoplastic and immunomodulating agents (33.3% of

aflibercept subjects versus 13.2% of laser subjects), and genitourinary system and sex hormones (73.3% of aflibercept subjects versus 55.3% of laser subjects).

Several deviations from the protocol in terms of study design or conduct were reported during the study.

Efficacy results

Results of the primary objective – treatment success

The primary objective of the study was to assess the efficacy of aflibercept in subjects diagnosed with ROP in comparison to laser at 24 weeks after starting study treatment. 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 defined as ROP (according to the inclusion criteria) requiring treatment. Unfavourable 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.

Of the total 146 eyes (71 subjects with 2 eligible eyes and 4 subjects with 1 eligible eye) treated with aflibercept, 126 (86.3%) eyes (59 subjects with 2 eligible eyes and 8 subjects with 1 eligible eye) met the response criterion. In the laser arm, of the total 72 eyes (34 subjects with 2 eligible eyes and 4 subjects with 1 eligible eye) treated with laser, 61 (84.7%) eyes (28 subjects with 2 eligible eyes and 5 subjects with 1 eligible eye) met the response criterion. The number of subjects (eyes) who met the response criteria was numerically higher in the aflibercept arm than in the laser arm. The data were analysed by a Bayesian statistical model for the FAS, and the estimated response probability (median of the posterior distribution) was 85.5% of subjects in the aflibercept arm and 82.1% subjects in the laser arm. 90% credible intervals are provided for the probability of response. As the 90% credible interval for the treatment difference does not exclude -5%, the pre-defined success criterion was not met and noninferiority of aflibercept compared to laser treatment could not be concluded, although the aflibercept arm numerically showed slightly better outcomes. The posterior probability that the response probability for aflibercept is greater than the one for laser minus 5 percentage points was 88.4%.

A sensitivity analysis was performed using the central reading center assessments. Using the Bayesian model, the estimated response probability (median of posterior distribution) for subjects with absence of active ROP and unfavourable structural outcomes at 24 weeks was 80.9% in the aflibercept arm and 77.5% for subjects in the laser arm. Based on the reading center assessments, 92 (63.0%) of total 146 eyes in the aflibercept treatment arm and 53 (73.6%) of total 72 eyes in the laser treatment arm had absence of active ROP and unfavourable structural outcome.

Results of secondary objectives

A second treatment modality for ROP was either rescue treatment as defined in the protocol or any other surgical or non-surgical treatment for ROP (e.g. IVT anti-VEGF injection, ablative laser therapy, cryotherapy, or vitrectomy) after study start.

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

Using a Bayesian model, the estimated probability (median of posterior distribution) for subjects to require an intervention with a second modality from baseline until week 24 was 7.2% in the aflibercept arm and 9.6% in the laser arm. Of the 75 aflibercept subjects in the FAS, 71 (94.7%) subjects had 2 eligible eyes for the analysis and 4 (5.3%) subjects had 1 eligible eye. After bilateral treatment with aflibercept, intervention with a second treatment modality was given to 7 subjects. After unilateral treatment, no subjects required intervention with a second treatment modality.

Of the 38 laser subjects in the FAS, 34 (89.5%) subjects had 2 eligible eyes for the analysis and 4 (10.5%) subjects had 1 eligible eye. After bilateral treatment with laser, intervention with a second treatment modality was given to 5 subjects. After unilateral treatment, no subjects required intervention with a second treatment modality.

Recurrence of ROP from baseline to week 24

Recurrence of ROP until week 24 was defined as the need for retreatment or rescue treatment in cases where the question "presence of active ROP requiring treatment" had been previously answered by investigators with "no". Using a Bayesian model, the estimated probability for subjects to have a recurrence of ROP from baseline until week 24 was 16.1% in the aflibercept arm and 6.3% in the laser arm. Of the 75 aflibercept subjects in the FAS, 71 (94.7%) subjects had 2 eligible eyes for the analysis and 4 (5.3%) subjects had 1 eligible eye. 12 (16.0%) subjects had recurrence in both eyes after bilateral treatment with aflibercept and 8 (10.7%) subjects had recurrence in 1 eye after bilateral treatment. No subject had a recurrence in their treated eye after unilateral treatment. Of the 38 laser subjects in the FAS, 34 (89.5%) subjects had 2 eligible eyes for the analysis and 4 (10.5%) subjects had 1 eligible eye. Two (5.3%) subjects had recurrence in both eyes after bilateral treatment with laser, and 2 (5.3%) subjects had recurrence in 1 eye after bilateral treatment. No subject had a recurrence in their treated eye after unilateral treatment.

Pharmacokinetic/pharmacodynamic and immunogenicity results

In the clinical development program of aflibercept for the treatment of ROP, pharmacokinetics (PK) and immunogenicity data were derived from a total of 75 subjects treated with aflibercept 0.4 mg per eligible eye at baseline of Study 20090, mostly injected bilaterally on the same day.

Concentrations of free and bound aflibercept were listed by sample time point throughout the treatment period and summarized by descriptive statistics overall and by the subgroups baseline weight (< 1000 g, 1000 g to < 1500 g, 1500 g to < 2000 g, 2000 g to < 2500 g, and ≥ 2500 g), gender, race (Japanese vs. Non-Japanese), gestational age, oxygen supplementation at baseline, history of sepsis, history of necrotizing enterocolitis, and history of intraventricular hemorrhage. Relevant information on medical history and medication during pregnancy, relevant medication during the breastfeeding period and feeding type was also collected.

Mean concentrations of free (pharmacologically active) aflibercept declined until week 4 after dosing (mean concentration of 133 ng/mL at week 4), and declined further thereafter to values below or close to the lower limit of quantification (LLOQ) within approximately 8 weeks after start of treatment. Over time, with decreasing concentrations of free aflibercept (binding to VEGF by aflibercept's mode of action), levels of bound aflibercept increased up to week 4, and declined thereafter as well.

Exploratory sub-population analysis revealed no relevant effects on free or bound aflibercept concentrations with respect to baseline body weight, gestational age, gender, region (Japanese vs. Non-Japanese), race, oxygen supplementation at baseline, history of sepsis, history of necrotizing enterocolitis, and history of intraventricular hemorrhage. Subjects with the highest concentrations of free and bound aflibercept had AEs representing medical events expected in a population of preterm

infants. There was no indication that subjects with higher individual concentrations have clusters of AEs, beyond those caused by the underlying condition of prematurity.

Effects on blood pressure

Blood pressure (BP) was considered a marker of potential systemic anti-VEGF effects. BP was measured prior to blood collection, and if possible, prior to any other intervention, with a completely automated device, appropriate for use in infants, from screening up to week 24 (visit 14 / end of study). Any relationship of aflibercept plasma concentrations to blood pressure was evaluated for the first 4 weeks after start of treatment. Mean values of systolic BP (SBP) were similar in both treatment arms at baseline (aflibercept arm: 76.4 mmHg; laser arm: 75.4 mmHg) as well as at week 24 (aflibercept arm: 86.7 mmHg, laser arm: 88.8 mmHg). Over the study duration of 24 weeks, there was an increase of approximately 10 mmHg in the aflibercept arm and approximately 14 mmHg in the laser arm, reflecting body weight gain and organ development. Mean values of diastolic BP (DBP) were similar in both treatment arms at baseline (aflibercept arm: 44.1 mmHg and laser arm: 44.9 mmHg) as well as at week 24 (aflibercept arm: 51.6 mmHg and laser arm: 52.5 mmHg). Over the study duration of 24 weeks, there was an increase of approximately 8 mmHg in both arms, reflecting body weight gain and organ development.

Exploratory analysis of the influence of gestational age on the change from baseline in SBP and DBP revealed no relevant differences between aflibercept and laser treatment. Similarly, the relationship of baseline body weight (BW) and change from baseline in SBP and DBP revealed no relevant differences between aflibercept and laser treatment. Exploratory analyses showed that plasma aflibercept concentrations were not related to changes in SBP or DBP.

In summary, considering the challenging measurement conditions in the neonatal intensive care unit setting, a high variability of BP values was observed in both treatment arms. The increase of blood pressure over time is considered to be reflective of organ maturation and body weight gain in the range expected for this population of premature infants. No discernible differences between the two treatment arms were noted.

Immunogenicity

One subject had a treatment-emergent anti-drug antibody (ADA) development of low titer; neutralizing ADAs were negative. The ADA development did not appear to affect efficacy and safety in this subject (treatment responder).

Safety results

Ocular AEs

Overall, 43 patients (38.1 %) experienced ocular AEs, with no clinically relevant differences between treatment groups. The most frequent ocular AE overall was 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%; laser 7.9%) in the eye disorders System Organ Class (SOC); and conjunctivitis (aflibercept 4.0%, laser 10.5%) in the infections and infestations SOC

Overall, 9 patients (4.1%) experienced at least one ocular SAE. There were no clinically relevant differences between treatment groups. The most frequent ocular SAE was retinal haemorrhage (10 patients, 8.8 %) (6 patients, 2.8 % overall). The most common related ocular AE, conjunctival haemorrhage, occurred more frequently with aflibercept compared to laser (4 patients (5.3 %) in the aflibercept 0.4 mg group versus 0 patients (0%) in the laser group). All other related ocular AEs

occurred with low incidences (< 3 % overall) and in comparable proportions of patients across treatment groups.

The majority of ocular AEs were mild or moderate in severity; severe ocular AEs were reported for 5 patients (6.7 %) in the aflibercept group, and 4 patients (10.5 %) in the laser group. The proportion of subjects reported with ocular SAEs was 13.3% in the aflibercept arm and 7.9% in the laser arm, and the proportion of subjects with ocular TESAEs was 8.0% and 7.9%.

Non-ocular AEs

Overall, the non-ocular (systemic) TEAEs were more frequent in the laser arm (aflibercept 52.0% vs. laser 63.2%); the systemic events reflected the underlying prematurity of the study population with typical comorbidities in both treatment arms.

The proportion of subjects reported with systemic SAEs was lower in the aflibercept arm (24.0%) compared to the laser arm (36.8%). The proportion of subjects with systemic TESAEs was also lower in the aflibercept arm (6.7%) compared to 18.4% in the laser arm.

There were 3 subjects (2.7%), in the aflibercept arm with a fatal outcome of AEs related to pulmonary complications of preterm birth, assessed as unrelated to the study treatment all of which occurred approximately 4 to 9 weeks after the final study treatment. One subject in the aflibercept arm had non-neutralizing, low titer (1:30) anti-drug antibodies at week 12; this subject was a treatment responder.

There was no association of aflibercept treatment and increased blood pressure or proteinuria.

Overall, the observed AE profile was consistent with those reported with the IVT administration of aflibercept throughout its clinical development program in adults. Most AEs can be attributed to the IVT injection procedure, the patient population, or the progression of the underlying disease being treated. The safety data in Study 20090 are consistent with the established safety profile of aflibercept and no new safety concern was identified.

2.3.3. MAH's discussion on clinical aspects

Efficacy

Aflibercept was efficacious in the treatment of ROP. Patients treated with aflibercept 0.4 mg were more likely to achieve treatment success (defined as absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after the first study treatment) compared with laser therapy, which can be considered clinically relevant even though the primary endpoint did not demonstrate statistical significance.

In a sensitivity analysis where missing outcomes of active ROP and unfavourable structural outcomes at Week 24 were imputed from the results observed at the Week 20 visit, treatment success was statistically significantly higher for aflibercept 0.4 mg when compared with laser (85.5% vs 82.1 %). However, non-inferiority of IVT aflibercept therapy to conventional laser therapy was not demonstrated (90% credible interval for treatment difference was −8.0% – +16.2%; the posterior probability that the response rate for aflibercept is greater than the one for laser minus 5 percentage points was 88.4%, i.e. below 95%).

Other secondary efficacy endpoints were also in favour of aflibercept treatment. Among the patients receiving aflibercept 0.4 mg at Baseline, 7.2 % needed additional intervention with another treatment modality and 4.8% patient had unfavourable structural outcomes at Week 24; these unfavourable structural outcomes are associated with poor vision in the long term and thus important predictors of the vision. In contrast, among the patients receiving laser treatment at Baseline, 9.6 % required intervention with another treatment modality, and 6.9 % had unfavourable structural outcomes at Week 24.

The proportion of patients with recurrence of ROP, as defined as any post-baseline study intervention up to 24 weeks after initial treatment, was higher in aflibercept groups than in the laser group (16.1% vs. 6.3 %).

This may be explained as laser photocoagulation therapy is known to destruct peripheral tissue responsible for continuous elevation of VEGF. Hence it is hypothesised that laser photocoagulation, albeit unable to inhibit existing excessive VEGF and therefore having a slower onset, may minimise the risk of ROP recurrence at the cost of an increased risk for less favourable structural and visual outcome.

Safety

The incidence of ocular and non-ocular AEs and SAEs was generally balanced across treatment groups. The only PT consistently reported at a higher incidence in the aflibercept groups than in the laser group was conjunctival haemorrhage. None of the events of conjunctival haemorrhage was severe in intensity or considered an SAE.

Apart from conjunctival haemorrhage (5.3 % overall), very few AEs were suspected by the Investigator to be related to study treatment or procedure (13.3 % overall for ocular AEs, 0.5 % for non-ocular AEs).

Non-ocular AEs and SAEs were generally typical comorbidities in preterm infants, and no clinically relevant differences were seen between treatment groups.

No significant new safety concern emerged from this study.

Conclusions

Aflibercept 0.4 mg was an efficacious treatment for preterm neonates with ROP; patients treated with aflibercept 0.4 mg were more likely to achieve treatment success compared with laser therapy, which is considered clinically relevant.

Aflibercept treatment is safe and well tolerated in patients with ROP. The observed safety profile was as expected in a preterm population, and ocular AEs/SAEs were generally consistent with the established profile for aflibercept in adults.

Considering the results of the study and the high unmet medical need for new treatment options for ROP patients, Bayer AG intends to submit a Type II variation to reflect the study results in the EU SmPC.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of the FIREFLY study, 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 follow the several points discussed and agreed in the PIP, such as: indication, population, criteria of participation in the study, endpoints, number of patients (102 in total) and duration of the treatment. Regarding the study design, discussions were held on the number of arms (which differed from the RAINBOW study) 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 a follow-up study (not part of the PIP) until they are 5 years of age to assess ocular effects (including those related to IVT administration), clinical and neurodevelopmental outcomes.

As the conclusion of the PIP, the MAH has commit to:

- develop or identify an accurate application device to ensure accuracy for administration of 10

microliters.

- provide data at the time of marketing authorisation application on structural abnormalities at 1 year of chronological age (estimated to occur approximately 9 months after treatment) from at least 50% of the subjects

Overall, the FIREFLY study has been conducted in compliance with the PIP as agreed by the PDCO. However, the efficacy and safety data will be assess by the CHMP Rapporteur at the time of the Type II variation to extent the indication of EYLEA to the treatment of patients with ROP. Thus, at this stage, no conclusion on the benefice/risk balance can be drawn.

☒ Fulfilled:

No further action required in the frame of this variation, however, the MAH should commit to submit this variation application by 31 November 2021.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: EYLEA Active substance: Aflibercept

Study title	Study number	Date of completion	Date of submission of final study report
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)	20090	12/02/2021	July 2021
An Extension Study to Evaluate the Long-term Outcomes of Subjects Who Received Treatment for Retinopathy of Prematurity in Study 20090	20275	Ongoing	The planned completion date of the study is Q3/2025. An interim analysis report is expected to be submitted by Q4/2021 with the variation application.