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Newcastle University

Health Technology Briefing
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Aflibercept for previously untreated retinopathy of prematurity in children

Company/Developer	Bayer AG

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28139	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Retinopathy of prematurity (ROP) is a condition that can occur when a baby is born prematurely, which affects blood vessels in a part of the eye called the retina. The retina is at the back of the eye. It detects light and sends messages to the brain, which allows us to see. In severe ROP, blood vessels do not develop how they should in the retina. These abnormal blood vessels grow because of a substance called vascular endothelial growth factor (VEGF) and they can later turn into damaging scar tissue. This can cause serious loss of vision or blindness if it is not diagnosed or treated early. Most babies who have ROP will have a mild form of the condition which will not require any treatment and will get better on its own. However, for babies with more advanced ROP, treatment is required. Laser therapy is the most common treatment option, however this comes with the risk of scarring and permanent vision damage. Other options can include anti-VEGF agents or surgery, however these treatment options can be limited.

Aflibercept is an engineered protein that has been designed to attach to and block the effects of VEGF-A. It can also attach to other proteins such as placental growth factor (PlGF). VEGF-A and PlGF are involved in stimulating the abnormal growth of blood vessels in patients with ROP. By blocking these factors, aflibercept reduces the growth of abnormal blood vessels and controls leakage and swelling. Aflibercept, therefore, works by changing the amount of blood that gets to the retina. Aflibercept is administered through an injection into the eye. If recommended, it would serve as an additional treatment option for treatment-naïve ROP.

Proposed Indication

For the treatment of treatment-naïve retinopathy of prematurity (ROP) in babies with a gestational age at birth ≤ 32 weeks or birth weight ≤ 1500g.[1]

Technology

Description

Aflibercept (Eylea) is an ophthalmological, anti-neovascularisation agent. It is a recombinant fusion protein consisting of portions of human vascular endothelial growth factor (VEGF) receptor 1 and 2 extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. 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.[2] By blocking these factors, aflibercept reduces the growth of abnormal blood vessels and controls leakage and swelling.[3] Aflibercept, therefore, works by changing the amount of blood that gets to the retina.[4]

Aflibercept is in clinical development for the treatment of ROP. In phase III clinical trials (NCT04004208, NCT04101721) aflibercept is administered as an intravitreal (IVT) injection in each eligible eye.[1,5]

Key Innovation

Currently treatment options are limited.[6] Laser treatment is the standard of care, however some premature babies are too unwell and fragile to receive laser treatment, and laser also risks scarring of the retina and permanently damaging vision. Vision loss can be devastating, hence new treatment is required to improve futures and outcomes of babies and their families.[7] ROP is characterised by abnormal development of the retinal vascularisation in preterm infants with a young gestational age (≤ 32 weeks) only and has been associated with disturbances in the levels of VEGF. Thus, anti-VEGF products such as aflibercept, are capable of treating ROP based on clinical positive feedbacks.[8] The VEGF inhibitor aflibercept injected into the eye targets elevated intraocular levels of VEGF.[6] If recommended, aflibercept would serve as an additional treatment option for treatment-naïve ROP.

Regulatory & Development Status

Aflibercept currently has Marketing Authorisation in the UK/EU for the treatment of adult patients with:[2]

- Neovascular age-related macular degeneration
- Visual impairment due to macular oedema secondary to retinal vein occlusion
- Visual impairment due to diabetic macular oedema
- Visual impairment due to myopic choroidal neovascularisation

Aflibercept is also currently licensed in the UK/EU for the treatment of ROP with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease in preterm infants.[2]
Aflibercept has the following regulatory designations/awards:[9]

- An FDA Orphan drug designation in the USA in 2019 for the treatment of ROP

Aflibercept is currently in phase II and III trials for the treatment of diabetic macular oedema, neovascular age-related macular degeneration, proliferative vitreoretinopathy, colorectal cancer, macular telangiectasia, thyroid eye disease, and ocular melanoma.[10]

Patient Group

Disease Area and Clinical Need

ROP is an eye condition that can occur when a baby is born too early (premature) or if the baby has a birth weight less than 3 pounds (~1,360g).[11] This can cause blood vessels in the eye to not develop normally, causing damage to the retina.[3] These abnormal blood vessels grow because of VEGF and they can later turn into damaging scar tissue.[12] Risk factors for developing ROP are dominantly low gestation and low birth weight, but infants receiving postnatal oxygen supplementation and poor postnatal weight gain have also been associated with ROP.[13] Infants at risk of ROP require regular ophthalmic screening to ensure the early detection and management.[14] Many extremely preterm infants will develop some degree of ROP, although in most cases this never progresses beyond mild disease which resolves spontaneously without treatment. A small proportion develop potentially severe ROP, which can cause blindness if left untreated.[14] There are five different stages of ROP, ranging from mild (stage 1) to severe (stage 5). Most babies with ROP will have stage I or II ROP which will require no treatment and where eventually normal vision develops. Some babies with stage 3 ROP can recover with no treatment and go on to have healthy vision, whereas others need treatment to prevent further damage.[11]

ROP develops in an estimated 60% of infants weighing less than 1,500g at birth while severe ROP is uncommon, with the incidence of ROP requiring treatment being 4% in the UK .[14,15] In England 2022-23, there were 352 finished consultant episodes (FCE) and 311 admissions for ROP (ICD-10 code H35.1). This resulted in 827 FCE bed days and 105 day cases.[16]

Recommended Treatment Options

There are currently no NICE recommended treatment options for ROP.[17] Many babies with ROP have mild cases and get better without treatment.[11] However, for more severe cases there are various treatment options available, outlined by the Royal College of Ophthalmologists in the UK. These include laser therapy, cryotherapy, anti-VEGF agents and vitrectomy surgery.[13] Laser therapy is the most common treatment option, and it reverses severe ROP about 90% of the time. In cases where laser therapy will not work well, anti-VEGF agents are injected inside the eyes.[12] Ranibizumab is currently the only anti-VEGF licensed for use in preterm infants.[13]

Clinical Trial Information

Trial	**FIREFLEYE; NCT04004208, EudraCT 2018-002611-99;** 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)	**FIREFLEYE next; NCT04015180, EudraCT 2018-003180-54;** An Extension Study to Evaluate the Long-term Outcomes of Subjects Who Received Treatment for Retinopathy of Prematurity in Study 20090 **Phase III** – active, not recruiting

	Phase III – completed **Location(s):** 14 EU countries, UK, and other countries **Study completion date:** February 2021	**Location(s):** 12 EU countries, UK, and other countries **Primary completion date:** July 2025
Trial Design	Randomised, open label, parallel assignment	Non-randomised, open label, parallel assignment
Population	N=113 (actual); babies with treatment-naïve ROP with a gestational age at birth ≤ 32 weeks or birth weight ≤ 1,500 g	N=96 (actual); babies who were participants in Study 20090 (NCT04004208); aged up to 13 months
Intervention(s)	Aflibercept administered via IVT injection of Dose A aflibercept per eligible eye at baseline	No study treatment will be administered. The treatments to be evaluated in this study were administered in Study 20090.
Comparator(s)	Laser photocoagulation treatment in each eligible eye at baseline	No study treatment will be administered. The treatments to be evaluated in this study were administered in Study 20090.
Outcome(s)	Primary outcome measure(s): • Proportion of participants with absence of active ROP and unfavourable structural outcomes [time frame: At 24 weeks after starting study treatment]. Active ROP was defined as ROP requiring treatment. Unfavourable structural outcomes included retinal detachment, macular dragging, macular fold, or retrolental opacity. See trial record for full list of other outcomes.	Primary outcome measure(s): • Binocular best-corrected visual acuity in Snellen equivalent [time frame: At 5 years of age.] • Proportion of subjects with ocular adverse events (AE) and serious adverse events (SAE) [time frame: Up to 5 years of age.] • Proportion of subjects with systemic AEs and SAEs [time frame: up to 5 years of age.] See trial record for full list of other outcomes.
Results (efficacy)	Treatment success was 85.5% with intravitreal aflibercept vs 82.1% with laser photocoagulation (between-group difference, 3.4% [1-sided 95% credible interval, −8.0% to ∞]). Rescue treatment was required in 4.8% (95% CI, 1.9% to 9.6%) of eyes in the intravitreal aflibercept group vs 11.1% (95% CI, 4.9% to 20.7%) of eyes in the laser photocoagulation group.[18]	-
Results (safety)	The serious adverse event rates were 13.3% (ocular) and 24.0% (systemic) in the intravitreal aflibercept group compared with 7.9% and 36.8%, respectively, in the laser	-

	photocoagulation group. Three deaths, which occurred 4 to 9 weeks after intravitreal aflibercept treatment, were considered unrelated to aflibercept by the investigators.[18]	

Clinical Trial Information

Trial	**BUTTERFLEYE;** NCT04101721, **EudraCT** 2019-001764-29; Randomized, Controlled, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Compared to Laser Photocoagulation in Patients With Retinopathy of Prematurity **Phase III** – completed **Location(s):** 5 EU countries, USA, and other countries **Study completion date:** August 2022
Trial Design	Randomised, open label, parallel assignment
Population	N=127 (actual); babies with treatment-naïve ROP with a gestational age at birth ≤ 32 weeks or birth weight ≤ 1,500 g
Intervention(s)	Aflibercept administered as a single IVT injection per eligible eye at baseline
Comparator(s)	Laser photocoagulation treatment in each eligible eye at baseline
Outcome(s)	Primary outcome measure(s): • Percentage of participants with absence of active ROP and unfavourable structural outcomes from baseline to week 52 of chronological age [time frame: baseline to week 52 of chronological age]. Active ROP was ROP requiring treatment and unfavourable structural outcome was defined as retinal detachment, macular dragging, macular fold, or retrolental opacity. For participants with both eyes enrolled in the study, both eyes must have met the endpoint. Participants with only one study eye enrolled were responders if the respective eye responded. See trial record for full list of other outcomes.
Results (efficacy)	In both trials, approximately 80% of aflibercept-treated infants achieved an absence of both active ROP and unfavourable structural outcomes at 52 weeks of age, which is better than would have been expected without treatment.[19]
Results (safety)	Comparing aflibercept to laser, ocular adverse events (AEs) among patients occurred in 18% versus 26% in BUTTERFLEYE, with serious ocular AEs occurring in 6.5% versus 11% in BUTTERFLEYE. AEs in both FIREFLEYE and BUTTERFLEYE trials were consistent with infant prematurity or to the injection procedure, and with the AEs in similar ROP trials.[19]

Estimated Cost

The National Health Service (NHS) indicative price for one aflibercept 4mg/100µL solution for injection vial and one aflibercept 3.6mg/90µL solution for injection pre-filled syringe is £816.00 each (hospital only).[20]

Relevant Guidance

NICE Guidance

- NICE guideline. Developmental follow-up of children and young people born preterm (NG72). August 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Ranibizumab in Retinopathy of Prematurity (2201) [230401P]. May 2023.
- NHS England. 2013/14 NHS Standard Contract for Peadiatric Surgery: Neonates. E02/S/c.
- NHS England. 2013/14 NHS Standard Contract for neonatal critical care. E08/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology (Paediatrics). D12/S/b.

Other Guidance

- The Royal College of Paediatrics and Child Health. UK screening of retinopathy of prematurity guideline. March 2022.[14]
- The Royal College of Ophthalmologists. Treating Retinopathy of Prematurity in the UK. March 2022.[13]

Additional Information

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