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HEALTH TECHNOLOGY BRIEFING
NOVEMBER 2020

Faricimab for diabetic macular oedema

NIHRIO ID	12423	**NICE ID**	10418
Developer/Company	Roche Products Ltd	**UKPS ID**	657185

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Faricimab is in clinical development for adults with diabetic macular oedema (DMO). DMO is a type of eye disease where blood vessels leak fluid into the retina. Vision loss occurs when the fluid reaches the macula (the centre of the retina that provides sharp vision) and builds up, causing swelling. Over time, DMO can cause central vision to become blurred, eventually these changes become permanent. Current treatments use steroid implants, or an injection of anti-vascular endothelial growth factor-A (VEGF-A), in the eye to stop the condition from worsening. Faricimab is a new antibody that targets two growth factors, VEGF-A and anti-angiopoietin-2 (Ang-2), simultaneously. These growth factors promote the production of new blood vessels, which faricimab blocks. Growth of weaker, leaky blood vessels exacerbates DMO so halting this process would help reduce a patient's chance of developing further eyesight complications. Faricimab is administered as an injection into the eye. Faricimab would be the first antibody to target both VEGF-A and Ang-2 and results so far indicate it would take longer to re-treatment, compared to a treatment that targets VEGF-A only.

PROPOSED INDICATION

Adult patients diagnosed with DMO.[1-4]

TECHNOLOGY

DESCRIPTION

Faricimab (RO6867461, RG 7716) is a novel anti- Ang-2 and VEGF-A bispecific antibody. It binds to both Ang-2 and VEGF-A, which are involved in DMO pathogenesis, with high affinity and specificity.[5] The fragment crystallizable (Fc) region of faricimab has been manufactured to remove binding interactions with Fc γR and Fc Rn (part of the immune cell response) for reduced effector function and faster systemic, but not ocular, clearance.[6]

Faricimab is currently in phase III development for patients with DMO (Rhone-X, NCT04432831; RHINE, NCT03622593; YOSEMITE, NCT03622580). In the clinical trials, patients in Arm A are administered an intravitreal (IVT) injection of 6.0mg faricimab into the effected eye once every 8 weeks after 6 x 4 weekly injections of 6.0mg faricimab, whereas patients in Arm B are administered an IVT injection of 6.0mg faricimab into the effected eye following a personalised treatment interval (PTI) after 4 x 4 weekly injections of 6.0mg faricimab. PTI can be considered as a protocol-driven treat-and-extend regimen (intervals adjusted in 4 week increments to a maximum of 16 weeks).[a]

INNOVATION AND/OR ADVANTAGES

Faricimab acts via a novel mechanism of action, through the simultaneous targeting of both VEGF-A and Ang-2. It is hypothesized that this will lead to improved efficacy and durability outcomes in DMO patients.[5]

In a Phase II randomised trial (NCT02699450) faricimab demonstrated statistically significant visual acuity gains compared to ranibizumab (active comparator) in treatment-naïve patients, which suggest benefit of simultaneous inhibition of VEGF-A and Ang-2. In addition, a pre-specific analysis demonstrated there was great probability for patients treated with 6.0mg faricimab to exhibit a longer time to re-treatment in comparison to ranibizumab-treated patients.[5]

There are currently no therapies recommended for DMO that target both VEGF-A and Ang-2 simultaneously.[7,8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Faricimab does not currently have marketing authorisation in the EU/UK for any indication.

[a] Information provided by Roche Products Ltd

Faricimab is also in phase III clinical development for wet macular degeneration.[9]

PATIENT GROUP

DISEASE BACKGROUND

DMO is the most common cause of sight loss in people with diabetes. It affects the central area of the retina, called the macula, which is responsible for fine detail vision both near and far away. DMO occurs when blood vessels damaged by high blood sugar leak into the macular region resulting in a fluid build-up and retention that can impair sight. There are two subtypes of DMO:[10,11]

- Centre-involving – where the centre of the macula (fovea) is affected and/or the immediate surrounding area
- Non-centre involving (extra-foveal)

In the early stages of DMO a patient's vision may not be affected straight away. However, as retinopathy progresses this can lead to changes in sight, such as dark/smudged spots, blurring/loss of focus, object distortion and colour fade. Damage from DMO cannot currently be reversed and any loss of sight is permanent.[10]

People are at greater risk of developing DMO if they have long-term diabetes, high blood pressure, poorly controlled blood sugar or high cholesterol, or if they smoke or are pregnant.[12]

CLINICAL NEED AND BURDEN OF DISEASE

DMO is responsible for most vision-loss experienced by patients with diabetes and approximately 7% of individuals with diabetes have DMO.[5,13]

In England (2019-20) there were 839 finished consultant episodes (FCE) for patients with type 1 diabetes with ophthalmic complications (ICD-10 code E10.3, which includes DMO) with 1,438 FCE bed days. There were 1,576 FCE for patients with type 2 diabetes with ophthalmic complications (ICD-10 code E11.3, which includes DMO) with 2,136 FCE bed days.[14]

In 2010, it was estimated that around 7.12% (166,325) of persons with diabetes in the England had DMO in one or both eyes, and of these, 64,725 individuals had clinically significant DMO reducing the visual acuity to poorer than 6/6 in at least one eye. The overall health and social care costs were estimated at £116,296,038.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

If a patient has non-centre involving DMO then laser treatment is commonly used. Patients with centre-involving DMO are not recommended for laser treatment, as it can cause scarring in the central vision. If a centre-involving DMO patient's central foveal thickness (CFT) is <400µm then treatment using an intravitreal (IVT) implant that secretes a steroid may be considered, however this is not universally adopted given the potential rise in intraocular pressure. For patients with CFT >400µm anti-VEGF IVT injections are given.[16,17]

CURRENT TREATMENT OPTIONS

Pharmacological options for DMO include:[13,16]

- IVT steroid implants such as dexamethasone (Ozurdex) or fluocinolone acetonide (Iluvien)
- IVT injections of anti-VEGF such as aflibercept (Eylea) and ranibizumab (Lucentis)

PLACE OF TECHNOLOGY

If licenced faricimab will offer an alternative treatment for patients with DMO.

CLINICAL TRIAL INFORMATION

Trial	**Rhone-X; NCT04432831; 2020-000402-29;** A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Patients With Diabetic Macular Edema **Phase III -** Recruiting **Location(s):** EU (inc UK), US, Canada, and other countries **Primary completion date:** August 2023
Trial design	Open label, single group assignment
Population	N = 1800 (planned), aged 18 years and older, previous enrolment and completion in NCT03622580 (RHINE) or NCT03622593 (YOSEMITE).
Intervention(s)	Faricimab 6.0mg administered by intravitreal (IVT) injection in the eye according to personalised treatment interval (PTI) which can be considered as a protocol-driven treat-and-extend regimen (maximum interval 16 weeks).[b]
Comparator(s)	-
Outcome(s)	• Incidence and Severity of Ocular Adverse Events [Time Frame: Up to 2 years] • Incidence and Severity of Systemic (Non-Ocular) Adverse Events [Time Frame: Up to 2 years] • Number of Participants with Presence of Anti-Drug Antibodies (ADAs) at Baseline and Incidence of ADAs

[b] Information provided by Roche Products Ltd

	During the Study [Time Frame: From Baseline up to 2 years]
Results (efficacy)	-
Results (safety)	-

Trial	**RHINE; NCT03622593; 2017-005105-12;** A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients With Diabetic Macular Edema (RHINE) **Phase III –** Active, not recruiting[c] **Location(s):** EU (inc UK), US, Canada and other countries **Primary completion date:** December 2020
Trial design	Randomised, triple masked, parallel assignment.
Population	N = 1070 (planned), age 18 years and older, documented diagnosis of diabetes mellitus (Type 1 or Type 2), hemoglobin A1c (HbA1c) of less than or equal to (≤)10% within 2 months prior to Day 1, macular thickening secondary to DME involving the centre of the fovea, decreased visual acuity attributable primarily to DME.
Intervention(s)	• Arm A: Faricimab 6.0mg administered by IVT injection into the eye once every 8 weeks (Q8W) after 6 x 4 weekly injections • Arm B: Faricimab 6.0mg administered by IVT injection as a PTI after 4 x 4 weekly injections. PTI can be considered as a protocol-driven treat-and-extend regimen (intervals adjusted in 4 week increments to a maximum of 16 weeks)[c]
Comparator(s)	• Arm C: Active comparator, Aflibercept (Eylea) administered by IVT injection into the eye once every 8 weeks • Matched placebo (sham procedure) for each arm
Outcome(s)	• Average Change From Baseline in Best-Corrected Visual Acuity (BCVA) at 1 Year [Time Frame: Baseline (Day 1) and 1 year] • See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**YOSEMITE; NCT03622580; 2017-005104-10;** A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients With Diabetic Macular Edema (YOSEMITE)

[c] Information provided by Roche Products Ltd

	Phase III – Active, not recruiting **Location(s):** EU (not inc UK), US, and other countries **Primary completion date:** December 2020
Trial design	Randomised, triple masked, parallel assignment.
Population	N = 940 (actual), age 18 years or older, documented diagnosis of diabetes mellitus (Type 1 or Type 2), hemoglobin A1c (HbA1c) of less than or equal to (≤) 10% within 2 months prior to Day 1, macular thickening secondary to DME involving the centre of the fovea, decreased visual acuity attributable primarily to DME
Intervention(s)	• Arm A: Faricimab 6.0mg administered by IVT injection into the eye once every 8 weeks (Q8W) after 6 x 4 weekly injections • Arm B: Faricimab 6.0mg administered by IVT injection at PTI after 4 x 4 weekly injections. PTI can be considered as a protocol-driven treat-and-extend regiment (intervals adjusted in 4 week increments to a maximum of 16 weeks)[d]
Comparator(s)	• Arm C: Active comparator, Aflibercept (Eyelea) administered by IVT injection into the eye once every 8 weeks • Matched placebo (sham procedure) for each arm
Outcome(s)	• Average Change From Baseline in Best-Corrected Visual Acuity (BCVA) at 1 Year [Time Frame: Baseline (Day 1) and 1 year] • See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**BOULEVARD; NCT02699450;** A Multiple-Center, Multiple-Dose, Randomized, Active Comparator-Controlled, Double-Masked, Parallel Group, 36-Week Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Efficacy of RO6867461 Administered Intravitreally in Patients With Diabetic Macular Edema **Phase II –** Completed **Location(s):** US **Study completion date:** December 2017
Trial design	Randomised, double masked, parallel assignment.
Population	N = 229 (actual), age 18 years or older, macular edema associated with diabetic retinopathy, decreased visual acuity attributable primarily to DME, diagnosis of diabetes mellitus.
Intervention(s)	• Arm B: 1.5 mg faricimab administered by IVT injection into the eye once every fourth week up to Week 20,

[d] Information provided by Roche Products Ltd

	for a total of 6 administrations, followed by an observational period up to Week 36 • Arm C: 6 mg faricimab administered by IVT injection into the eye once every fourth week up to Week 20, for a total of 6 administrations, followed by an observational period up to Week 36
Comparator(s)	• Arm A: Active comparator, 0.3 mg ranibizumab every fourth week up to Week 20, for a total of 6 administrations, followed by an observational period up to Week 36
Outcome(s)	• Mean Change from Baseline in BCVA Letter Score at Week 24, in Treatment-Naive Participants [Time Frame: Baseline, Week 24] • See trial record for full list of other outcomes.
Results (efficacy)	In treatment-naïve patients, 6.0 mg faricimab, 1.5 mg faricimab, and 0.3 mg ranibizumab resulted in mean improvements of 13.9, 11.7, and 10.3 ETDRS letters from baseline, respectively. The 6.0-mg faricimab dose demonstrated a statistically significant gain of 3.6 letters over ranibizumab (P = 0.03). In both patient populations, faricimab resulted in dose-dependent reductions in CST, improvements in DRSS score, and longer time to re-treatment during the observation period compared with ranibizumab.[5]
Results (safety)	Faricimab showed no new or unexpected safety signals.[5]

ESTIMATED COST

Cost of faricimab was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance. Aflibercept for treating diabetic macular oedema (TA346). July 2015
- NICE Technology appraisal guidance. Dexamethasone Intravitreal implant for treating diabetic macular oedema (TA349). July 2015
- NICE Technology appraisal guidance. Ranibizumab for treating diabetic macular oedema (TA274). February 2013
- NICE Clinical Guideline. Type 2 diabetes in adults: diagnosis and management (NG28). August 2019
- NICE Clinical Guideline. Type 1 diabetes in adults: diagnosis and management (NG17). July 2016

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/S/a

OTHER GUIDANCE

- Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. 2020[16]
- European Society of Retina Specialists (EURETINA). Guidelines for the management of diabetic macular edema. 2017[18]

ADDITIONAL INFORMATION

REFERENCES

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.