National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Faricimab for treating wet age-related macular degeneration [ID3898]

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Roche Products Ltd	The licence wording is anticipated to be: [redacted] Therefore we consider the wording of the remit to be appropriate.	Thank you for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Roche Products Ltd	Faricimab offers the potential to address the significant unmet need in nAMD for more durable treatments that sustain clinical benefits with fewer injections, reducing the burden of treatment for patients, caregivers, clinicians and the healthcare system. While anti-VEGF monotherapy has been shown to improve outcomes, frequent injections are often required[1]. Regular trips to hospital for monitoring and treatment has a significant impact on patients' lives. Faricimab is a first-in-class, dual pathway inhibitor that targets both VEGF-A and Angiopoietin-2, two key drivers of retinal vascular disease. It has demonstrated non-inferior visual acuity outcomes to aflibercept with >75% of patients achieving ≥12 week treatment intervals and >45% achieving 16 week intervals at week 48. Faricimab provides an opportunity to reduce the burden of hospital visits which will have a positive impact for patients and clinicians who are delivering busy nAMD services. Therefore we believe that timely NICE guidance for Faricimab would be valuable to both patients and the NHS.	Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche Products Ltd	We consider this section to be accurate and complete.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	Roche Products Ltd	The technology is defined inappropriately. Please change to, 'Faricimab does not currently have marketing authorisation in the UK for the treatment of neovascular (wet) age-related macular degeneration.'	Thank you for your comments. The definition of the technology within the scope has been updated.
Population	Roche Products Ltd	The "Population" definition should remove mention of "untreated" and "active" to enable consistency with NICE TA155, TA294 and TA672 guidance[2-4]. [redacted]	Thank you for your comments. The population section has been updated as suggested.
	Bayer Plc Ltd	We suggest the wording is changed to "adults with wet age-related macular degeneration" to better align with the draft remit/appraisal objective. This will maintain consistency and remove the suggestion that the appraisal is only considering faricimab as a first-line treatment i.e. an "untreated" population	Thank you for your comments. The population section has been updated as suggested.
Comparators	Roche Products Ltd	Aflibercept, brolucizumab, and ranibizumab are licensed treatments for patients with nAMD with associated NICE guidance (TA294, TA672 and TA155) [2-4]. All three of these technologies are part of the treatment pathway for this patient population and are appropriate to include as comparators to faricimab in this appraisal. Unlicensed bevacizumab (Avastin©) is not a relevant comparator for this appraisal. Bevacizumab does not have a marketing authorisation for wet age-related macular degeneration and has been developed and manufactured for intravenous use in the treatment of a number of cancers. [redacted]	Thank you for your comments. The scope is intended to be broad, so as not to exclude potentially relevant comparators. Bevacizumab is currently used within the NHS in England for the treatment of wet AMD and is considered an appropriate

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		[redacted] Best supportive care is also not considered to be a relevant comparator, as patients should be offered treatment with established technologies, either aflibercept, brolucizumab or ranibizumab (TA294, TA672 and TA155) [2-4].	comparator for this appraisal. Best supportive care is included to capture the available treatments for any patients who cannot have the listed comparators. Therefore, bevacizumab and best supportive care have been retained as comparators in the scope. The appraisal committee will consider treatments which are used in clinical practice for all people within the marketing authorisation.
	Bayer Plc Ltd	Bevacizumab is not an appropriate comparator to faricimab. Bevacizumab cannot be considered 'routine practice' or 'best alternative care' as it is not licensed for use in the eye and its use in the NHS is very low.	Thank you for your comments. The scope is intended to be broad, so as not to exclude potentially relevant comparators. Bevacizumab is currently used within the NHS in England for the treatment of wet AMD and is considered

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			an appropriate comparator for this appraisal. The appraisal committee will consider treatments which are used in clinical practice for all people within the marketing authorisation.
Outcomes	Roche Products Ltd	Yes, the listed outcomes capture the most important health-related benefits and harms.	Thank you for your comment. No action needed.
Economic analysis	Roche Products Ltd	Both phase III clinical trials, TENAYA and LUCERNE, met their primary endpoint with best corrective visual acuity (BCVA) gains from baseline with faricimab dosed up to Q16W being non-inferior to aflibercept Q8W[7]. [redacted]	Thank you for your comments. No action needed.
	Bayer Plc Ltd	The head-to-head trials of faricimab versus aflibercept used an injection frequency of every 8-weeks for aflibercept. However, the SmPC for aflibercept allows patients to follow a treat-and-extend regimen whereby the time between injections can be extended beyond 8-weeks. The comparison of faricimab with aflibercept should consider a treat-and-extend regimen for aflibercept which is established practice in the NHS.	Thank you for your comments. No action needed.

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		Clinical evidence for the treat-and-extend regimen for aflibercept comes from two trials in which the majority of patients received aflibercept at an interval between injections that was greater than 8 weeks (1, 2). References 1. Ohji M, Takahashi K, Okada AA, Kobayashi M, Matsuda Y, Terano Y; ALTAIR Investigators. Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR : A Randomized Controlled Trial. Adv Ther. 2020 Mar;37(3):1173-1187. doi: 10.1007/s12325-020-01236-x. Epub 2020 Feb 3. PMID: 32016788; PMCID: PMC7089719. 2. Mitchell P, Holz FG, Hykin P, Midena E, Souied E, Allmeier H, Lambrou G, Schmelter T, Wolf S. Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration: the ARIES study. Retina. 2021 Mar 22. doi: 10.1097/IAE.0000000000003128. Epub ahead of print. PMID: 33782365	
Equality and Diversity	Roche Products Ltd	Visual impairment resulting from wet nAMD is recognised as a disability and so the patient population under consideration in this appraisal is a protected group under the Equality Act of 2010[8].	Thank you for your comment. The committee will take into account that faricimab would be used in people with visual impairment when formulating its recommendations.

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Other considerations	Roche Products Ltd	In response to the subgroup suggestion within the draft scope, "*lesion is classic or occult neovascularisation in nature"*: The results of the subgroup analyses in phase III studies TENAYA and LUCERNE showed a relevant benefit in terms of BCVA improvement from baseline to year 1 (averaged over weeks 40, 44 and 48) and was not suggestive of sub-group specific differences for all faricimab patients regardless of lesion subtype[9]. Therefore, this suggested subgroup analysis is not considered appropriate as there are no difference in outcomes that would be clinically applicable. The availability and cost of future biosimilar products is uncertain for the following reasons: • There are currently no licensed biosimilar products available for nAMD and no confirmed timelines for when these will be made available in the UK. Predicting the cost of future biosimilars is challenging. Whilst we are aware of differing pricing strategies across disease areas with different treatment pathways and market dynamics, an extrapolation based on this information may not necessarily lead to an accurate representation of future acquisition costs and market share in the nAMD setting.	Thank you for your comments. This subgroup has been retained to be consistent with scopes of other technology appraisals relevant to this population. The company submission allows the opportunity to highlight any relevant subgroup analyses and uncertainties. The appraisal committee will consider evidence relating to these as part of the decision-making process. No action needed.

Innovation	Roche Products Ltd	Yes. Faricimab is the first bispecific antibody designed for intravitreal injection (IVT) that neutralises two distinct pathways of retinal disease: Ang-2 and VEGF-A. Faricimab has been developed using CrossMab (monoclonal antibody) technology. It independently binds and neutralises both Ang-2 and VEGF-A with high specificity and potency without steric hindrance. The Fc portion of the antibody has been specifically engineered for intraocular use to reduce systemic exposure and inflammatory potential[10]. Ang-2 has been shown to play a role in maintenance of the blood-retinal barrier via its effect on pericyte survival and endothelial cell integrity. Pre-clinical evidence suggests that dual inhibition of VEGF-A and Ang-2 can have synergistic benefits including reducing leakage and microvascular inflammation[11-13]. Faricimab may therefore lead to improved vascular stabilisation and retinal function in patients with nAMD. Studies TENAYA and LUCERNE are identical Phase III, multi-centre, randomized, active comparator controlled, double-masked, parallel-group, 112-week studies, evaluating the efficacy, safety, durability, and pharmacokinetics of the 6 mg dose of faricimab administered at up to 16-week intervals compared with aflibercept monotherapy every 8 weeks (Q8W) in patients with nAMD. The two phase III clinical trials (TENAYA and LUCERNE) demonstrated non-inferior efficacy outcomes with faricimab dosed up to Q16W versus aflibercept Q8W: • **Outcomes:** Year 1 results from the Phase III TENAYA and LUCERNE clinical trial demonstrated robust visual acuity gains for faricimab which were non-inferior to aflibercept. Analysis of anatomical endpoints demonstrated that the mean change in central subfield thickness was comparable from baseline through week 48 with faricimab up to Q16W and aflibercept Q8W[6]. Faricimab demonstrated a mean change in BCVA of 5.8 letters versus 5.1 for aflibercept (mean difference of +0.7, 95% CI: -1.1, +2.5) and 6.6 letters versus 6.6 letters	Thank you for your comments. The appraisal committee will consider the innovative nature of this technology during the appraisal. No action needed.

		for aflibercept (mean difference of 0.0, 95% CI: -1.7, +1.8), in TENAYA and LUCERNE, respectively[6]. • **Treatment burden:** Robust visual acuity gains and comparable anatomical results were achieved with faricimab with >75% of patients achieving ≥12 week treatment intervals and >45% achieving 16 week intervals at week 48. The median number of injections up to week 56 of TENAYA and LUCERNE was 8 injections for aflibercept compared to 6 injections for faricimab. Patients, caregivers and the NHS could benefit from increased treatment intervals and reduced injections that faricimab offers compared to anti-VEGF monotherapies. It is unlikely that the QALY calculations will fully capture the reduction in burden associated with fewer faricimab injections[6]. A major challenge for anti-VEGF therapy is the requirement for frequent administration of intravitreal injections and monitoring visits. In recent years, Treat-and-Extend regimens have been used to reduce the treatment burden of anti-VEGF therapy by extending the interval between intravitreal injections. However, recent real-world data studies indicate that the mean number of injections per year using this regimen are still high[14]. The substantial treatment burden and need for frequent office visits, fear and anxiety related to intravitreal injections, disappointed patient expectations, and lack of motivation to continue treatment are cited as key reasons for non-persistence with IVT anti-VEGF regimens[15]. As vision outcomes correlate with the frequency of injections, poor treatment compliance can negatively impact patient outcomes. Under treatment of nAMD in clinical practice reflects the burden of frequent therapy and visits on patients, caregivers and the healthcare system, and results in a decrease in the VA observed over the course of therapy[16-21]. So, patients, caregivers and the NHS could tangibly benefit from increased treatment intervals and reduced injections that faricimab is able to offer compared to currently available anti-VEGF monotherapies. It is unlikely that the QALY calculations will fully capture the reduction in burden associated with fewer faricimab injections.	

		Overall faricimab should be considered a highly innovative therapy which provides benefit to patients and the NHS in the management of nAMD. The addition of faricimab to clinical practice should be considered as a step-change in the management of nAMD.	

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Questions for consultation	Roche Products Ltd	**Have all relevant comparators for faricimab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for age-related macular degeneration?** As per our comments in the comparators section, unlicensed bevacizumab is not an appropriate comparator, neither can it be considered to be part of routine use or a best practice treatment option [redacted] Furthermore, best supportive care is also not considered to be a relevant comparator as patients would either receive aflibercept, brolucizumab or ranibizumab in routine practice. Aflibercept, brolucizumab and ranibizumab are the only relevant comparators to this appraisal. **How should best supportive care be defined?** Best supportive care is typically defined as no treatment or "watchful waiting", however we do not consider best supportive care to be a relevant comparator for these patients as it is not reflective of routine clinical practice in the UK. **Are the outcomes listed appropriate?** Please see the response to the "Outcomes" section above. **Are there any subgroups of people in whom faricimab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Are the subgroups suggested in 'other considerations appropriate?** Please see the response to the "Other considerations" section above. **Where do you consider faricimab will fit into the existing NICE pathway, Age-related macular degeneration (2018)?**	Thank you for your comments. Please see individual responses below: <u>Comparators</u> The scope is intended to be broad, so as not to exclude potentially relevant comparators. Bevacizumab is currently used within the NHS in England for the treatment of wet AMD and is considered an appropriate comparator for this appraisal. Best supportive care is included to capture the available treatments for any patients who cannot have the listed comparators. Therefore, bevacizumab and best supportive care have been retained as comparators in the scope.

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		Faricimab would be positioned as an alternative treatment option for 'Adults with late age-related macular degeneration (wet active)', under the section: 'Treating late age-related macular degeneration (wet active)'. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** ● **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which faricimab will be licensed;** ● **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** ● **could have any adverse impact on people with a particular disability or disabilities.** Please see the response to the "Equality" section above. **Do you consider faricimab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Please see the response to the "Innovation" section above.	The appraisal committee will consider treatments which are used in clinical practice for all people within the marketing authorisation. <u>Subgroups</u> The subgroup in 'other considerations' has been retained to be consistent with scopes of other technology appraisals relevant to this population. The company submission allows the opportunity to highlight any relevant subgroup analyses and uncertainties. The appraisal committee will consider evidence relating to these as part of the decision-making process. <u>Equality</u> The committee will take into account that faricimab would be used in people with

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		Do you consider that the use of faricimab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please see the response to the "Innovation" section above. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** None **Would it be appropriate to use the cost comparison methodology for this topic?** [redacted]. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** [redacted] **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes, change in BCVA is clinically relevant. The phase III trials TENAYA and LUCERNE both met their primary endpoint of non-inferiority in mean change in BCVA from baseline to week 48. Faricimab demonstrated a mean change in BCVA of 5.8 letters versus 5.1 for aflibercept (mean difference of +0.7, 95% CI: -1.1, +2.5) and 6.6 letters versus 6.6 letters for aflibercept (mean difference of 0.0, 95% CI: -1.7, +1.8), in TENAYA and LUCERNE, respectively[6]. The mean change in BCVA is a key driver in the economic modelling of faricimab versus the comparators.	visual impairment when formulating its recommendations. Innovation The appraisal committee will consider the innovative nature of this technology during the appraisal. No action needed.

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		Is there any substantial new evidence for the comparator technology/ies that has not been considered? None. **Are there any important ongoing trials reporting in the next year?** The evidence submission will contain Year 1 data from TENAYA and LUCERNE, Year 2 data will be available in Q1/Q2 2022. References 1. Ciulla, T. et al. Visual Acuity Outcomes and Anti–Vascular Endothelial Growth Factor Therapy Intensity in Neovascular Age-Related Macular Degeneration Patients: A Real-World Analysis of 49 485 Eyes. Ophthalmology Retina. 2020; 4(1):p19-30. 2. National Institute for Clinical Excellence [NICE]. Aflibercept solution for injection for treating wet age-related macular degeneration; final appraisal document [TA294]. Published July 2013. 3. National Institute for Clinical Excellence [NICE]. Brolucizumab for treating wet age-related macular degeneration; final appraisal document [TA672]. Published February 2021. 4. National Institute for Clinical Excellence [NICE]. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration; final appraisal document [TA155]. Published August 2008, Last updated May 2012.	

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		5. Roche Products Limited. *Data on file: Bevacizumab market share (from Freedom of Information requests) in UK for nAMD in time period June - September 2020.* 2021 [redacted] 7. Khanani, A.M. et al. Faricimab in Neovascular Age-Related Macular Degeneration: 1-Year Efficacy, Safety, and Durability in the Phase 3 TENAYA and LUCERNE Trials. Presented at: The Association for Research in Vision and Ophthalmology Annual Meeting, on May 6, 2021. 8. Office for Disability Issues; HM Government. Guidance on matters to be taken into account in determining questions relating to the definition of disability; Equality Act 2010. 2010 9. Roche Products Limited. *Data on file: Internal advisory board minutes.* 2021 10. Klein, C. et al. Engineering therapeutic bispecific antibodies using CrossMab technology. Methods. 2019; 154(1):p21-31. 11. Regula, J. T. *et al.* Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. EMBO Molecular Medicine. 2019; 11: e10666. 12. Regula, J. T. et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. EMBO Mol. *Med.* 2016; 8: p1265–1288.	

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		13. Iwata, D. et al. Anti -VEGF/Ang2 bi-specific antibody ameliorates endotoxin-induced uveitis in mice. Investigative ophthalmology and visual science*. Abstract.* 2014; 55 (13): p2354–2354. 14. Yang, Y. Downey, L. Mehta, H. Mushtaq, B. Narendran, N. Patel, N. Patel, P. J. Ayan, F. Gibson, K. Iqwe, F. and Jeffery, P. Resource Use and Real-World Outcomes for Ranibizumab Treat and Extend for Neovascular Age-Related Macular Degeneration in the UK: Interim Results from TERRA. Ophthalmology and Therapy. 2017 Jun;6(1):175-186. 15. Ehlken C, Ziemssen F, Eter N, et al. Systematic review: non-adherence and non-persistence in intravitreal treatment. Graefes Arch Clin Exp Ophthalmol. 2020;258:2077-2090. 16. Gohil R, Crosby-Nwaobi R, Forbes A, et al. Caregiver burden in patients receiving ranibizumab therapy for neovascular age related macular degeneration. PLoS One 2015;10:e0129361. 17. Prenner JL, Halperin LS, Rycroft C, et al. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. Am J Ophthalmol 2015;160:725-31. 18. Varano M, Eter N, Winyard S, et al. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD Patient and Caregiver Survey. Clin Ophthalmol 2015;9:2243-50 19. [CATT] Comparison of Age-related Macular Degeneration Treatments Trials Research Group, Maguire MG, Martin DF, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-	

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		related macular degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2016;123:1751-61 20. Vukicevic M, Heraghty J, Cummins R, et al. Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration. Eye 2016;30: 413-21 21. Monés, J., Singh, R. P., Bandello, F., Souied, E., Liu, X. & Gale, R. (2020). Undertreatment of Neovascular Age-Related Macular Degeneration after 10 Years of Anti-Vascular Endothelial Growth Factor Therapy in the Real World: The Need for A Change of Mindset. Ophthalmologica, 243(1), 1-8.	
	Bayer Plc Ltd	**Would it be appropriate to use the cost comparison methodology for this topic?** The SmPC for aflibercept allows patients to follow a treat-and-extend regimen whereby injection intervals can be extended beyond 8-weeks. Economic analyses should consider the reduced number of injections (and hence cost) of aflibercept when this regimen is used. If faricimab has comparable annual costs (and efficacy) compared to aflibercept following a treat-and-extend regimen then it may be appropriate to use the cost comparison methodology	Thank you for your comments. No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- Novartis Pharmaceuticals UK