CASE AUTH/3764/4/23

BAYER v ROCHE

Allegations about the promotion of Vabysmo (faricimab)

CASE SUMMARY

This case concerned three promotional claims for faricimab. Bayer alleged one claim, which appeared twice in a slide deck, was misleading. The two other claims appeared in a sponsored supplement to a named publication. Bayer alleged that one claim was misleading, incapable of substantiation and amounted to a misleading comparison of faricimab to other anti-VEGF treatments, and that the other claim was inconsistent with faricimab's summary of product characteristics.

There was an appeal by Roche of four of the Panel's rulings of breaches of the Code.

The outcome under the 2021 Code was:

Breach of Clause 6.1 (x2) [Panel's breach rulings upheld at appeal]	**Making a misleading claim**
Breach of Clause 6.2 [Panel's breach ruling upheld at appeal]	**Making an unsubstantiated claim**
Breach of Clause 14.1 [Panel's breach ruling upheld at appeal]	**Making a misleading comparison**

No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that information, claims and comparisons must not be misleading**
No Breach of Clause 11.2	**Requirement that a medicine must be promoted in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from Bayer about Roche Products Ltd.

COMPLAINT

The complaint wording is reproduced below:

> "We write pursuant to the Prescription Medicines Code of Practice Authority ('PMCPA') Constitution and Procedure ('Procedure') paragraph 5.3 of the Association of the British Pharmaceutical Industry ('ABPI') Code of Practice for the Pharmaceutical Industry 2021 ('the Code').
>
> Since December 2022, Bayer plc ('Bayer') has been in dialogue with Roche Products Ltd ('Roche') at a senior level regarding a number of concerns relating to promotion by Roche of its product faricimab (Vabysmo) in the UK.
>
> **Intercompany dialogue**
>
> Intercompany dialogue has occurred with Roche between 21 December 2022 and 20 April 2023, relating to a number of promotional materials for faricimab. Complaints were first raised by Bayer in a letter of 21 December 2022, followed by intercompany exchange on these points in January and February, and new complaints relating to claims in a different promotional item were raised by Bayer on 22 March 2023, to which Roche responded on 4 April 2023. In total 7 letters have been exchanged between our respective [senior medical employees]. Copies of all letters exchanged are provided. There were also some short telephone conversations, mainly regarding practicalities such as agreeing acceptable deadlines for response. During this process, a number of matters have been successfully resolved between our companies.
>
> However, there remain three promotional claims for faricimab, involving two different promotional materials, where Bayer has been unable to reach agreement with Roche. Bayer has also raised concerns with Roche concerning their conduct during intercompany dialogue [ICD letter 7]. In each letter from Roche to Bayer [ICD letters 2,4 and 6] there have been attempts made to raise speculative concerns regarding Bayer activities, these allegations being based solely on points made by Bayer during intercompany dialogue when explaining the rationale for our complaints against Roche. This pattern of behaviour has culminated [ICD letter 6] in two explicit demands for Bayer to produce materials for review by Roche, with a deadline of 10 working days for response. Bayer has informed Roche [ICD letter 7] that we consider this approach to be against the spirit of intercompany dialogue and the spirit of the Code, and also against the guidance provided by the PMCPA regarding conduct of intercompany dialogue. We have declined to provide any materials to Roche and have asked Roche to communicate separately with us if they believe they have concrete grounds to raise a complaint about a specific Bayer material.
>
> As a result of failure to reach agreement on the unresolved complaints, and in the light of Roche's conduct during the ICD process, we have now concluded that further progress cannot be made at an intercompany level. Bayer would now like to bring

these matters to the attention of the PMCPA for adjudication, and have informed Roche of our intention to do so [ICD letter 7].

Technical background: aflibercept and faricimab

Bayer's product aflibercept (Eylea®) and Roche's product faricimab are both biological medicines in the anti-vascular endothelial growth factor (anti-VEGF) class. Vascular endothelial growth factor (VEGF-A) is known to be the major mediator responsible for the development of pathophysiological changes in both diabetic macular oedema (DMO) and neovascular (wet) age-related macular degeneration (nAMD).

Faricimab was first licensed and made available in the UK in May 2022. Aflibercept was first licensed and made available in the UK in November 2012, almost 10 years earlier than faricimab.

Aflibercept and faricimab are both large therapeutic protein molecules, produced by recombinant technology in Chinese Hamster Ovary (CHO) cells. Both products are licensed for intravitreal use in the treatment of nAMD and visual impairment due to DMO. Both are recommended for use by NICE in these indications and appear in the NHS England commissioning recommendations for medical retinal vascular medicines as options for the treatment of nAMD and DMO.

The two drugs operate in a similar manner, each binding and inhibiting the activity of two key factors involved in the pathology of nAMD and DMO: VEGF-A plus one other, the 'extra' factor differing between the two products (aflibercept binds VEGF-A and placental growth factor (PlGF); faricimab binds VEGF-A and angiopoietin-2 (Ang-2)).

Technically, aflibercept is a fully human, recombinant fusion protein consisting of the constant region (Fc domain) of immunoglobulin G1(IgG1) fused to extracellular VEGF receptor sequences of human VEGF receptors 1 and 2. In other words, aflibercept is an antibody-derived fusion protein. Its structure enables it to act as a decoy receptor, binding both VEGF-A and PlGF with higher affinity than their native receptors.

PlGF has been shown to have actions distinct from VEGF. PlGF can act separately from VEGF-A in stimulating the proangiogenic response. PlGF-activated signalling, via VEGF receptor 1, is also distinct from VEGF-A-mediated signalling, due to the phosphorylation of different tyrosine residues on the receptors, leading to specific regulation of downstream targets.

Technically, faricimab is a humanised recombinant monoclonal IgG antibody that selectively binds with high affinity to two separate targets, VEGF-A and Ang-2, thereby inhibiting binding of these factors to their native receptors.

Aflibercept binds through a 1:1 stoichiometric 'trap' mechanism, with each molecule designed to catch, hold and block ('trap') one target. Faricimab binds through a bispecific mechanism, with one molecule capable of binding both targets. **We are unaware of any evidence to show that binding two targets via a bispecific molecular design is inherently clinically advantageous to binding two targets separately via a 1:1 'trap' mechanism.** Faricimab has been shown in the primary

endpoints of large phase III trials only to be non-inferior to aflibercept in nAMD and DMO i.e. comparable in terms of its clinical efficacy and safety.

As we indicated previously, both products are in the same therapeutic class. In other words, they are sufficiently similar in their actions that the World Health Organisation (WHO) considers that they sit within the same subgroup of the WHO Anatomical Therapeutic Chemical (ATC code) despite faricimab being almost 10 years later in its launch than aflibercept. The ATC code is a unique code assigned to each medicine according to the organ or system it works on and how it works within that system. Each medicine's ATC code is recorded in its SmPC. Both aflibercept and faricimab sit within the S01LA subgroup, aflibercept being S01LA05 and faricimab S01LA09. S01LA covers antineovascularisation agents used in the eye; S01LA is in turn a subgroup of ocular vascular disorder agents (S01L) which sits within ophthalmologicals (S01), all covered by the Sensory Organs class (S)). There are 9 drugs in the S01LA sub-class, of which faricimab is the most recent to be added:

A schematic representation of some of the therapeutic molecules in this class, including faricimab and aflibercept is provided below.

[Image showing variation in molecular structure of originator biologics used in ophthalmology provided]

To summarise:

- Faricimab and aflibercept are two biological molecules in the same therapeutic class
- Both bind VEGF-A plus a second pathologically relevant target: faricimab via a bispecific mechanism and aflibercept via a 1:1 'trap' mechanism.
- Faricimab has been shown to be clinically non-inferior to aflibercept in large phase III studies in nAMD and DMO.
- There is no evidence that, based on molecular structure alone, an antibody with a bispecific binding mechanism offers any therapeutic advantage over an antibody derived fusion protein with a 1:1 'trap' binding mechanism
- Aflibercept was licensed and available in the UK almost 10 years before faricimab

1. Claim in faricimab promotional slide deck: '*The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'*

This claim appears on slides 5 and 12 of this deck. It is the view of Bayer that this claim is misleading and, therefore, in breach of Clause 6.1.

As we have set out above, faricimab is a humanised recombinant monoclonal IgG antibody. Aflibercept is a fully human, recombinant fusion protein derived from an antibody in that it consists of the constant region (Fc domain) of immunoglobulin G1(IgG1) fused to extracellular VEGF receptor sequences. Aflibercept is produced in the same way as a therapeutic antibody (in CHO cell culture) and binds another factor of potential pathological relevance in retinal vascular diseases (PlGF) in addition to VEGF-A.

By claiming that faricimab is *'The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'* Roche may be technically accurate **but only in their use of the word 'antibody'.** Bayer therefore contends that this claim is misleading as the reader will tend to assume as a result that **(i) faricimab is the <u>first and only</u> biologic anti-VEGF treatment in nAMD and DMO to bind not one but two potentially relevant targets and (ii) as a result of this, faricimab offers benefits over other treatments**.

As we have explained above, faricimab is not the first and only biologic anti-VEGF treatment in nAMD and DMO to have a dual action i.e. to bind not one but two potentially relevant targets. Aflibercept, a recombinant fusion protein, is licensed in both indications for which faricimab is licensed and has been available in the UK for over ten years. Aflibercept binds VEGF-A and placental growth factor (PlGF), both of which play a role in pathological neovascularisation. PlGF is not simply another version of VEGF-A: PlGF can act separately from VEGF-A in stimulating the proangiogenic response. PlGF-activated signalling, via VEGF receptor 1, is also distinct from VEGF-A-mediated signalling, due to the phosphorylation of different tyrosine residues on the receptors, leading to specific regulation of downstream targets.

Bayer is of the view that health professionals are unlikely to be concerned with the technical distinctions and classifications of 'fusion protein' versus 'antibody'. As already discussed above, aflibercept and faricimab molecules have many technical similarities, from drug class (WHO ATC class SL01LA), to method of manufacture (via recombinant technology in CHO culture), to presence of the Fc portion of human IgG. Bayer believes most prescribers would consider that the matter of whether a particular molecule is an antibody, or an antibody-derived fusion protein, is largely irrelevant in comparison to its pharmacokinetic and pharmacodynamic features and clinical benefits compared to other therapeutic options in its class. Similarly, the 'bispecific' binding mechanism has not been proven to offer any clinical benefit in comparison to the aflibercept binding mechanism.

In the view of Bayer, this claim is designed to lead a health professional towards the belief that faricimab will offer their patients unique therapeutic benefits because it implies incorrectly that no anti-VEGF medicine available until the launch of faricimab has offered more than anti-VEGF-A inhibition alone. We believe this is a logical conclusion – why else would Roche make 'first and only' a feature of a promotional statement about the pharmacology of faricimab? It is clear Roche believes that statements of novelty and uniqueness would resonate with prescribers.
Roche stated in their letter to Bayer dated 23 February 2023 that *'Bayer remains concerned that ophthalmologists are unlikely to be concerned with the technical distinctions and classifications of 'fusion protein' versus 'antibody' but rather to focus on the mechanism of action. Respectfully, this is not a Code of Practice issue'.* It is the view of Bayer that Roche is incorrect in this assertion. We believe that the clinical priorities and concerns of the target audience for a promotional claim are highly relevant to the application of the Code, as such factors are integral to what weight the audience will place on different parts of the claim, how they will interpret its meaning and how likely it is to mislead. Accordingly, the final medical signatory should carefully consider such issues during the review and certification process. It is an abiding and well-tested principle of the Code that if the overall impression given by a promotional statement is likely to mislead, then it may still be found in breach of the Code – even if

qualifiers make it technically accurate. **Bayer considers the word 'antibody' to be a qualifier of an otherwise misleading claim, as prescribers do not choose between biological drugs in the same class and for the same indications based on whether they are antibodies or antibody-derived fusion proteins**.

Furthermore, **there is no evidence of any significant clinical benefit offered by faricimab over aflibercept in either nAMD or DMO.** The pivotal studies for faricimab showed it to be non-inferior to aflibercept based on the primary endpoint of vision improvement (mean change in best-corrected visual acuity from baseline). Nor were these studies designed as a fair test of the durability of faricimab versus aflibercept, aflibercept being restricted to a fixed 8-weekly dosing regimen after the initial three monthly loading doses, despite extension to 16 week dosing intervals as part of a 'treat and extend' regimen being permitted by the Eylea SmPC. In contrast, faricimab was permitted extension of treatment intervals after monthly loading.

In addition, the contribution of Ang-2 inhibition to the treatment effect and clinical response for nAMD and DMO has yet to be established and remains an area of controversy and evolving scientific understanding. In 2022, as part of the US Food and Drug Administration's assessment of faricimab, the US Center for Drug Evaluation and Research reviewed the evidence on this point and concluded that there remained questions about the clinical contribution of Ang-2 inhibition when in combination with anti-VEGF. Roche has stated in ICD [ICD letter 6 – *related to a different unresolved complaint discussed later in this letter]* that the FDA has no regulatory standing in the GB and therefore its conclusions cannot be used when considering this point. However, the FDA is a scientific body of international renown. The quality of its scientific review process is widely acknowledged and respected internationally. Our view is therefore that published conclusions of the FDA following a review of the body of evidence on a particular topic should not be disregarded simply because of its lack of regulatory standing within a particular country, but rather should be considered in a balanced manner alongside other relevant high quality evidence.

Roche stated in its letter to Bayer of 20 January 2023 [ICD letter 2] that '*Bayer has not provided any concrete evidence of how any of the UK faricimab materials characterising it as a bispecific antibody in accordance with the SmPC, gives it any "special therapeutic benefit" over and above its competitors.'*

In response to this point, Bayer would like to direct the attention of the PMCPA to the promotional claim '*Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy'* which appeared in a promotional supplement on faricimab in [named publication]. This claim is the subject of a further Code complaint from Bayer, the specifics of which are discussed in detail below. This claim clearly implies a special therapeutic benefit attributable to faricimab's dual mode of action, in comparison to competitor drugs blocking only VEGF-A. Roche has attempted to substantiate this claim to Bayer only by reference to the mode of action of faricimab as it appears in the SmPC. The promotional supplement in which the claim appears was prepared by Roche in the same month as Bayer was in receipt of the letter denying that Roche is using faricimab's bispecific mode of action in accordance with the SmPC as the basis for promotional claims of clinical benefit.

In summary, Bayer maintains that the claim faricimab is '*The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'* is misleading in breach of Clause 6.1 of the Code.

- Faricimab is neither the first nor the only molecule licensed for these indications in the UK which targets two factors involved in retinal angiogenesis. As detailed in the technical section above, aflibercept also targets two different pathologically relevant factors which may act independently; is classified in exactly the same WHO ATC subgoup as faricimab based on its mode of action within the eye; and was licensed and available in the UK almost 10 years before faricimab.
- Claiming *'The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'* in promotion for faricimab is likely to mislead, as the attention of health professionals will naturally focus on the statement 'first and only' rather than the qualifier 'antibody'. Health professionals in ophthalmology are unlikely to view the technical distinctions between antibodies and fusion proteins as being relevant to their clinical decision-making.
- The claim carries a clear implication that the bispecific mechanism of action of faricimab provides additional clinical benefits over and above other anti-VEGF agents used in retinal vascular disease, something that has not been established. This implication is being leveraged in other promotional materials for faricimab. There is no evidence of a clinical benefit of faricimab over aflibercept related to its structural or pharmacodynamic differences: in the primary outcomes of its phase III pivotal studies, faricimab has shown itself only to be non-inferior to aflibercept.

2. Claims in promotional supplement for faricimab in [named publication]

In February 2023, a promotional supplement entitled 'Intravitreal faricimab (Vabysmo, Roche Products Ltd) for neovascular age-related macular degeneration: general considerations and implementation recommendations by an expert panel of UK retina specialists' appeared in [named publication].

The supplement contains a consensus pathway document for the treatment of neovascular age-related macular degeneration (nAMD) with faricimab, based on expert roundtables held in September 2022 and January 2023. These roundtables were commissioned and funded by Roche and the participants were a group of eminent UK experts in this field.

(a) Off-label promotion of faricimab

Page 4 of the promotional supplement contains the following statement relating to use of faricimab in patients with nAMD switching from another anti-VEGF:

'Alternatively, clinicians may decide to switch without loading, treat at the same interval as that most recently followed for the previous anti-VEGF agent, and assess on OCT at follow-up to determine treatment response (improved, worse or unchanged) and an appropriate maintenance regimen.'

The Summary of Product Characteristics for faricimab states that initiation of therapy in nAMD should commence with 4 monthly doses:

'The recommended dose for Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses'

There is nothing in the faricimab SmPC to suggest that the requirement for 4 initial monthly loading doses does not apply in patients with nAMD who are being switched from another treatment to faricimab. The statement in the consensus that clinicians may choose to switch to faricimab from another anti-VEGF without 4 initial monthly doses is therefore not in accordance with the marketing authorisation for the product.

Bayer appreciates that an expert panel, based on their clinical expertise and experience, may legitimately make recommendations as part of a consensus that do not align with the marketing authorisation of the product under consideration. However, if a pharmaceutical company chooses to quote an off-label consensus recommendation for their product within a promotional item or activity, this would be considered off-label promotion in breach of Clause 11.2 of the Code.

These concerns were put to Roche by Bayer in a letter dated 22 March 2023 [ICD letter 5], to which Roche responded in a letter dated 4th April [ICD letter 6]. Roche argued that the use of the term 'recommended' in the SmPC in relation to initial monthly loading doses does not amount to a mandate, and thus did not accept that promotion of faricimab use without four initial monthly loading doses is inconsistent with the SmPC.

Bayer considers that Roche has made an unusual and incorrect interpretation of common regulatory terminology. For example, dosages and routes of administration specified in an SmPC are also typically described as 'recommended', including the doses and routes of administration of both faricimab and aflibercept, but promotion of different doses and/or routes of administration to those recommended in the SmPC would not be considered as consistent with the terms of the marketing authorisation.

The MHRA has stated that: *'A marketing authorisation or product licence defines a medicine's terms of use: its summary of product characteristics outlines, among other things, the indication(s), recommended dose(s), contraindications, and special warnings and precautions for use on which the licence is based, and it is in line with such use that the benefits of the medicine have been judged to outweigh the potential risks.'* . In a UK publication clarifying definitions and terminology relating to unlicensed and off-label use of medicines, the authors determined that use of a licensed medicine outside the recommended dose regimen falls under the definition of off-label prescribing.

Off-label promotion is of particular concern where a product is subject to additional monitoring for adverse reactions by the licensing authority and its promotional material bears an inverted black triangle, as is the case for faricimab. Bayer is also not aware of any evidence to support the efficacy and safety of the use of faricimab without the recommended 4 monthly loading doses.

Bayer therefore alleges that by promoting use of faricimab outside the terms of its marketing authorisation, Roche is in breach of Clause 11.2 and has also failed to maintain high standards in breach of Clause 5.1 of the Code.

b) Promotional claim incapable of substantiation: *'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy'*

On page 4 of the [named publication]promotional supplement the following unreferenced statement occurs:

'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in nAMD considered non-responders and partial responders to anti-VEGF monotherapy'

Whilst this statement may be the opinion of the consensus authors, its use in a promotional item constitutes a promotional claim by Roche. Bayer also considers that this promotional statement is an implied comparison intended to lead the reader to believe that, by inhibiting Ang-2, faricimab provides additional benefits in poor responders with nAMD over and above continued anti-VEGF monotherapy.

In our letter to Roche dated 22 March 2023 [ICD letter 5] Bayer requested substantiation for this claim from Roche under the terms of Clauses 6.1 and 18.2 of the Code. In Roche's response of 4 April 2023 [ICD letter 6] Roche stated that this claim can be substantiated with the SmPC for faricimab, quoting the following statement:

'Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.'

Bayer does not consider the pharmacological information provided by Roche from the Vabysmo SmPC was sufficient to substantiate the claim, as it does not relate to any clinical benefits to be expected in non-responders and partial responders to anti-VEGF monotherapy. Indeed, the faricimab SmPC contains no data relating the efficacy of faricimab in non-responders or partial responders to other therapies as the pivotal studies were conducted only in treatment-naive patients and Bayer is not aware of any other evidence supporting such a claim.

Although Ang-2 is upregulated in patients with nAMD and plays a role in pathologic neovascularization, its clinical and therapeutic importance is unclear. In comparison, VEGF appears to play a major role in neovascularization in nAMD based on the well-established clinical efficacy of anti-VEGF agents. For example, the addition of Ang-2 inhibition with nesvacumab (an experimental monoclonal antibody binding and inhibiting Ang-2) to VEGF inhibition with aflibercept did not demonstrate added clinical benefits over and above aflibercept alone. Last year, as part of the FDA's assessment of faricimab, the US Center for Drug Evaluation and Research reviewed the evidence regarding the clinical contribution of Ang-2 inhibition when in combination with anti-VEGF and concluded that questions remained on this point. Bayer is not aware of any relevant evidence which has become available since 2022.

It is therefore clear that the clinical value of Ang-2 inhibition in the treatment of nAMD, and any added benefit over VEGF inhibition alone, remains an area of controversy and emerging scientific opinion. Promotional material discussing areas of scientific and clinical uncertainty should therefore contain balanced reference to all points of view (as stated in the supplementary information to clause 6.1 of the Code) in order to permit the reader to form their own opinion of the value of a medicine and the clinical relevance of its pharmacodynamic properties.

In the same letter of 4 April [ICD letter 6] Roche also dismissed the conclusions of the FDA that the clinical contribution of Ang-2 inhibition when in combination with anti-VEGF remains unproven. Roche takes this view on the grounds that the MHRA is the only relevant regulatory body for GB healthcare professionals. As already stated above, whilst Bayer agrees that the FDA has no regulatory standing in GB, we consider that the FDA is nevertheless a scientific body of international renown. The quality of its scientific review process is widely acknowledged and respected. The published conclusions of the FDA following a review of the body of evidence on a particular topic should therefore not be disregarded, but rather should be considered in a balanced manner alongside other relevant high quality evidence.

Bayer therefore maintains that this promotional statement is an implied comparison intended to lead the reader to believe that, by inhibiting Ang-2, faricimab will provide additional clinical benefits in poor responders with nAMD over and above continued anti-VEGF monotherapy. The wording in the SmPC referred to by Roche does not support this claim, the SmPC does not address the use of faricimab in anything other than treatment-naïve patients, and no other reference has been provided in substantiation. As explained above, the issue of the additive clinical benefit of Ang-2 inhibition in nAMD, over and above use of VEGF-A inhibition alone, remains an open question and is an area of evolving scientific opinion. Particular care is therefore required when discussing this topic promotionally and this has not been displayed in [the promotional supplement].

This claim also provides concrete evidence of how, by characterising faricimab as a bispecific antibody in promotional materials, a special therapeutic benefit over and above its competitors is being implied in the absence of any evidence to substantiate such an assertion – something that has been denied by Roche during intercompany dialogue [ICD letter 2 regarding promotional slide deck: see complaint 1 above].

Bayer therefore maintains that this claim is misleading, incapable of substantiation and amounts to a misleading comparison of faricimab to other anti-VEGF treatments, in breach of clauses 6.1, 6.2 and 14.1 of the Code.

Conclusion

We have set out above the ways in which Bayer believes 3 claims (at paragraphs 1, 2(a) and 2(b)) which have been used by Roche in two promotional materials [slide deck and supplement] breach the Code.

Given Roche's refusal to withdraw promotional materials [slide deck] and [supplement] and cease all use of the statements referred to above, and in the absence of any indication during intercompany dialogue that progress may be

made on these matters, Bayer would now be grateful for adjudication from the PMCPA."

When writing to Roche, the PMCPA asked it to consider the requirements of Clauses 6.1, 6.2,11.2, 14.1 and 5.1 of the Code.

ROCHE'S RESPONSE

The response from Roche is reproduced below:

"Roche is committed to the appropriate use of medicines, protecting the safety of patients and maintaining high standards in the ethical promotion of its medicines. It is therefore disappointing to receive a complaint of this nature and we set out below evidence to substantiate why we do not consider there to be any breach of the ABPI Code of Practice (the '**Code**') by Roche.

In addition, Roche strongly refutes any suggestion made by Bayer that our conduct during this inter-company dialogue has not been within the spirit of the Code. In fact, our approach has always been driven by the aim of resolving these issues via the inter-company dialogue process. All topics we have raised in our correspondence related directly to those raised by Bayer in their initial letters, so we considered it prudent to highlight them directly as part of the ongoing dialogue.

Roche has subsequently sent these issues as a separate correspondence, with the aim of seeking resolution through a successful inter-company dialogue, with Bayer.

The following addresses the issues escalated to the PMCPA for adjudication:

1. Claim in faricimab promotional slide deck: 'The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'

Bayer alleges that the claim 'The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO' on slides 5 and 12 of the slide deck is misleading and, therefore, in breach of Clause 6.1. Their concern is that a 'reader will tend to assume as a result that (i) faricimab is the first and only biologic anti-VEGF treatment in neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DMO) to bind not one but two potentially relevant targets; and (ii) as a result of this, faricimab offers benefits over other treatments.'

Roche disagrees with Bayer's interpretation of this claim, and with their extrapolation that the claim implies additional therapeutic benefit of faricimab.

In support of Roche's claim, the following facts are respectfully presented to reinforce the differentiation between the properties of faricimab and aflibercept, and which we believe adequately demonstrates the low likelihood of any hypothetical misinterpretation of Roche's claim.

Aflibercept is not an antibody
As stated in section 5.1 (Pharmacodynamic properties) of the aflibercept SmPC, aflibercept is a soluble decoy receptor consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

Indeed, Bayer concede this point in their letter of complaint; *'By claiming that faricimab is "The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO" Roche may be technically accurate but only in their use of the word "antibody".'*

Faricimab is a bispecific antibody generated using CrossMab technology, which is based on the framework of a 150-kDa human IgG1. It comprises two different heavy chains and two different light chains, with one ligand-binding arm binding Vascular Endothelial Growth Factor-A (VEGF-A) and the other binding Angiopoeitin-2 (Ang-2).

Aflibercept is not bispecific
At the time of Bayer's initial complaint, the main reference to aflibercept's mode of action on the Eylea (aflibercept) UK website (not active since Feb 2023) was Papadopolous *et al* (2012) , which states '*Like bevacizumab and ranibizumab, VEGF Trap binds multiple isoforms of VEGF-A but in contrast to these antibodies the VEGF Trap was designed to also bind the related VEGFR1 ligands, VEGF-B and PlGF.*' (Aflibercept was referred to as 'VEGF Trap' at time of publication of this paper).

This same information is replicated in the technology review for aflibercept's NICE TA294 for nAMD which states '*Aflibercept solution for injection (Eylea, Bayer Pharma) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein which binds to all forms of VEGF-A, VEGF-B, and the placental growth factor. Aflibercept solution for injection prevents these factors from stimulating the growth of the fragile and permeable new blood vessels associated with wet age-related macular degeneration. Aflibercept solution for injection has a UK marketing authorisation 'for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD)''* and NICE TA346 for DMO which similarly states that '*Aflibercept (Eylea, Bayer Pharma) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein that binds to all forms of VEGF-A, VEGF-B, and the placental growth factor. VEGF is involved in the pathogenesis of diabetic macular oedema (DMO). Aflibercept has a UK marketing authorisation for 'the treatment of adults with visual impairment due to diabetic macular oedema*''.

A comprehensive list of the molecular targets of the current anti-VEGF therapies is presented in table 1 of Uemura *et al* (2021). Of note, three authors of this paper are employees of Bayer Consumer Care AG.

[screenshot of Table 1 provided]

Again, this same table and the references above reinforce the fact that faricimab is indeed truly bispecific, binding only to VEGF-A and Ang-2, whilst aflibercept has

three molecular targets. Roche are therefore unclear where the root of any potential misinterpretation of our claim may lie.

Aflibercept does not target two distinct pathways in nAMD and DMO
The aflibercept SmPC describes the mode of action of aflibercept as follows: '*Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (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*.'

This is expanded upon by Uemura *et al (2021); 'VEGF-A binds VEGFR1 and VEGFR2, whereas VEGF-B and PlGF only bind VEGFR1'*.

The signalling of the VEGF family of ligands through the VEGF receptors is complex, but the overlapping binding of VEGF-A, -B and PlGF to VEGFR-1 clearly indicate a **common signalling pathway**, which they act upon under a variety of different cellular conditions. The relevance of this to ocular disease is still an active area of research.

It is important to differentiate a therapy having multiple molecular targets, from having an impact on multiple biochemical pathways.

As noted in the faricimab SmPC , '*faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of **two distinct pathways** by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).*
Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation.
By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability'.

Given the information provided here shows clear and distinct properties of both aflibercept and faricimab, Roche does not accept the allegation that the claim 'The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO' is misleading and in breach of 6.1. Aflibercept is not bispecific, nor an antibody, and does not target two distinct pathways in nAMD and DMO, whereas faricimab **is** a bispecific antibody targeting two distinct pathways in nAMD and DMO. As such, Roche's claim to be 'the first and only', is factually accurate and can be substantiated.

Moreover, since the claim in question is merely a description of the properties of faricimab and its mode of action, it is also difficult to understand how any impression of additional therapeutic benefit can be left with the reader.

As such, Roche does not accept the allegation that the claim above is misleading, and Roche does not consider there has been a breach of clause 6.1 of the Code.

2. Claims in promotional supplement for faricimab in [named publication]

(a) Alleged off-label promotion of faricimab

Bayer alleges that the statement *'Alternatively, clinicians may decide to switch without loading, treat at the same interval as that most recently followed for the previous anti-VEGF agent, and assess on OCT at follow-up to determine treatment response (improved, worse or unchanged) and an appropriate maintenance regimen'*, on page 4 of the document [promotional supplement] is not in accordance with the marketing authorisation for the product and thus off-label promotion in breach of clauses 11.2 and 5.1.

Roche would like to refer to the SmPC for faricimab which states that:
'The recommended dose for Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses'. [Extract – full wording in provided SmPC]

Roche would like to consider extracted wording from the SmPC for aflibercept as there is a clear mandate here for how to initiate treatment:
'The recommended dose for Eylea is 2 mg aflibercept, equivalent to 0.05 mL. Eylea treatment is initiated with one injection per month for three consecutive doses.' [Extract – full wording in provided SmPC]

Similarly in the ranibizumab SmPC:
'Treatment in adults is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment'. [Extract – full wording in provided SmPC]

The wording within the faricimab SmPC provides a recommendation that faricimab is administered by intravitreal injection every 4 weeks for the first four doses; however, this is not a mandate. This is in contrast to other IVT therapy labels, aflibercept and ranibizumab, which clearly mandate that treatment is initiated with the specified number of loading doses.

Roche intentionally sought a broad and flexible label to allow clinical choice for HCPs when selecting an appropriate treatment regimen for individual patients. The phase III clinical trials, which provide supporting evidence for the faricimab marketing authorisation for nAMD, were conducted in a treatment-naïve population (as is consistent with the development programmes of other IVT treatments, aflibercept and ranibizumab). Consequently the label does not provide specific recommendations for those patients switching from anti-VEGF agents to faricimab. How to manage such switches is a clinical decision by the treating physician, based upon the recommendations in the SmPC. The Roche material in question was developed in collaboration with an expert panel of UK retina specialists, as such demonstrating that the UK clinical community also considers the faricimab SmPC wording as a

recommendation when relating to loading doses. Roche, therefore, considers the above statement to be consistent with the faricimab SmPC.

Roche also considers the context of this statement within the promotional item as an important factor for the allegation of off-label promotion. The document in question is a promotional supplement titled: 'Intravitreal faricimab (Vabysmo®, Roche Products Ltd) for neovascular age-related macular degeneration: general considerations and implementation recommendations by an expert panel of UK retina specialists' ([copy provided]). The statement identified by Bayer is found within a 12 page document. There are several prominent statements within the document which make reference to the recommended posology:

[Page 3] Preferred practice in the management of treatment-naïve patients with nAMD
Treatment initiation with a loading phase of monthly intravitreal anti-VEGF injections is recommended, followed by a treat-and-extend (T&E) regimen based on visual acuity and optical coherence tomography (OCT) assessment. Treatment may be extended by 2- or 4-week increments up to a maximum of 16 weeks based on disease activity and in accordance with the recommended drug posology

[Page 4] Switching of anti-VEGF agents for patients with persistent or refractory disease activity due to nAMD
Switching between anti-VEGF agents with or without a loading phase may be considered for patients with nAMD showing an unsatisfactory or inadequate treatment response after monthly loading injections (e.g., non-responders) and for patients with recurrent or persistent exudative disease activity despite high/maximal (monthly) retreatment frequency (e.g., partial responders).

[Page 4 – including the statement raised by Bayer] Switching to faricimab in nAMD
For patients with nAMD considered refractory to anti-VEGF monotherapy and naïve to dual Ang-2/VEGF-A inhibition, a switch to faricimab with a reloading phase of monthly injections may help to avoid undertreatment and secure maximum initial benefit.

Alternatively, clinicians may decide to switch without loading, treat at the same interval as that most recently followed for the previous anti-VEGF agent, and assess on OCT at follow-up to determine treatment response (improved, worse, or unchanged) and an appropriate maintenance regimen.

[Page 8] Posology
The recommended dose for Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses. Thereafter, treatment may be individualised using a T&E approach following an assessment of the individual patient's anatomic and visual outcomes.

This context is important as it provides balance and objectivity to the statement in question. Roche's position is to recommend loading in all patients starting treatment with faricimab. This recommendation is repeated several times within the promotional item in question. However, as the faricimab label allows clinical choice, Roche does not

accept Bayer's interpretation that it is off-label promotion to make a statement such as '*Alternatively, clinicians **may** decide to switch without loading'*.

Roche does not accept the allegation by Bayer that this is an off-label recommendation and consider it consistent with the SmPC. As such, Roche does not consider this to be in breach of Clauses 11.2 and 5.1 of the Code.

b) Promotional claim incapable of substantiation: 'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy' [promotional supplement]

Bayer alleges that this promotional claim is misleading and incapable of substantiation and therefore in breach of clauses 6.1, 6.2 and 14.1.

Roche's response during inter-company dialogue, dated 4th April 2023 referred to the faricimab SmPC, section 5.1, and Roche still considers the faricimab SmPC as relevant evidence. Firstly, the role of the MHRA as the UK regulatory body is to assess the evidence for faricimab and thus the impact of Ang-2 inhibition. Secondly, although the data used to inform the label is related to treatment-naïve patients, the mechanism of action of angiopoietin-2 is important when considering how the drug may act in previously treated patients.

'Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.'

Roche considers that patients who are non-responders or partial responders to anti-VEGF-A monotherapy are naïve to the effect of Ang-2 inhibition and as such could benefit from bispecific Ang-2 and VEGF-A blockade as outlined in the SmPC.

In support of Roche's claim we would like to present the following evidence taken from preclinical studies, clinical trials and clinical practice data.

Preclinical studies

Chae *et al* published a 2010 paper which demonstrated that in glioma cells, ectopic expression of Ang-2, when combined with anti-VEGFR2 treatment, was still able to destabilise vessels and increase vascular permeability. The effects of VEGFR2 inhibition were diminished by not allowing vessels to return to a normal state. This suggests, through a preclinical model, that when Ang-2 is not inhibited it is still able to cause vascular permeability in the presence of anti-VEGF treatment thus providing potential for benefit through additional Ang-2 blockade.

Clinical Trials

Roche would also like to provide clinical trial evidence that supports the outcome seen in the preclinical model.

Roche would like to refer to the Bayer phase II studies in DMO and nAMD, RUBY and ONYX respectively, which studied low dose and high dose intravitreal nesvacumab given with intravitreal aflibercept. Nesvacumab was an experimental therapy targeting Ang-2. Development of this treatment has subsequently ceased. Patients in RUBY could be treatment-naïve or previously treated for DMO (around 40% of patients, treatment not specified) and patients in ONYX were treatment-naïve nAMD patients. The trials were designed to demonstrate superior clinical benefits in terms of BCVA over and above aflibercept alone, and this endpoint was not met. However, regarding clinically relevant anatomical outcomes, the RUBY study (DMO) did in fact show superior outcomes for the high dose combination. The authors (among them Bayer employees) state:

'*In conclusion, the RUBY study did not show additional benefits in vision with intravitreal nesvacumab + aflibercept over IAI monotherapy in patients with DME. However, there were some indications of additional anatomic benefit with combination therapy particularly in OCT-measured endpoints, including reduction in CST, patients with resolution of fluid in the foveal center, and patients achieving macular thickness ≤300 µm and a trend toward more patients demonstrating improvement in DRSS scores. The indication of positive anatomic effects may warrant further investigation of the role of anti-Ang2 agents in combination with anti-VEGF therapy*.'

In ONYX (nAMD), qualitative grading of retinal fluid showed numeric trends in favour of combination therapy compared to intravitreal aflibercept alone and again the authors conclude these numeric trends may warrant further investigation of the role of anti-Ang-2 in combination with anti-VEGF.

These data provided early evidence on the relevance of combined Ang-2 and VEGF inhibition in the treatment of nAMD and DMO.

Evidence from faricimab clinical trials

The faricimab MHRA marketing authorisation was based on assessment of the phase II and phase III clinical trial programme for faricimab, thus providing an aggregated summary of faricimab trial evidence. As described above, the faricimab SmPC supports the relevance of Ang-2 inhibition. As such, concluding additional clinical benefit **may** be conferred if VEGF-A inhibition alone has been inadequate is a reasonable interpretation of the clinical trial evidence.

'Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitises blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.'

Evidence from clinical practice

The trend towards positive anatomic effects in a largely treatment-naïve clinical trial population has now been demonstrated in clinical practice in previously treated nAMD patients switched to intravitreal faricimab treatment. This is alongside improvements in other clinical outcomes, namely visual acuity and treatment intervals. Roche would like to refer to the following:

- Khanani *et al* conducted a multicenter, retrospective chart review on patients treated with faricimab for nAMD. Three hundred and thirty-five patients with 376 eyes had a follow-up visit after one injection of faricimab. Of these, 337 were previously treated with anti-VEGF. The authors describe *'Positive results in both visual and anatomical parameters for patients with various treatment history are currently demonstrating the efficacy of faricimab'.*
- Leung *et al* retrospectively reviewed 190 eyes with nAMD who had previously been treated with anti-VEGF. The authors found that after at least three faricimab injections patients with persistent fluid and/or high treatment demands had '*slightly improved vision and CSTs even in treatment-resistant neovascular ARMD eyes and was associated with longer dosing intervals than for ranibizumab or aflibercept*.'
- Rush *et al* conducted a study looking at previously treated nAMD patients with a high anti-VEGF treatment frequency and signs of disease activity who went on to be treated with intravitreal faricimab. They demonstrated, with statistical significance, that patients switched to intravitreal faricimab had improvements in their anatomical outcomes at the end of a four month period during which they received three faricimab injections. The comparator group were patients previously treated with intravitreal aflibercept.
- Stanga *et al* assessed real world outcomes in nAMD patients treated with faricimab through a retrospective case series of nine patients (eleven eyes). Three of the nine patients were treatment-naïve. The previously treated group had a mean previous treatment interval of 36 days, indicative of a high treatment frequency. In the case series, all patients demonstrated an improvement in best corrected visual acuity and anatomic parameters after commencing faricimab treatment.

The data presented at the recent ARVO congress continues to provide supporting evidence:

- Sim et al presented data at the 2023 Association for Research in Vision and Ophthalmology (ARVO) (a recent international conference), looking at 102 previously treated eyes with nAMD who were unable to achieve less than 5 weekly anti-VEGF injection intervals. When switched to intravitreal faricimab, visual acuities were maintained and anatomical outcomes were improved after the fourth injection with a statistically significant increase in percentage of dry maculae ($p<0.001$).
- Ibrahim et al, Raslan et al and Patel et al all presented posters, at the same conference, which demonstrated similar outcomes. Patients who were switched to faricimab from other anti-VEGF treatment showed improvements in anatomical outcomes after a minimum of two faricimab injections.

Roche believes that the preclinical, clinical trial and clinical practice data presented demonstrate the clinical value of Ang-2 inhibition in the treatment of nAMD in patients considered to be non-responders and partial responders to anti-VEGF monotherapy. Whilst this may be an area of emerging scientific opinion, Roche do not believe that it is an area of controversy as the trends demonstrated and discussed above are consistent, and the clinical outcomes in the real world are reproducible.

Context of the statement

Roche again considers the context of this statement within the promotional item as an important factor. This is a broad document which discusses the clinical and scientific place of faricimab and was developed with eminent UK experts who have several decades of research and clinical experience between them. The use of the word 'may' implies that this is not a statement of fact and further evidence to support the statement is emerging. However, from the evidence seen by the group of experts at the time of writing, they felt there is potential for additional benefit with faricimab in treating patients considered to be non-responders and partial responders to other treatments.

Bayer alleges that the promotional claim, 'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy' is incapable of substantiation. Roche has presented a range of evidence to support the claim, spanning from preclinical data to clinical trial data to clinical practice data. The breadth of evidence demonstrates the additional benefit that inhibition of Ang-2 confers. The preclinical data provides a hypothesis that is then borne out through both clinical trial and clinical practice data demonstrating improvements in clinical outcomes ranging from visual acuity to anatomical improvements to treatment intervals.

As such, Roche does not accept the allegation that the claim above is misleading nor incapable of substantiation and Roche does not consider there has been a breach of clauses 6.1, 6.2 and 14.1 of the Code.

Summary

1: Claim in faricimab promotional slide deck: *'The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'*

It is the view of Bayer that this claim is misleading and, therefore, in breach of Clause 6.1.

Roche does not accept the allegation this claim is misleading and in breach of 6.1. Aflibercept is not bispecific, nor an antibody, and does not target two distinct pathways in nAMD and DMO, whereas faricimab **is** a bispecific antibody targeting two distinct pathways in nAMD and DMO. As such, Roche's claim to be 'the first and only', is factually accurate and can be substantiated.

2(a): Claims in promotional supplement for faricimab in[named publication]

It is the view of Bayer that the statement: *'Alternatively, clinicians may decide to switch without loading, treat at the same interval as that most recently followed for the*

previous anti-VEGF agent, and assess on OCT at follow-up to determine treatment response (improved, worse or unchanged) and an appropriate maintenance regimen.' is inconsistent with the faricimab SmPC and so Bayer alleges breaches of Clause 11.2 and Clause 5.1 of the Code.

Roche does not accept the allegation this statement is inconsistent with the faricimab label. The faricimab SmPC allows clinical choice by **recommending** four loading doses, not mandating four loading doses. The context of the above statement is important, as within the material in question there are several statements recommending 4 loading doses when initiating faricimab. The material is a clinical consensus by leading UK experts, thus making it clear whilst Roche would ideally recommend 4 loading doses, the faricimab label does allow clinical choice.

2(b): Promotional claim incapable of substantiation: *'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy'*

It is the view of Bayer that this claim is misleading, incapable of substantiation and amounts to a misleading comparison of faricimab to other anti-VEGF treatments, in breach of clauses 6.1, 6.2 and 14.1 of the Code.

Roche does not accept these allegations. Ang-2 has proven impact on the pathophysiology of nAMD and DMO, and this is supported by the faricimab SmPC. If patients have responded inadequately to VEGF-A blockade alone, it is logical they may therefore potentially derive additional benefit through inhibition of Ang-2. Preclinical data provided a hypothesis which has been borne out through both clinical trial and clinical practice data demonstrating improvements in clinical outcomes ranging from visual acuity to anatomical improvements to treatment intervals.

Conclusion

Roche has set out in this letter evidence to refute each of Bayer's three allegations and we look forward to the PMCPA's adjudication in this matter."

PANEL RULING

The Panel noted the complaint concerned Roche's medicine Vabysmo (faricimab) which, like Bayer's medicine Eylea (aflibercept), was indicated for adults for the treatment of:

- neovascular (wet) age-related macular degeneration (AMD)
- visual impairment due to diabetic macular oedema (DMO).

Both medicines were administered as an intravitreal injection by qualified health professionals trained in intravitreal injections.

Bayer's Eylea was also indicated for adults for the treatment of:

- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- visual impairment due to myopic choroidal neovascularisation (myopic CNV).

The Panel noted Vabysmo had been licensed relatively recently, in May 2022, and was a black triangle medicine denoting that additional monitoring was required in relation to adverse reactions.

The Panel noted that Bayer had engaged in intercompany dialogue with Roche and that a number of matters appeared to have been successfully resolved. In accordance with Paragraph 5.3 of the Constitution and Procedure, the Panel considered it was not for it to revisit matters that had been resolved during the intercompany dialogue.

The matters before the Panel related to three claims which appeared in two promotional items: a slide deck and a supplement in [named publication].

Material 1: Slide deck

The Vabysmo promotional slide deck comprised 53 slides and was certified for use with GB healthcare professionals only. The metadata of the job bag stated 'This slide deck will be used reactively for DLPs [disease level partners] to send to customers on request' and indicated that it could be sent to customers requesting the slides for use in their own presentations via a pre-approved email and with the addition of a disclaimer stating the slides should be presented in their entirety and should not be edited.

The Panel considered the content and layout of the slide deck. The first slide contained the licensed indication for Vabysmo, NICE recommendations for its use in nAMD and DMO, the black triangle statement and adverse event reporting information. The prescribing information was provided next, followed by a slide headed 'Introducing faricimab' which outlined the content of the remainder of the deck which comprised 5 sections as follows:

1) Unmet needs in nAMD and DMO
2) Faricimab mechanism of action: dual pathway inhibition
3) The role of faricimab in nAMD
4) The role of faricimab in DMO
5) Getting started with faricimab.

The first matter for the Panel to consider was whether the claim 'the first and only bispecific antibody targeting two distinct pathways in nAMD and DMO' was misleading as alleged by Bayer. The Panel noted this claim appeared twice in the slide deck: firstly in the 'Unmet needs' section and secondly within the 'Faricimab mechanism of action' section.

The Panel noted the mechanism of action within Section 5.1 of the summary of product characteristics (SPC) stated 'Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).' The Panel further noted the clinical efficacy and safety section with Section 5.1 of the SPC indicated faricimab had been licensed for use in nAMD and DMO on the basis that it had demonstrated non-inferiority to aflibercept in the phase 3 clinical trials evaluating its clinical efficacy and had been shown to be comparable in terms of its safety.

The claim at issue appeared on the first slide in the 'Unmet needs' section (slide 5) where a timeline indicating specific milestones since the discovery of the VEGF pathway was presented. The slide was headed 'Over the last 20 years, therapies for nAMD and DMO have focused on targeting the VEGF pathway' and the timeline started with the discovery of the VEGF pathway

followed by the discovery that treatment with anti-VEGF antibodies suppressed cell tumour growth in vivo. Five further timepoints from 2007 to 2020 indicated the grant of European licences for intravitreal anti-VEGF therapies for nAMD and DMO. The last timepoint, 2022, stated 'GB licence received for faricimab, the first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'.

The next slide was headed 'Frequent injections of anti-VEGF treatments may be required to maintain visual and anatomical outcomes' and presented findings from retrospective reviews of real-world data. It highlighted that frequent injections can cause high patient and clinic burden and stated 'Patients with nAMD and DMO typically receive fewer anti-VEGF injections and experience worse visual outcomes in the real world, compared with patients receiving fixed, frequent therapy in randomised clinical trials'. These messages were reinforced by the results of the Clinical Survey Outcomes 2020 undertaken by the European Society of Retina Specialists (EURETINA) shown on the following slide and headed 'Treatment burden and extended duration of action have been identified as the greatest unmet needs with anti-VEGF treatments'.

The second iteration of the claim appeared in the section titled 'Faricimab mechanism of action: dual pathway inhibition'. The slide in question (slide 12) was headed 'Dual VEGF-A and Ang-2 inhibition with faricimab' and the claim appeared directly beneath, together with an image showing the effect of its Anti-VEGF-A and Anti-Ang-2 action. The Panel noted the two preceding slides outlined the role of the angiopoietin pathway in maintaining vascular stability and homeostasis and that in retinal diseases Ang-2 promotes vascular instability by blocking Ang-1–Tie2 signalling. The following slide, the last in the section, was headed 'VABYSMO (faricimab) is now licensed in GB and recommended by NICE' and included the licensed indication, contraindications and the NICE recommendations in nAMD and DMO.

The remainder of the slide deck covered the clinical data (efficacy and safety) underpinning the licensed indications, the posology and method of administration of faricimab and special warnings and precautions for use.

The Panel noted that while Bayer accepted the claim was technically accurate 'but only in its use of the word "antibody"', Bayer alleged the claim was misleading as the reader would tend to assume that (i) faricimab was the first and only biologic anti-VEGF treatment in nAMD and DMO to bind not one but two potentially relevant targets and that (ii) as a result of this, faricimab offered benefits over other treatments.

The Panel considered it had to decide whether the claim and how it was presented created ambiguity or misleadingly implied any wider clinical benefit over other medicines in the class.

Roche submitted the claim was a description of the properties of faricimab and its mode of action and did not give the impression of additional therapeutic benefit.

Notwithstanding the above, the Panel was mindful that the slide deck could be sent reactively to health professionals for their use with members of their teams; it considered it was therefore imperative that the messaging was unambiguous to avoid any risk of misinterpretation and incorrect information being promulgated in such team presentations. In the Panel's view, while the material was intended for health professionals specialising in ophthalmology, some might not be familiar with the detail of the Vabysmo SPC given its recent licence, although it was likely most would be familiar with the established medicines in the category.

The Panel considered the immediate and overall impression to health professionals reading the material. It noted the requirements of Clause 6.1 and, in particular, that claims must not mislead either directly or by implication, by distortion exaggeration or by undue emphasis and that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

In the Panel's view the language used ('the first and only bispecific antibody targeting two distinct pathways in nAMD and DMO') had been designed to be eye-catching and was intended to clearly distinguish Roche's medicine from other medicines in the same therapeutic area.

The Panel noted the claim appeared in the first two sections of the slide deck, neither of which mentioned any other medicines by name. Both sections were separate from later sections where clinical information regarding the safety and efficacy of Vabysmo, its posology and method of administration were found.

In relation to the first iteration of the claim in the 'Unmet needs' section, the Panel noted that the claim appeared on a timeline that referred to dates when anti-VEGF therapies had been licensed for nAMD and DMO. The Panel queried how reference to faricimab's distinct mechanism of action on this timeline could be seen as anything other than implying additional clinical benefit. In the Panel's view, the initial part of the sentence ('GB licence received for faricimab …') might have further compounded this misleading impression. The Panel ruled a **breach of Clause 6.1**.

In relation to the second iteration, the Panel noted the inclusion of the claim in the context of the mechanism of action section. The Panel noted the slide including the claim clearly stated the mechanism of action as dual VEGF-A and Ang-2 inhibition immediately above the claim and that the slide followed on from three explaining the role of VEGF-A and Ang-2 in retinal diseases, and descriptions of the angiopoietin pathway in both physiological conditions and in retinal vascular diseases. While the Panel noted the next and final slide in this section was regarding Vabysmo's GB licence and NICE recommendation, this was immediately followed by a section detailing faricimab's clinical efficacy and safety data, including its non-inferiority trials with aflibercept, and also that the job bag metadata required the slides to be presented in their entirety and not edited.

The Panel considered, that on the balance of probabilities, the inclusion of the claim at issue within the context of the mechanism of action section, did not create a misleading impression that there was clinical benefit. The Panel therefore, on balance, ruled **no breach of Clause 6.1**.

Material 2: Promotional Supplement – Consensus document

The Panel noted the document [promotional supplement] reported the outcomes of a consensus steering group meeting of an expert panel of UK retina specialists to discuss the nAMD pathway for Vabysmo that was organised and funded by Roche. The document titled 'Intravitreal faricimab (Vabysmo▼, Roche Products Ltd) for neovascular age-related macular degeneration: general considerations and implementation recommendations by an expert panel of UK retina specialists' was published as a promotional supplement in [named publication] which was distributed to health professionals working in ophthalmology. The document was also approved for proactive distribution by Roche to health professionals as printed and digital versions.

The Panel noted Roche's involvement in the development of the supplement was declared at the outset, at the top of the front cover, and the inclusion of the adverse event reporting statement and a signpost to the prescribing information for Vabysmo indicated that the material was intended to be promotional. Roche's involvement in the project was also highlighted in the introduction which explained the purpose of the supplement as a summary of the expert panel's pathway consensus and recommendations. The supplement reflected evidence-based best practice as well as clinical experience in the treatment of nAMD and suggested pathway recommendations for integrating faricimab as a treatment option for nAMD into UK clinical practice as part of evolving medical retina treatment protocols.

The supplement contained seven pages of substantive content divided into two main sections, as follows:

- Integrating faricimab for nAMD into UK clinical practice – consensus recommendations
    - Dual Ang-2 and VEGF inhibition in nAMD
    - Preferred practice in the management of treatment-naïve patients with nAMD
    - Integrating faricimab into existing nAMD treatment pathways
    - Switching of anti-VEGF agents for patients with persistent or refractory disease activity due to nAMD
    - Switching to faricimab in nAMD
    - Service organisation and implementation of faricimab in nAMD clinic services
    - Treatment suspension in nAMD
- Review of pivotal clinical trial data, marketing authorisation and NICE guidance
    - [Overview of the Phase III TENAYA and LUCERNE clinical trials]
    - Faricimab marketing authorisation
    - NICE guidance for faricimab in nAMD
    - Discussion
    - Conclusion

Bayer's allegations concerned the 'Switching to faricimab in nAMD' section which consisted of the following three bullet points. Bayer's allegations related to the first two of these three bullet points.

- 'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy.
- For patients with nAMD considered refractory to anti-VEGF monotherapy and naïve to dual Ang-2/VEGF-A inhibition, a switch to faricimab with a reloading phase of monthly injections may help to avoid undertreatment and secure maximum initial benefit.
- Alternatively, clinicians may decide to switch without loading, treat at the same interval as that most recently followed for the previous anti-VEGF agent, and assess on OCT [optical coherence tomography] at follow-up to determine treatment response (improved, worse, or unchanged) and an appropriate maintenance regimen.'

a) Alleged off-label promotion of faricimab

In relation to the supplement, Bayer firstly alleged that the third bullet point (above) was not in accordance with the marketing authorisation as there was nothing in the SPC which suggested that the requirement for four initial monthly loading doses did not apply to patients switching from another treatment to faricimab.

Roche submitted that it had intentionally sought a broad and flexible label to allow for clinical choice for health professionals when selecting an appropriate treatment regimen for individual patients.

The Panel recognised clinicians may prescribe medicines outside of their licensed indications if in their clinical judgement it is appropriate to do so and that the purpose of the promotional supplement was to report the consensus recommendations of an expert panel. The Panel nonetheless considered it was imperative that promotional material was not inconsistent with the particulars listed in the summary of product characteristics, as required by Clause 11.2. The Panel noted the posology for use in nAMD in the GB SPC stated:

> 'The recommended dose for Vabysmo is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks for the first 4 doses.
>
> Thereafter, treatment may be individualised using a treat-and-extend approach following an assessment of the individual patient's anatomic and visual outcomes. The dosing interval may be extended up to every 16 weeks, and extensions in increments of up to 4 weeks should be considered, based on the physician's judgement of the individual patient's anatomic and/or visual outcomes. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reductions of up to 8 weeks may be implemented if deemed necessary (see section 5.1). Treatment intervals shorter than 21 days between injections have not been studied.
>
> Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections.'

The Panel noted that the supplement included this wording from the GB SPC posology section in full towards the end of the supplement in the marketing authorisation section and again in the GB prescribing information. In addition, the requirement for treatment initiation with a loading phase of monthly intravitreal injections was included in two sections at the beginning of the document: 'Preferred practice in the management of treatment-naïve patients with nAMD' and 'Integrating faricimab into existing nAMD treatment pathways'. The recommended dosing schedule was also shown on a flowchart depicting the 'Management of nAMD with faricimab: clinical pathway' on page 4 of the supplement. The Panel noted the bullet point at issue was located on page 4 below the flowchart.

The Panel considered the context of the supplement as a whole and that the bullet point at issue was a reflection of the expert panel's consensus opinion, based on their clinical experience about a potential treatment pathway for some patients switching from another anti-VEGF medicine.

In the Panel's view, the bullet point at issue could not be read in isolation: it followed on from and was integrally linked to the preceding point: 'For patients with nAMD considered refractory to anti-VEGF monotherapy and naïve to dual Ang-2/VEGF-A inhibition, a switch to faricimab with a reloading phase of monthly injections may help avoid undertreatment and secure maximum initial benefit.' The Panel considered both bullet points concerned nAMD patients refractory to anti-VEGF monotherapy and naïve to dual Ang-2/VEGF-A inhibition.

Noting the reference to a 'reloading phase' in the preceding bullet point, the Panel considered that this wording was such as would indicate that this was the usual approach when switching to faricimab, and that the third bullet point (the subject of the complaint) acknowledged that clinicians might, in some circumstances and for some patients, decide to switch without loading.

The Panel noted the Code did not prohibit the provision of information not included in an SPC if that information was not inconsistent with the particulars listed in that SPC. In this regard, while the Panel took into account the recommended loading dose in the SPC, it noted the SPC was silent on loading doses in relation to switching; the data in the SPC appeared to be based on treatment naïve patients. The Panel therefore considered that, on balance, Bayer had not established that the bullet point in relation to switching without a loading dose was inconsistent with the particulars listed in the SPC and, accordingly, it ruled **no breach of Clause 11.2**.

Noting its comments above, the Panel considered Bayer had not established that Roche had failed to maintain high standards and therefore it ruled **no breach of Clause 5.1**.

b) Promotional claim allegedly incapable of substantiation

Bayer further alleged that the first bullet point in the 'Switching to faricimab in nAMD' section of the supplement, 'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy', was misleading and not capable of substantiation and constituted an implied comparison with other medicines in the class.

The Panel noted that in relation to this claim, Bayer was not questioning that Vabysmo inhibited both Ang-2 and VEGF-A pathways but whether the implication of additional benefits could be substantiated. The Panel noted Roche submitted the claim was substantiated by section 5.1 of the SPC and that preclinical study data had provided a hypothesis which had been borne out in the clinical trials and in clinical practice with the data demonstrating improvements in clinical outcomes ranging from visual acuity to anatomical improvements to treatment intervals. Roche further submitted the use of the word 'may' implied that the claim was not a statement of fact and that further evidence to support it was emerging. Roche contended that from the evidence seen by the group of experts at the time of writing they felt there was potential for additional benefit with faricimab for patients considered to be non-responders and partial responders to other treatments.

The Panel noted that Roche appeared to accept the claim was a comparison with other medicines in the class and that it concerned an area where scientific opinion was emerging; Roche did not believe that it was an area of controversy.

The Panel noted the supplementary information to Clause 6.1 required that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine and that the supplementary information to Clause 6.1 stated that 'data derived from *in vitro* studies, studies in healthy volunteers and in animals must not be used in such a way that misleads as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance'. Regarding emerging clinical or scientific opinion, the supplementary information to Clause 6.1 stated that when a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material.

The Panel considered that it was not necessarily unacceptable to refer to areas of emerging clinical or scientific opinion, so long as the information presented was not misleading in terms of the clinical benefits of one treatment compared to another.

In the Panel's view, the claim was ambiguous; it did not state what the additional benefits were that may be conferred from use of faricimab in nAMD patients considered non-responders and partial responders to anti-VEGF monotherapy. In this regard, the Panel considered it was likely some health professionals would interpret the claim broadly as a superiority claim. The Panel considered the statement had omitted important qualification regarding the clinical benefit of Ang-2 inhibition in addition to VEGF inhibition and therefore was not a balanced or fair comparison. The Panel considered that health professionals, on the balance of probabilities, were likely to have been misled as to the clinical significance of the Ang-2 inhibition for faricimab compared to anti-VEGF therapies. The Panel, noting the non-inferiority trials available, considered the comparative claim created a misleading impression and the Panel therefore ruled **breaches of Clauses 6.1 and 14.1**.

The Panel, also noting the nature of the data upon which the claim was based, considered the claim created a misleading impression that was not capable of substantiation. The Panel ruled **breaches of Clause 6.2**.

APPEAL BY ROCHE

Roche's written basis for appealing is reproduced below.

> "Further to Roche's notification of intent to appeal the PMCPA Panel rulings in the above mentioned case please find details of the appeal below. To support the Appeal Board's consideration in this matter Roche has provided additional context in the Appendix [provided] before appealing specifically the breaches ruled of Clauses 6.1 (x2), 6.2 and 14.1.
>
> **Slide deck: Appeal of breach ruled of Clause 6.1:**
>
> Both neovascular age-related macular degeneration (nAMD) and Diabetic macular oedema (DMO) are multifactorial diseases with complex pathogenesis. The leading hypothesis is that VEGF overexpression and other pro-angiogenic factors are the main cause of both conditions. However, the underlying causes of each disease vary, and there are other factors that contribute to their development. For example, while inflammation is a trigger for the processes that lead to the development of DMO, in nAMD inflammation seems to be the consequence of retinal pigment epithelium and Bruch membrane alterations. Both nAMD and DMO can cause significant vision loss which negatively impacts patients' quality of life.
>
> The unmet need section (slides 4–7) communicates that despite the advances in nAMD and DMO treatment modalities, there are still patients for whom their number of treatments is a burden or their functional outcomes are not satisfactory and they represent an ongoing clinical unmet need.
>
> The intent of the timeline slide (slide 5) is to provide a visual summary of regulatory and clinical development milestones in the evolution of nAMD and DMO treatment

modalities. It is clearly titled '*Over the last 20 years, therapies for nAMD and DMO have focused on targeting the VEGF pathway*'. There is no language on the slide in regards to efficacy to imply that faricimab is better compared to therapeutics that have come before. Faricimab in the context of the timeline slide, simply represents another regulatory and clinical development milestone and adds to the available therapeutic options that target VEGF.

The statement "the first and only" does not directly indicate superiority, but it does imply that it is different. This difference is in its structure (bispecific antibody) and pathway targets (VEGF-A and Ang-2) as described in the Summary of Product Characteristics (SPC).

Calling out the bispecific nature of faricimab, including targets within two specific pathways (as detailed within the Appendix [provided]), simply communicates how faricimab differs from other treatment options that have come before. The identification of faricimab as an antibody is factually accurate (as acknowledged by Bayer in their correspondence), aiming to provide precision to the reader regarding the development of this particular kind of molecule within the evolution of intravitreal therapeutics.

Together, "the first and only" in this context, implies simply that no other examples exist, but without a value judgement on whether it's "better" than something else. This slide would never be used in isolation, which was acknowledged by the Panel, but rather as part of a complete presentation. The mode of action section follows on directly from this section. In addition, the bulk of the slide deck (slides 14–48) describe the clinical data, where the statement 'faricimab was comparable with aflibercept' was stated 14 times; the studies were clearly identified as 'non-inferiority' (slides 15 and 32); and the statement 'faricimab was non-inferior to aflibercept' mentioned twice in the slide titles (slides 21 and 38).

The Panel ruled a breach of Clause 6.1 on the basis that the reference to faricimab's distinct mechanism of action on the timeline (slide 5) could be seen as anything other than implying additional clinical benefit and that the initial part of the sentence ('GB licence received for faricimab …') might have further compounded this misleading impression.

Roche believes that this ruling is based on perception rather than any data or evidence that can be quantified and the Panel potentially conflating 'difference' with 'superiority'. Roche has not in any way tried to infer superiority on the basis that faricimab is different to other anti-VEGF treatments that have come before.

Furthermore, Roche is not clear how the Panel's ruling regarding the initial part of the sentence ('GB licence received for faricimab …') further compounds the misleading impression. There was never any issue raised by Bayer regarding this matter. This is purely a fact on what is intended as a regulatory timeline with the receipt of a European licence similarly referenced for other treatments. The fact that it is a GB licence rather than a European licence is a consequence of Brexit.

In summary, with the timeline slide Roche intended to:

1. Communicate that a new therapeutic option is available;

2. outline how it is structurally different to previous therapeutics; and
3. include as a statement of fact to provide a complete succinct summary of the new therapeutic option directly referenceable to the SPC: *"Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A)."*

In light of the additional context, Roche would be grateful if the Appeal Board would reconsider the Panel ruling in relation to a breach of Clause 6.1.

[Named publication] supplement consensus paper: Appeal of breaches ruled of Clauses 6.1, 6.2 and 14.1:

The context of the consensus paper reflects evidence-based best practice as well as clinical experience in the treatment of nAMD, by eminent UK experts.

In this instance, the panel ruled breaches of Clauses 6.1 and 14.1 on the basis that the text '*Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy*' was construed as a comparative claim and creating a misleading impression. The Panel also noted the nature of the data upon which the claim was based was not capable of substantiation and ruled a breach of Clause 6.2.

It is widely accepted that there are non-responders and partial responders to treatments. The intent of the stated text was to identify a patient group, which in the view of the clinicians, MAY benefit from a therapeutic trial of faricimab, given that the response to date had been clinically sub-optimal. The cohort referred to is not based on the drug treatment, it is a cohort within the nAMD patient group. The clinical consensus thus rules out any potential comparison to any other treatments by default and cannot be interpreted as an unsubstantiated claim.

To reiterate, nAMD is a multifactorial disease with complex pathogenesis and a common understanding there are non responders and partial responders to treatment. In the context of this consensus paper, this cohort may benefit from a treatment that is known to differentially target factors associated with the disease. This is of particular significance given that disease progression could lead to sight loss. This is in no way intended to be a claim of superiority or comparison to any other anti-VEGF treatments.

Roche considers the Vabysmo SPC an appropriate reference to support the above statement.

In summary:

1. The intent of the text was to reflect current clinical consensus opinion of which underserved patient populations' clinicians might be justified with a therapeutic trial of faricimab;
2. Roche does not consider the claim to be misleading or making any such comparison between faricimab and anti-VEGF treatments that do not target Ang-2; and

3. The SPC for Vabysmo provides an appropriate reference for the statement in this context

Roche would be grateful if the Appeal Board would reconsider rulings of the Panel in relation to the breaches of Clause 6.1, 6.2 and 14.1 in this instance."

RESPONSE FROM BAYER

Bayer's written basis for responding to the appeal is reproduced below.

"Bayer supports the Panel's rulings of Code breaches against Roche. Our response to Roche's letter of appeal dated 23 September 2024, is as follows.

Background to Case AUTH/3764/4/23

Bayer's product aflibercept (Eylea®) and Roche's product faricimab (Vabysmo®) are both biological medicines in the anti-VEGF (vascular endothelial growth factor) class, sufficiently similar in their chemistry and mode of action that the World Health Organisation (WHO) considers that they sit within the same subgroup of the WHO Anatomical Therapeutic Chemical (ATC code) S01LA.

Faricimab was first licensed and made available in the UK in May 2022. Aflibercept (in its 2mg dose formulation) was first licensed and made available in the UK in November 2012, almost 10 years earlier than faricimab. In this appeal "aflibercept" refers only to aflibercept 2mg, the only aflibercept dose available at the time of the original complaint. The shared licensed indications for aflibercept and faricimab are neovascular (wet) age-related macular degeneration (nAMD) and visual impairment secondary to diabetic macular oedema (DMO), both common, serious and progressive retinal conditions which carry a high risk of blindness in untreated patients. The key driver of pathological angiogenesis in both these indications, and the primary target of drugs in the anti-VEGF class, is VEGF-A.

The technical background to this complaint has been outlined in detail and referenced in Bayer's original letter of complaint dated 25 April 2023 and so will not be repeated in full here.

It is important to note that there are two ways in which the word "bispecific" can be understood. There is the narrow technical definition (a single biological molecule designed to bind two different specific targets **at the same time on different binding domains within the same molecule**) and the more general way in which the term may commonly be understood (e.g. by health professionals who are not experts in molecular science), which is a biological molecule that targets and binds two different things i.e. has a dual action.

In this context, there are 3 key technical points which Bayer would like to bring to the particular attention of the Appeal Board as they consider this case.

1. Aflibercept and faricimab each bind VEGF-A plus a second pathologically relevant target.

- Aflibercept is a fully human antibody-derived fusion protein which binds VEGF-A plus placental growth factor (PlGF) via a 1:1 'trap' mechanism; in other words, each molecule of aflibercept binds either one molecule of VEGF-A or one molecule of PlGF. Both "arms" of the Y-shaped aflibercept molecule bind to its target molecule simultaneously to form the "trap", rather like two hands holding a ball.
- Faricimab is a humanised recombinant monoclonal antibody which binds VEGF-A plus angiopoetin-2 (Ang-2) via a bispecific mechanism ; in other words, each molecule of faricimab simultaneously binds both VEGF-A and Ang-2, one target on each arm of the Y-shaped faricimab molecule.

In the context of nAMD and DMO, **binding a second target in addition to VEGF-A via a simultaneous mechanism (faricimab) has not been shown to have any clinical advantages to binding a second target via a 1:1 trap mechanism (aflibercept).**

2. In addition, **the clinical relevance of therapeutic Ang-2 blockade remains an area of controversy** and emerging scientific understanding, with no consensus existing on its clinical benefits in nAMD or DMO.

3. **Faricimab has been shown in the primary endpoints of large phase III studies in nAMD and DMO only to be clinically non-inferior to aflibercept** i.e. comparable in terms of its clinical efficacy and safety.

To summarise, aflibercept and faricimab are drugs in the same class, each offering a dual action by binding a second target in addition to the most physiologically important factor in nAMD/DMO pathogenesis, VEGF-A. Aflibercept has been licensed and available in the UK for many years prior to faricimab. Faricimab has been shown in its phase III studies only to be clinically non-inferior to aflibercept 2mg. There is no clinical evidence to support faricimab having any specific clinical benefits either as a result of its simultaneous dual binding action or because it binds to Ang-2.

Original Complaint

Bayer asserted that claims used by Roche in two promotional materials [slide deck and supplement] were in breach of the Code:

1. Claim in faricimab promotional slide deck: '*The first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'.* A breach of Clause 6.1 was ruled.

2. Claims in promotional supplement for faricimab in [supplement in named publication], *'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy'***.** Breaches of Clauses 6.1, 6.2 and 14.1 were ruled.

The crux of the complaints ruled in breach, and this appeal, is as follows.

In the above promotional materials Roche has highlighted technical biochemical and functional differences between faricimab and other drugs in its class in the context of

unmet patient need, and has also promoted faricimab explicitly as having potential clinical benefits in patients as a direct result of these biochemical features. Strong and eye-catching promotional language has been used *("first and only")* and it has been implied incorrectly that faricimab is unique in its class of anti-VEGF therapies in offering something other than VEGF-A inhibition alone.

It is therefore Bayer's position that Roche has pursued a deliberate promotional strategy through various promotional materials, with the intent of creating a perception amongst prescribers that faricimab may offer patients additional clinical benefits purely because of its dual binding capability and its binding of Ang-2, despite an absence of clinical evidence capable of substantiating such an inference.

Roche has claimed repeatedly in its responses to Bayer and the PMCPA, and in its letter of appeal, that it is presenting only simple statements of fact about faricimab's structure and mode of action without any intended clinical inferences, whilst in its promotional materials leveraging such references to mode of action in a way which is misleading as to the potential clinical benefits of their product.

To give an example, in January 2023, Bayer was in receipt of a letter from Roche in intercompany dialogue, explicitly denying that Roche is using faricimab's bispecific mode of action, in accordance with the SmPC, as the basis for promotional claims of clinical benefit ["*Bayer has not provided any concrete evidence of how any of the UK faricimab materials characterising it as a bispecific antibody in accordance with the SmPC, gives it any 'special therapeutic benefit' over and above its competitors*"].

However, in the faricimab promotional supplement (discussed in part 2 of this Appeal), Roche included a claim that "*Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy",* which clearly makes **a direct link between faricimab's mode of action and a claim of clinical benefit**.

Furthermore, in a letter to Bayer in intercompany dialogue and again in its letter of appeal in defence of this claim, Roche has attempted to substantiate this statement **only by reference to a description of the faricimab mode of action in the SmPC, a document containing no data on use in non- or partial responders to other anti-VEGFs.** Bayer interprets this as confirmation that Roche is seeking in its promotion of faricimab to imply a link between mode of action and the potential for added clinical benefit, despite the absence of any clinical evidence to support such a suggestion.

It is therefore the view of Bayer that the PMCPA Panel correctly interpreted Roche's intentions in the promotional materials at issue in Case AUTH/3764/4/23 and ruled these claims as misleading. Accordingly, Bayer respectfully asks the Appeal Board to reject Roche's appeal.

Original Panel decision and Roche appeal

Part 1: Summary of Panel decision on the use of *"First and only bispecific antibody"* slide deck produced by Roche for use by health professionals – breach of Clause 6.1 when used in context of implied comparison with other anti-VEGFs. Bayer demonstrated to the satisfaction of the Panel that this suggested a clinical benefit from

structural and functional differences to other molecules in the class, which could not be substantiated.

There are two ways in which this claim is misleading:

- It implies that faricimab is the first and only molecule in the anti-VEGF class to offer a dual binding action, when aflibercept also binds another target in addition to VEGF-A and was launched in 2012
- It implies that farcimab's dual action in binding Ang-2 is a clinically relevant distinction from other treatment options in the same class, when no evidence exists to support this.

It is important to note that the Panel highlighted the promotional nature of the statement in question:

"In the Panel's view the language used ('the first and only bispecific antibody targeting two distinct pathways in nAMD and DMO') had been designed to be eye-catching and was intended to clearly distinguish Roche's medicine from other medicines in the same therapeutic area."

This ruling is aligned with a long-standing Code convention that claims such as *"first and only"* are inherently promotional. Use of such a claim implies a deliberate attempt to position faricimab as having some special benefit, distinct from its competitors. As such, **there should be clear evidence of the clinical relevance of such a claim**. Case AUTH/2016/7/07 (Novartis v Bristol-Myers Squibb, Promotion of Sprycel) makes this clear. In this case, Bristol-Myers Squib had claimed that '*Sprycel is the first and only therapy to bind to both active and inactive conformations of the BCRABL'*, a statement that was chemically correct but which the Panel ruled was misleading in breach of Clause 7.2 **because it implied that this structural feature conferred clinical benefit** when no correlation had been clinically proven between the clinical activity of dasatinib (Sprycel) and its binding profile. Exactly the same situation exists with faricimab.

In its letter of appeal, Roche asserts that use of *" 'first and only' does not directly indicate superiority, but it does imply that it is different"* and *"simply represents another regulatory and clinical development milestone*" However, as seen in Case AUTH/2016/7/07, the use of "first and only" goes further than a statement of fact and constitutes a promotional claim with an implication of associated clinical benefit, which therefore needs to be substantiated. The intention of the timeline slide was thus not to present an overview of characteristics of the available products, as Roche claims, but to promote faricimab by implying clinical advantages over other drugs in its class.

Whilst Bayer accepts that some technical differences exist between the faricimab and aflibercept molecules, these products have been shown in large phase III studies to be non-inferior in terms of clinical efficacy and safety. Health professionals are unlikely to be concerned with the technical distinctions and classifications of 'fusion protein' versus 'antibody' as features of a molecule, unless there is an associated clinical benefit.

Likewise the prominent characterisation by Roche of faricimab's binding action as "first and only" may create confusion as to whether it is the binding of a second target in

addition to VEGF-A that is the most important “first and only” feature of the faricimab molecule (something aflibercept was doing 10 years before faricimab was launched), or the fact that each molecule of faricimab binds two targets at the same time, a technical feature of no proven clinical relevance. Bayer therefore questions the motivation for Roche calling out faricimab’s structure and mode of action in this particular way, if not to create a strong impression that these features are of clinical relevance with an associated perception of faricimab having a clinical benefit over other therapeutic options in the same class.

The Panel also queried how reference to faricimab’s distinct mechanism of action on this timeline could be seen as anything other than implying additional clinical benefit. The PMCPA has declared that the statement in question was *“designed to be eye-catching*”; and *“was intended to clearly distinguish Roche’s medicine from other medicines in the same therapeutic area”.* In the Panel’s view, the initial part of the sentence *(‘GB licence received for faricimab ...’*) might have further compounded this misleading impression.

Roche has stated repeatedly that the slide would not be used in isolation, despite Roche’s control over use of the deck being minimal as it is intended to be distributed to health professionals for use by the health professionals with their teams – teams presumably including the nurses and allied health professionals who perform the majority of anti-VEGF injections in the UK. Regardless, Bayer contends that the Panel was correct in their interpretation of Roche’s promotional intent hence this statement would **remain misleading whether or not the slide containing it appeared in the context of the full presentation or was used in isolation**. Additionally, where a slide deck is intended for independent use by health professionals, it is especially important that all the contents are clear and unambiguous.

Bayer notes Roche’s statement in their letter of 23 September 2024 that *“despite the advances in nAMD and DMO treatment modalities, there are still patients for whom their number of treatments is a burden or their functional outcomes are not satisfactory and they represent an ongoing clinical unmet need”.* Bayer agrees completely with Roche on this clinical point **but believes Roche’s statement confirms their motivation for using the language *“first and only”* in this section of the slide deck is to imply potential <u>clinical</u> utility of their product arising purely from a difference in its mode of action** – in other words, this is intended to be a promotional claim relating to clinical benefit, as recognised by the Panel.

Bayer believes that the existence of patients with an unmet clinical need places an even greater responsibility on pharmaceutical companies to ensure that our promotion adheres to the spirit and letter of the Code. Promotion must not raise false hope in clinicians that a product might offer clinical advantages to their patients facing sight loss from nAMD or DMO despite treatment. Roche has presented no clinical evidence to support their inference that faricimab can help these patients where other drugs have failed. Roche have likewise (in part 2 of this Appeal) directly claimed in promotional material that faricimab may benefit patients who have failed to respond well to other treatments, because of its mode of action. **The promotional messaging linking faricimab mode of action to implied clinical benefit is therefore consistent across different Roche promotional materials.**

Bayer contends that reference in promotional material to the uniqueness of a molecular structure or mode of action of a molecule **cannot be interpreted as anything other than an attempt to imply a difference in molecular feature has some special clinical merit or additional benefit.** The supplementary information to Clause 6.1 of the Code therefore states that "*data derived from in vitro studies, studies in healthy volunteers and in animals must not be used in such a way that misleads as to its significance. Extrapolation of such data to the clinical situation, whether overt or implied, should only be made where data exist to show that there is direct clinical relevance and significance*."

The existence of a dual-target mode of action amongst anti-VEGFs is not unique to faricimab but is also a feature of aflibercept, launched 10 years earlier. No clinical benefit of faricimab over aflibercept, nor of Ang-2 inhibition, has been demonstrated in patients with nAMD or DMO. Nor has any clinical benefit been demonstrated in relation to simultaneous binding of dual targets (faricimab), compared to 1:1 stoichiometric "trap" binding of two different targets (aflibercept).

The clinical relevance of Ang-2 inhibition is an area of emerging scientific understanding, as defined within Clause 6.1 of the Code. This point was discussed extensively in Bayer's original letter of complaint and has not been disputed at appeal by Roche. As such, any promotional material referencing potential benefits of Ang-2 inhibition, whether directly or by implication, should be balanced and sufficiently complete to allow the reader to reach their own conclusion as to the validity of any such claim. No attempt has been made in any of the Roche materials referencing Ang-2 blockade to present a balanced overview of data for and against the potential clinical relevance of this pathway to patients with nAMD.

Roche states in its letter of appeal in relation to this decision that it believes *"this ruling is based on perception rather than any data or evidence".* This is exactly the point of Bayer's original complaint. Clause 6.1 of the Code exists to ensure that the way in which readers perceive a claim made by a pharmaceutical company does *"not mislead either directly or by implication"* as to the clinical benefits of its product. Bayer believes that the perception of the Panel in interpreting this claim was exactly the same as the perception of a prescriber would be i.e. that the material is implying faricimab offers potential clinical benefits over its competitors, benefits that have never previously been available. It is an important and long-established principle of the Code, reflected in Code case precedent over decades, that the **perception** of a promotional statement or activity is of paramount importance in a ruling of whether or not the Code has been breached.

Bayer therefore respectfully asks the Appeal Board to uphold the Panel's ruling of a breach of Clause 6.1 for the use of *"First and only bispecific antibody"*.

<u>Part 2</u>: Summary of Panel decision on the use of *"Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy"* – breaches ruled of Clauses 6.1, 6.2 and 14.1. This statement was taken from outputs of a Roche-organised and Roche-funded expert panel and appeared in a promotional journal supplement produced and paid for by Roche.

The Panel noted that this was an area of emerging scientific opinion. Roche had effectively extrapolated *in vitro* data to imply clinical benefit, as recognised by the Panel. This has always been unacceptable under the Code. Bearing in mind the phase III pivotal trial data for faricimab in nAMD comprised a non-inferiority study (against aflibercept) in treatment-naïve patients and in the absence of other relevant data, it is difficult to see how this claim could possibly be substantiated. As such it was ruled as misleading.

Bayer notes that in its letter of appeal Roche does not attempt to dispute that the clinical relevance of Ang-2 is a matter of emerging scientific opinion and unresolved controversy within the medical retina community.

In intercompany dialogue with Bayer (relating to the "first and only" claim discussed in part 1 of this appeal) Roche stated that *"Bayer has not provided any concrete evidence of how any of the UK faricimab materials characterising it as a bispecific antibody in accordance with the SmPC, gives it any 'special therapeutic benefit' over and above its competitors"*. Bayer contends that the statement *"Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy*" appearing in the Roche-sponsored faricimab promotional supplement provides just such concrete evidence, Roche has repeatedly attempted to substantiate this claim of clinical benefit only by reference to the faricimab SmPC which contains no data on use of faricimab in this patient subgroup.

Furthermore, Roche's efforts to justify this claim of superiority in a difficult-to-treat patient subgroup purely by reference to the SmPC, which contains no relevant data, underlines the wider strategy and intent of faricimab promotion, seen in both materials at issue in Case AUTH/3764/4/23, of using presentation of facts about faricimab's mode of action and Ang-2 binding to imply clinical benefit in a way that is likely to mislead the reader and is not capable of substantiation. Such a misleading claim is especially serious when dealing with unmet need in a cohort of patients potentially facing blindness.

With regard to the claim of clinical benefit in the supplement, Roche states in its letter of appeal *"The intent of the stated text was to identify a patient group, which in the view of the clinicians, MAY benefit from a therapeutic trial of faricimab, given that the response to date had been clinically sub-optimal. The cohort referred to is not based on the drug treatment, it is a cohort within the nAMD patient group. The clinical consensus thus rules out any potential comparison to any other treatments by default and cannot be interpreted as an unsubstantiated claim".*

Bayer has a number of concerns with this response from Roche.

- The consensus statement was the view of expert clinicians as Roche states, but critically **was elicited during a consensus meeting organised and funded by Roche, appeared in a publication developed and funded by Roche, and was disseminated to UK health professionals via a Roche-sponsored promotional supplement in [named publication].** By established Code case precedent, when such a document is created in this way by a pharmaceutical company, the entire contents are inherently promotional and therefore the

specific statement in question constitutes a promotional claim. Code case precedent is also clear that a pharmaceutical company's stated "intent" of a promotional text does not matter; it is its likely impact on the reader that constitutes whether or not the material is compliant.

- Roche emphasises the word *"MAY"* in its letter of appeal [B]. If legitimisation of otherwise unfounded statements is possible merely by using "may" (or similarly unemphatic words), this opens many possibilities for companies to make unsubstantiated promotional claims.
- The promotional material containing the statement is clearly designed by Roche to direct clinicians in their use of faricimab in nAMD, including promoting its use in a specific subgroup of patients by implying it may have added benefits by virtue of its mode of action. The clinical relevance of Ang-2 blockade remains an area of controversy and emerging scientific understanding. Roche did not provide any additional context on this point to provide balance in the material, as required by Clause 6.1. Additionally, in its appeal arguments Roche has not disputed that Bayer and the Panel had correctly characterised clinical benefits of Ang-2 inhibition in nAMD as unproven and an area of scientific controversy.
- Bayer also fails to see how a promotional claim that faricimab may be of benefit in patients who have responded sub-optimally to other treatments can constitute anything other than a comparative claim against those other treatments – **in effect, the promotional material is claiming that faricimab may offer clinical benefits in patients where other treatments have failed.**
- Roche has still not provided in its defence **any** clinical data to substantiate the claim that faricimab may offer benefits in a treatment-resistant subgroup of patients, nor any evidence of clinical superiority to other treatments in nAMD. Instead, Roche has restated that the SmPC for faricimab is *"an appropriate reference"* for this statement, despite the fact that **the faricimab SmPC contains no data on the safety and efficacy of faricimab in patients who have failed to respond to other treatments.** The pivotal studies for faricimab in nAMD, TENAYA and LUCERNE, were conducted solely in **treatment-naïve** patients. Bayer therefore considers that this statement by Roche in its appeal again highlights the misleading link that Roche is attempting to make between faricimab's mode of action and its potential clinical benefits.

Conclusion

Bayer maintains that the Panel was correct in its rulings of breaches of Clauses 6.1 (x2), 6.2 and 14.1 in Case AUTH/3764/4/23, having accurately perceived how the statements at issue could potentially mislead clinicians concerning the potential clinical benefits of faricimab in nAMD. Roche has failed to explain the clinical relevance of its promotional claims relating to faricimab mode of action and it has also failed to substantiate that clinical relevance.

Bayer therefore respectfully asks the Appeal Board to uphold the rulings and reject the appeal by Roche."

APPEAL BOARD RULING

Material 1: Slide deck

The claim at issue was 'GB licence received for faricimab, the first and only bispecific antibody targeting two distinct pathways in nAMD and DMO'.

The Appeal Board considered that reference to a medicine's mechanism of action was important for readers. However, context was also important and the Appeal Board noted that the Panel had ruled no breach in relation to the same wording in a different context, within the mechanism of action section.

The matter for the Appeal Board to consider was whether the appearance of the claim, on a timeline that referred to dates when anti-VEGF therapies had been licensed for nAMD and DMO on slide 5 in the 'Unmet needs' section of the presentation, was misleading and implied additional clinical benefit of faricimab.

It was not disputed that the available evidence from Phase III studies showed that faricimab was non-inferior to aflibercept in nAMD and DMO. Roche submitted that the statement 'faricimab was comparable with aflibercept' was stated 14 times; the studies were clearly identified as 'non-inferiority' (slides 15 and 32); and the statement 'faricimab was non-inferior to aflibercept' was mentioned twice in the slide titles (slides 21 and 38).

In the Appeal Board's view, use of the claim on the timeline which referred to other milestones such as 'European licence received for intravitreal anti-VEGF therapies' for DMO and nAMD, could not be for any purpose other than to differentiate Roche's product from anti-VEGF therapies. The term 'first and only' implied special merit, particularly given that other milestones on the timeline used no such terminology. The Appeal Board considered the inclusion of statements such as 'faricimab was comparable with aflibercept' 14 times, on subsequent slides of a slide deck to be sent to healthcare professionals reactively, did not negate the primary impression of additional clinical benefit.

The Appeal Board concluded that the implied clinical significance was misleading as alleged and upheld the Panel's ruling of a **breach of Clause 6.1**. Roche's appeal on this point was unsuccessful.

Material 2: [Named publication] Supplement – Consensus document

The Appeal Board observed that the second claim at issue read 'Bispecific Ang-2 and VEGF-A blockade may confer additional benefits in patients with nAMD considered non-responders and partial responders to anti-VEGF monotherapy' and appeared in a promotional consensus document.

Roche submitted the intent of the claim was not intended to be of superiority or comparison to other anti-VEGF treatments but was to identify a patient group, which in the view of the clinicians, 'MAY benefit from a therapeutic trial' of faricimab (emphasis added by Roche), given that the response to date had been clinically sub-optimal.

There was no dispute that faricimab inhibited both Ang-2 and VEGF-A pathways. The matter before the Appeal Board was whether the implication of additional benefits was misleading and whether the claim could be substantiated, taking into account the available data.

The Appeal Board took account of the purpose of the document, which was promotional, and observed that the title of the document included 'general considerations and implementation recommendations by an expert panel of UK retina specialists'.

In the Appeal Board's view, the claim at issue implied that faricimab held some additional benefits; use of the term 'may' did not negate this impression. The Appeal Board considered that health professionals were likely to have been misled as to the clinical significance of the Ang-2 inhibition for faricimab compared to anti-VEGF therapies. The comparative claim created a misleading impression and the Appeal Board upheld the Panel's rulings of a **breach of Clauses 6.1 and 14.1**. Roche's appeal on these points were unsuccessful.

The Appeal Board, taking into account the non-inferiority trials available, considered the claim created a misleading impression that was not capable of substantiation and it upheld the Panel's ruling of a **breach of Clause 6.2**. Roche's appeal on this point was unsuccessful.

Complaint received **25 April 2023**

Case completed **13 January 2025**