CASE AUTH/3366/7/20

BAYER V NOVARTIS

Promotion of Beovu

Bayer Plc complained about a journal advertisement (ref BRO20-CO22, March 2020) for Beovu (brolucizumab) placed by Novartis Pharmaceuticals UK Ltd in the April 2020 edition of Eye News. The claim at issue was 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48[1]' which appeared as the second of two headline claims in the advertisement, printed in dark pink font.**

Beovu was indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD). Bayer marketed Eylea (aflibercept) which was also indicated in adults for the treatment of neovascular (wet) AMD. Eylea and Beovu were biological anti-angiogenic therapies administered by injection into the eye and acted by inhibiting vascular endothelial growth factor (anti-VEGF). Eylea had been approved by the National Institute for Health and Care Excellence (NICE) for use in the treatment of neovascular (wet) AMD.

1 Use of secondary endpoints and footnotes

Bayer stated that the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48[1]' was based on a secondary, exploratory endpoint (resolution of total retinal fluid) of two non-inferiority studies (Dugal et al 2020). Readers had to spot the double asterisk and then read several lines of small print footnotes to begin to appreciate the full context. The fact that this was a secondary endpoint was only revealed by the double asterisk aligned to a statement, in small, black type print, four lines below the claim in question. The primary endpoint in the relevant studies was non-inferiority in mean change in best corrected visual acuity (BCVA) from baseline to week 48. Beovu was found to be non-inferior to aflibercept in both studies. The primary endpoint of the studies (non-inferiority) was only mentioned eight lines below the claim in question, again, in small, bold, black type print.**

The footnote clarifying the primary study endpoint did not state the study outcome of non-inferiority having been met. Bayer contended that even if Novartis had included the primary outcome in the advertisement as a similar small type footnote (for example, by stating words to the effect that 'non-inferiority was met'), that would still be wholly insufficient given such prominent claims of outperformance and superiority in the claim.

Bayer was concerned that Novartis did not agree to stop using footnote qualifiers and state with a similar level of prominence (ie font size, position, colour etc) that the claim was based on an exploratory, secondary endpoint.

The secondary endpoint evidence to support the claim was exploratory, as evidenced in the European Medicines Agency (EMA) European Public Assessment Report (EPAR) for Beovu

Bayer alleged that to claim that Beovu 'outperformed' and had 'superior retinal fluid resolution' to Eylea without giving sufficient prominence to the primary outcome, and without sufficient prominence to the fact that the claims were based on an exploratory, secondary outcome, was misleading.

In Bayer's view, a health professional would only read the prominent 'outperformed' and 'superior' claims in large red typeface, and thus would be likely to miss the small print qualifiers in black font listed separately and at a significant distance below the claim. Bayer alleged that the claim was selected for prominence and had not been properly contextualised in its presentation to allow health professionals to independently assess the therapeutic value of the two medicines discussed. Readers were very likely to be left with the key take-home message that Beovu had overall 'outperformed' and was 'superior' to Eylea which was not the case. In the context of the EMA's comments in the EPAR and considering the PMCPA's previous decisions on such matters, use of terms such as 'outperformed' and 'superior' in the claim, with qualifying statements appearing in small typeface footnotes below, made the claim a misleading comparison in the context of Clause 7.2.

The Panel noted that both claims in the advertisement related to the secondary endpoints in the pivotal studies (HAWK and HARRIER). Below these two claims were 9 lines of small black footnote text which appeared to be the same font size as the prescribing information which featured immediately below. One sentence, in the seventh and eighth lines of the footnote, was bold and stated: 'The primary efficacy endpoint in both studies was non-inferiority in mean BCVA [best corrected visual acuity] change from baseline to Week 48 as measured by ETDRS'. The Panel noted that the explanation for the asterisks, **, used after the claim at issue, was given in the fourth line of the footnote text which stated: 'Secondary endpoint in HAWK and HARRIER, confirmatory analysis in HAWK only (1-sided p values for superiority of Beovu)'.

The Panel noted that the primary objective of both HAWK and HARRIER was to demonstrate that brolucizumab (Beovu: once every 12 weeks/8 weeks) was non-inferior to fixed-dose aflibercept with respect to the change in BCVA from baseline to Week 48. At Week 48, each brolucizumab arm demonstrated non-inferiority to aflibercept in BCVA change from baseline; $P < 0.001$ for each comparison. The Panel noted that Beovu was found to be non-inferior to aflibercept in both studies. This primary endpoint result was not referred to in the advertisement at issue.

The Panel noted that additional secondary efficacy end points included, *inter alia*, the status of SRF (subretinal fluid)/IRF (intraretinal fluid) and sub-RPE (retinal pigment epithelium) fluid, and presence of disease activity at Week 16. In both studies, patients received a complete ophthalmic examination (including BCVA and anatomic assessments [IRF/SRF /sub-RPE fluid and CST]) and were evaluated for adverse events every 4 weeks.

The Panel noted that Dugel *et al* stated that each of the 4 BCVA-related non-inferiority hypotheses of HAWK reached statistical significance (1-sided $P < 0.025$) and therefore

additional confirmatory superiority testing was conducted in HAWK to assess the superiority of brolucizumab regarding, *inter alia*, presence of IRF and/or SRF. The study authors stated that this additional confirmatory superiority testing of brolucizumab versus aflibercept was prespecified in HAWK (based on HARRIER learnings). Dugel *et al* stated that superior anatomic outcomes regarding retinal fluid and retinal thickness with brolucizumab 6 mg versus aflibercept could be concluded from HAWK and HARRIER at Weeks 16 and 48 in both studies. Formal demonstration of statistical superiority versus aflibercept was only demonstrated in HAWK.

The Panel considered that it was not necessarily unacceptable to include secondary endpoint data in promotional material without reference to the primary endpoint from a non-inferiority trial so long as such references complied with the Code and were not otherwise misleading.

The Panel noted that section 5.1 of the Beovu SPC referred to the percentage difference in patients with IRF and/or SRF fluid for Beovu versus aflibercept in HAWK and HARRIER at Weeks 16 and 48 as statistically significant. There was no mention in the SPC that this data was secondary endpoint data, however, the secondary endpoint evidence, used to support the claim at issue, was referred to as exploratory in the Beovu EPAR which stated that it could not be the basis for claims in the product information. The Panel considered that the content of the EPAR was relevant, particularly in relation to the requirement in the Code for claims to be balanced and reflect all the evidence. In the Panel's view, whilst it might not be unacceptable to refer to exploratory analyses in promotional material, the context was an important consideration and it questioned whether such data should be used as the basis for a robust comparison of medicines.

The Panel noted that Beovu was a new product at the time the advertisement was published and in that regard health professionals reading a specialist eye journal would be interested in the outcomes of its key registration studies, HAWK and HARRIER.

The Panel considered the immediate and overall impression to health professionals reading the advertisement. In the Panel's view, the bold claim at issue including the use of 'superior' and 'outperformed' would be the take home message and might imply that Beovu was overall clinically superior to aflibercept. The Panel was concerned that the impression of clinical superiority given by the claim was inconsistent with HAWK and HARRIER as reported in Dugel *et al* which concluded that Beovu was non-inferior to aflibercept in terms of its primary endpoint. The footnote which qualified the claim at issue by stating that it was based on a secondary endpoint was not sufficient to negate this misleading impression. Further the advertisement did not include the study outcome ie that Beovu was found to be non-inferior to aflibercept. The primary efficacy endpoint measure was included in another footnote, headed 'study design'.

The Panel noted its comments above and considered that the claim in question in the context of the advertisement at issue was misleading and the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Beovu vs aflibercept. A breach of the Code was ruled.

2 Presentation of emerging clinical and scientific debate

Bayer accepted that Beovu showed a formal statistically significant difference from Eylea (aflibercept) in terms of total retinal fluid resolution in one pivotal study, albeit that this was an exploratory, secondary endpoint. However, the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48[1]' was alleged to be misleading because it implied that total retinal fluid resolution had an accepted clinical relevance, when in fact the differential effect of resolution in different fluid compartments was increasingly considered to be more pertinent.**

During inter-company dialogue, Novartis acknowledged that there was ongoing clinical debate on the relative importance of the drying of fluid in different compartments of the retina, but stated that it was not, however, Novartis' position to tell clinicians how to engage in that debate. That responsibility fell on the prescriber who should decide whether the claims made were relevant to their clinical practice based on current evidence, clinical experience and guidelines.

Bayer stated that prescribers could not decide on relevance if they were not aware of the debate. Bayer contended that the debate was ignored by the prominent broad claim of superiority in respect to total fluid resolution as the drying of total fluid was not presented in the context of the drying of fluid in different retinal compartments. In that regard, the claim did not present the area of emerging scientific opinion in a balanced manner.

Bayer submitted that it was not in question that retinal fluid was important in diagnosing and assessing neovascular AMD and in making associated treatment decisions; however current scientific opinion was split over the clinical relevance of different types of retinal fluid.
When compared with aflibercept, Beovu had not been demonstrated to have a significantly greater impact on drying intra-retinal fluid (Dugal 2019 and Dugal 2017), the compartment that was increasingly recognized by clinical consensus to be the one most closely associated with poor visual outcomes.

Bayer stated that whilst it recognized that this was a complex and controversial area, the debate had not been resolved in favour of one generally accepted viewpoint. The claim presented the increased drying of total retinal fluid by Beovu as a definite clinical benefit in comparison with Eylea, and thereby indicated clinical 'outperformance' and 'superiority' to Eylea, whereas this had not been proven and was an area where scientific opinion was evolving. Since Novartis had failed to treat the issue of retinal fluid drying in a balanced manner, Bayer alleged the material was misleading.

The Panel considered that as noted in point 1 above the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48' might incorrectly imply that the results seen in the study directly translated into clinically meaningful benefits for Beovu over Eylea. In the Panel's view, the advertisement over-simplified the position in that it implied that Beovu clinically outperformed Elyea based on total fluid resolution when there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina.

The Panel noted its comments above and did not consider that the reader had been provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Beovu vs aflibercept in relation to its effect on retinal

fluid resolution. A breach of the Code was ruled. This ruling was upheld on appeal by Novartis.

3 Alleged misleading comparison re safety profiles

Bayer alleged that the promotional approach in the advertisement did not provide readers with all the facts necessary to interpret the claim objectively, because it did not discuss the differences between the safety profiles of the two products shown in the same studies. The advertisement not only misleadingly stated that Beovu 'outperformed' Eylea (aflibercept) based on an exploratory, secondary endpoint in non-inferiority studies, it also failed to acknowledge that a safety difference was identified during these same studies. The misleading nature of the advertisement was of concern to patient welfare as, when the advertisement was approved, the pivotal studies referenced had shown increased rates of intraocular inflammation and retinal artery occlusion with Beovu compared with Eylea (Dugal 2020). These safety concerns (specifically retinal artery occlusive events) with Beovu were specifically highlighted by the EMA in the summary of the initial CHMP opinion and retinal artery occlusion appeared in the Beovu SPC, but not in the Eylea SPC.

Bayer stated that the clinical importance of that initial observation had been highlighted by further events and details were provided. As a direct result, Beovu was currently subject to investigation of a new safety signal and was in the process of an update to its global prescribing information. In June 2020, some 8 months after first launch, the US label for Beovu was the subject of safety amendments to its label in the US, Australia and Switzerland . Bayer understood discussions were ongoing with the European regulators regarding a similar change to the Beovu SPC.

Whilst Bayer accepted that the safety signal was confirmed only after the advertisement was first approved, the advertisement's publication in April 2020 occurred after the first emergence of potential post marketing safety concerns in February 2020, and when it was already clear from the pivotal study that adverse events of direct relevance to the new safety signal occurred far more frequently with Beovu compared with Eylea (Dugal 2020). To compare the two products in the advertisement without presenting comparative differences in safety data between them from the pivotal studies, when an advantage based on an exploratory, secondary endpoint from the same studies was claimed, was therefore a misleading comparison by omission.

Bayer also submitted that these safety concerns remained relevant when it came to the general promotional approach for Beovu given that it was a newly launched medicine where post marketing safety experience was still evolving and there remained many uncertainties related to causation, risk factors, incidence and optimal treatment of adverse events. Given the evolving nature of the safety concerns associated with Beovu, Bayer was concerned that Novartis did not agree during inter-company dialogue to present a specific overview of the comparative safety differences between the two products (rather than simply rely on the prescribing information) in the context of making a superiority claim based on an exploratory, secondary endpoint from non-inferiority studies. On that basis, Bayer alleged that the ongoing promotional approach, typified by the advertisement, was neither balanced, nor objective, nor did it reflect a clear and up to date evaluation of all the evidence.

The Panel noted that it was agreed during inter-company dialogue that the emerging safety data was not relevant to the journal advertisement at the time of its publication as it had emerged after and was not reflected in the SPC at the time of the advertisement. Novartis had committed to appropriately representing all safety data as required by the Code in future material. The Panel noted that this matter had thus been settled and therefore it would make no rulings in that regard.

The Panel noted, however, that during inter-company dialogue Bayer had also raised concerns that the claim comparing efficacy should only have been made if a comparison of safety data was also provided. Bayer alleged that not doing so misled as to the overall clinical comparison between the medicines and was the allegation upon which the Panel would make its ruling.

The Panel noted that both medicines would only be administered by ophthalmologists experienced in intravitreal injections; this was a specialist area. Such health professionals, in the Panel's view, on the balance of probabilities, would not be misled that the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48' included a comparison of safety profiles.

The Panel did not consider that Bayer had shown, on the balance of probabilities, that presenting efficacy data from HAWK and HARRIER without presenting the comparative differences in safety data between Beovu and aflibercept was misleading by omission as alleged. No breaches of the Code were ruled.

Bayer Plc complained about a journal advertisement (ref BRO20-CO22, March 2020) for Beovu (brolucizumab) placed by Novartis Pharmaceuticals UK Ltd in the April 2020 edition of Eye News. The claim at issue was 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48**[1]' which appeared as the second of two headline claims in the advertisement, printed in dark pink font.

Beovu was indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD). Bayer marketed Eylea (aflibercept, launched in the UK in 2012) which was also indicated in adults for the treatment of neovascular (wet) AMD. Beovu was granted an EU marketing authorization in February 2020. Eylea and Beovu were biological anti-angiogenic therapies administered by injection into the eye and acted by inhibiting vascular endothelial growth factor (anti-VEGF). Eylea had been approved by the National Institute for Health and Care Excellence (NICE) for use in the treatment of neovascular (wet) AMD.

Bayer was particularly concerned about what it alleged was misleading and unbalanced promotion of a recently launched product which showed an unfavourable safety profile in its pivotal trials compared with its established comparator, aflibercept. Bayer also stated that Beovu was known to have generated a new safety signal within four months of first launch, leading to regulatory review of the label.

Novartis gave details of the safety signal (14 reports in the US of vasculitis) and explained that following confirmation of the signal (on 6 April 2020), it had informed, *inter alia*, the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA); neither had expedited processes nor asked for further actions beyond the standard processes for safety notifications and label updates. Nevertheless, discussions with the EMA were ongoing and the summary of product characteristics (SPC) was yet to be updated.

Novartis stated that it had since received confirmation of label updates from the US, Australian, Swiss and Japanese regulatory agencies and added that it continued to receive regulatory approvals for Beovu globally.

1 Use of secondary endpoints and footnotes

COMPLAINT

Bayer stated that the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48**[1]' was based on a secondary, exploratory endpoint (resolution of total retinal fluid) of two non-inferiority studies (Dugal *et al* 2020). Readers had to spot the double asterisk and then read several lines of small print footnotes to begin to appreciate the full context. The fact that this was a secondary endpoint was only revealed by the double asterisk aligned to a statement, in small, black type print, four lines below the claim in question. The primary endpoint in the relevant studies was non-inferiority in mean change in best corrected visual acuity (BCVA) from baseline to week 48. Beovu was found to be non-inferior to aflibercept in both studies. The primary endpoint of the studies (non-inferiority) was only mentioned eight lines below the claim in question, again, in small, bold, black type print.

In the advertisement, the footnote clarifying the primary study endpoint did not state the study outcome of non-inferiority having been met. During inter-company dialogue, Novartis agreed to include a statement that the primary endpoint of non-inferiority was met in future materials, but only as a footnote. Novartis did not agree to present that statement with a similar level of prominence (ie font size, position on the page and colour) as the information about outperformance and superiority of the exploratory, secondary endpoint outcome in the claim. Accordingly, Bayer contended that even if Novartis had included the primary outcome in the advertisement as a similar small type footnote (for example, by stating words to the effect that 'non-inferiority was met'), that would still be wholly insufficient given such prominent claims of outperformance and superiority in the claim.

Bayer stated that Novartis also did not agree to stop using footnote qualifiers and state with a similar level of prominence (ie font size, position, colour etc) that the claim was based on an exploratory, secondary endpoint. This was of concern to Bayer as the approach evidenced in the advertisement in question was still being used by Novartis. As this approach was still in use, inter-company dialogue had been unsuccessful to resolve Bayer's concerns about the ongoing use of a misleading superiority claim and relying on footnote qualifiers.
The secondary endpoint evidence to support the claim was exploratory, as evidenced in the European Medicines Agency (EMA) European Public Assessment Report (EPAR) for Beovu (copy provided):

> 'Regarding superiority testing, it is not understandable why visual acuity had not been selected despite it represents the primary endpoint's variable and the first key secondary. Moreover, as additional secondary endpoints, no hierarchy testing strategy had been set, and neither has a control been set for the risk alpha. Therefore, these superiority testing are **considered only as exploratory** [emphasis added], and cannot be the basis for claims in the product information' *[sic].*

Bayer stated that it was a well-established principle of the Code that claims must be capable of standing alone. In that regard, Bayer referred to Case AUTH/2705/3/14 which it stated concerned a matter decided by the Panel on similar facts to this complaint. The case

considered whether the primary endpoint of a study was prominently presented in a press release. The Panel ruled that a less prominent inclusion of the primary endpoint, later in the press release, was insufficient to enable the reader to properly assess how much weight to attach to the secondary endpoint findings in the heading. On that basis, the heading was considered misleading; a ruling of a breach of Clause 7.2 was upheld on appeal, the Appeal Board stating that there was a strong possibility that the heading would be incorrectly assumed to refer to the primary endpoint. Bayer contended that that ruling was consistent with the present case where there was a strong possibility that a prominent claim based on a secondary endpoint would incorrectly be assumed to refer to the primary endpoint, in particular when the words 'outperformed' and 'superior' were used in the headline.

Bayer additionally referred to Case AUTH/3062/8/18 which it also stated concerned an allegation that a leavepiece misrepresented a clinical trial, without any suggestion that there were any factual errors in the material. The Panel stated that while it was not unreasonable to present secondary endpoint data, there had to be proportionate emphasis and balance in terms of presenting the overall trial data and not disproportionate emphasis on results that favoured a company's product. The Panel considered the immediate impression to a busy health professional was a misleading comparison between the products. This was the intended primary take home message of the piece in question and later qualifications given were wholly insufficient to qualify the immediate impression given. Breaches of Clauses 7.2 and 7.3 were ruled.

In Case AUTH/3137/12/18 Bayer noted that the Panel ruled that a prominent claim in large font regarding better tolerability vs other regimens was in breach of the Code because the referenced studies and qualifying statement immediately beneath in a smaller typeface footnote did not negate the misleading impression created by the claim. This was ruled in breach of the Code by the Panel despite the qualifier to the claim appearing within the same visual field as the claim and a dagger symbol next to the claim referring the reader to the qualifier. That ruling was upheld on appeal.

Furthermore, the use of exploratory analyses was also considered in Case AUTH/2705/3/14 (cited above). In that case, the Panel stated that exploratory analyses should not be used as the basis for a robust comparison of medicines. Given that the Beovu EPAR clearly stated that the secondary endpoint of retinal fluid resolution in the pivotal studies referenced in the advertisement was exploratory, Bayer contended that it should not be used as the basis for a robust comparison between Eylea and Beovu. Given Novartis was seeking a decision on the point from the PMCPA, Bayer would invite the PMCPA to draw the same conclusion as the EMA in the EPAR statement that the secondary endpoint referenced in the claim should not be the basis for prominent claims of outperformance and superiority in promotional material, particularly so without clear and equally prominent reference to the non-inferiority primary endpoint.

Bayer alleged that to claim that Beovu 'outperformed' and had 'superior retinal fluid resolution' to Eylea without giving sufficient prominence to the primary outcome, and without sufficient prominence to the fact that the claims were based on an exploratory, secondary outcome, was misleading and in breach of Clause 7.2.

In Bayer's view, a health professional would only read the prominent 'outperformed' and 'superior' claims in large red typeface, and thus would be likely to miss the small print qualifiers in black font listed separately and at a significant distance below the claim. Bayer alleged that

the claim was selected for prominence and had not been properly contextualised in its presentation to allow health professionals to independently assess the therapeutic value of the two medicines discussed. Readers were very likely to be left with the key take-home message that Beovu had overall 'outperformed' and was 'superior' to Eylea which was not the case. In the context of the EMA's comments in the EPAR and considering the PMCPA's previous decisions on such matters, use of terms such as 'outperformed' and 'superior' in the claim, with qualifying statements appearing in small typeface footnotes below, made the claim a misleading comparison in the context of Clause 7.2.

RESPONSE

Novartis maintained the claim at issue met the requirements of Clause 7.2 of the Code as it was:

- accurate because it reflected the referenced evidence, namely the superior fluid resolution observed in the studies;
- balanced in that it did not exaggerate the effects described;
- fair, objective and unambiguous in that it neither includes opinion, and/or speculation, nor did it include any ambiguous language and
- based on the pivotal (referenced) studies, with contemporaneous evaluation of all evidence and reflected such evidence clearly.

Novartis noted specifically that, in addition to the above requirements, Clause 7.2 required that: '*Material* [emphasis added] must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. Further, the general section of the supplementary information to Clause 7 as a whole stated '… *claims* [emphasis added] in promotional material must stand alone as regards to accuracy etc. In general claims should not be qualified by the use of footnotes and the like'.

Novartis submitted that the claim specifically referred to a pre-specified endpoint that showed a significant difference in the Beovu pivotal studies (Dugal *et al*). That **claim** stood alone with no further information needed to understand it and the **material** as a whole was sufficiently complete to allow recipients to form their own opinion of the therapeutic value of the medicine. The claim and material, therefore, met the requirements of Clause 7.2.

Novartis noted that Bayer interpreted the double asterisk as qualifying information; however, Novartis maintained that the double asterisk appropriately linked to further information, which was of interest, but which did not qualify that claim. Novartis maintained that the claim itself stood alone without further information required to understand it.

Novartis also noted Bayer alleged a misleading claim regarding the use of 'outperform' and 'superior', with reference to the prominence of the primary endpoint and its position. Novartis maintained the primary endpoint was clearly legible and appropriate context was provided. The advertisement contained additional information below the claim and the print in question was clearly legible; the primary endpoint was also highlighted in bold print. The size of the print was in larger font than the prescribing information.

Novartis submitted that the context of the primary endpoint was provided clearly in the material ('The primary efficacy endpoint in both studies was non-inferiority in mean BCVA change from baseline to Week 48 as measured by ETDRS'). The material also contained further, extensive

detail regarding study design, dosing regimens and monitoring. Therefore, full context was provided for the primary endpoint, and the material as a whole was sufficiently complete to allow readers to form their own opinions of the therapeutic value of the medicine. The material contained more information than was required by the Code and in any event, in Novartis' view, the material met the requirements of Clause 7.2.

Novartis added that there was currently no requirement within the Code for the primary outcome measure to be more prominent than the secondary outcome. Clear context was provided in the material that this was a non-inferiority study with regard to the primary outcome. The secondary outcome measure was a pre-specified endpoint and in that regard, Beovu demonstrated superiority. That secondary outcome data was included in the SPC and the material was, therefore, not inconsistent with its particulars. The material provided readers with more than sufficient information in order to draw their own conclusions about the therapeutic value of the medicine.

Novartis was confused why Bayer had re-introduced the matter of the primary endpoint result. The matter had been raised and resolved in inter-company dialogue and in keeping with Paragraph 5 of the Constitution and Procedure and the principles of self-regulation, Novartis did not consider that the matter should be considered by the Panel nor should it make a ruling on that matter.

Novartis submitted that Bayer's reference to the EPAR was inappropriate. The EPAR was a regulatory document that informed other regulatory documents including, but not limited to, the product information, other labelling and packaging; it did not inform promotional claims in material. The definitive test of the Code sat with the SPC and the PMCPA. Clause 3.2 of the Code stated that 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics'. In that regard, the claim met the requirements of the Code with the relevant information contained within Section 5.1 of the SPC. Notwithstanding, the secondary endpoint and confirmatory analysis were pre-specified and found to be statistically significant.

Novartis disagreed with Bayer's contention that 'outperformed' and 'superior' were inappropriate descriptors of the data in question. Both terms were comparative and accurately reflected the fluid resolution data which showed that Beovu demonstrated superiority in drying of the retina and, therefore, outperformed aflibercept in this measure.

During inter-company dialogue, Bayer's concern with the use of the terms 'outperformed' and 'superior' was introduced and Bayer alleged that those terms were superlatives; Novartis disagreed. The issue was resolved in July 2020: it was agreed that the terms were not superlatives. However, at that point in the discussion, Bayer proposed new allegations that the terms, whilst not superlatives, were misleading. Novartis reiterated its position that the terms accurately reflected the evidence that Beovu showed statistically significant superiority in its drying effect and that that data was included in the SPC. Nonetheless, in an attempt to resolve the issue, Novartis proposed potentially more acceptable language. That offer was rejected by Bayer.

Novartis noted Bayer's reference to Case AUTH/2705/3/14 to support its allegation. Notable differences were evident between that case and the current complaint, not least that Case AUTH/2705/3/14 referred to a press release about a study where the primary endpoint was not met. That was in contrast to the Beovu registration studies where the primary endpoint was met

in both studies (Dugal *et al*). A press release was not a promotional piece and in the cited case, the press release could only legitimately have aimed to provide newsworthy information about the results of a clinical study. In that regard, the objectives, content and length of the press release were all important considerations and, in that case, the primary endpoint result was on the second page. That was clearly inappropriate, especially as the result was 'negative' and the headline might have misled readers to assume the primary endpoint was met. That was in direct contrast to the journal advertisement now at issue. The journal advertisement was a single A4 page and the main claims were restricted to about half the available space with the rest taken up by the prescribing information. In the context of a single page advertisement, Novartis believed the material was sufficiently complete and met all requirements of Clause 7.2.

Novartis also noted Bayer's reference to Case AUTH/3062/8/18 and again considered that there were some notable differences between the material in question in that case and the journal advertisement that Bayer had complained about.

Firstly, in Case AUTH/3062/8/18, the material was a 6-page leavepiece. The size of the material in question was relevant and pertinent for context when deciding on the requirements of Clause 7.2. In a single page advertisement, less information could be included than in a 6-page leavepiece, especially due to the necessary inclusion of the prescribing information.

Secondly, the claim referenced by Bayer, was a safety endpoint that showed superiority only during a 12 week titration period with comparable safety during the maintenance period and the end of the 24 week study. That was important context that was missing from Bayer's interpretation of Case AUTH/3062/8/18. Novartis noted the comment in the case report:

> 'The Panel considered that it was not unreasonable to present secondary endpoint data, nor was it unreasonable to present such data from the titration period, if it was presented in the context of the full study period and with proportionate emphasis.'

The claim now being complained about by Bayer, was statistically significant at 16 weeks, 48 weeks and this was maintained at 96 weeks, the completion of the study. There was nothing misleading about the claim as it was factually accurate and represented the totality of evidence in the study. The need for 'proportionate emphasis', as referenced by the Panel, would be relevant had superiority not been maintained throughout the study; for example, if superiority was only shown up to week 16. The superiority in retinal fluid drying was, in fact, maintained for the duration of the study.

With regard to Case AUTH/3137/12/18, Novartis again considered that there were notable differences; in particular, the fact that the claim referenced by Bayer did not reflect the totality of the available evidence and cherry picked data to suggest favourable outcomes. The claim now at issue did not do that: the claim was accurate and reflected the evidence as the data referenced was pre-specified, demonstrated statistically significant superiority and reflected all the evidence available. Given that Beovu was newly launched, the evidence could only reflect the development programme outcomes, particularly the registration studies.

Novartis also noted that Bayer had stated that in the inter-company dialogue Novartis did not agree to stop using footnote qualifiers. For clarity, that was not accurate. Novartis had explained that the footnotes were not qualifiers and they, in fact, provided readers with additional information. Novartis did not consider it was inappropriate to use footnotes to add information to a claim that stood alone. However, Novartis understood the requirements of the Code and would not advocate the use of footnote qualifiers to aid understanding of a claim.

For the reasons outlined above, Novartis denied a breach of Clause 7.2.

PANEL RULING

The Panel noted the comments from both parties about inter-company dialogue and whether the complaint should be considered by the PMCPA. The Panel noted, from Bayer's letter of complaint, it appeared that whilst Novartis agreed during inter-company dialogue that the result of the primary endpoint should be included in material and that the material should not simply state what the endpoint of the study was, Novartis did not agree to present that statement with a similar level of prominence (ie font size, position on the page and colour) as the claim about outperformance and superiority of the exploratory secondary endpoint. Both parties agreed that there was disagreement on the relative prominence of the secondary endpoint versus the primary endpoint in the claim in question.

The Panel noted that the advertisement at issue, published in Eye News in April 2020, stated 'Now authorised' in prominent typeface in the top righthand corner, and was titled 'For patients with wet AMD'. Below this title was Beovu's logo and directly below the logo, in prominent dark pink font, were two claims: 'Maintained a majority of eligible* patients on q12w [every 12 weeks] interval immediately after loading through Week 48' followed by the claim at issue, 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48** [both referenced to Dugel *et al* 2020]'.

The Panel noted that both claims in the advertisement related to the secondary endpoints in the pivotal studies (HAWK and HARRIER). Below these two claims were 9 lines of small black footnote text which appeared to be the same font size as the prescribing information which featured immediately below. One sentence, in the seventh and eighth lines of the footnote, was bold and stated: 'The primary efficacy endpoint in both studies was non-inferiority in mean BCVA [best corrected visual acuity] change from baseline to Week 48 as measured by ETDRS'. The Panel noted that the explanation for the asterisks, **, used after the claim at issue, was given in the fourth line of the footnote text which stated: 'Secondary endpoint in HAWK and HARRIER, confirmatory analysis in HAWK only (1-sided *p* values for superiority of Beovu)'.

The Panel noted that the primary objective of both HAWK and HARRIER was to demonstrate that brolucizumab (Beovu: once every 12 weeks/8 weeks) was non-inferior to fixed-dose aflibercept with respect to the change in BCVA from baseline to Week 48. At Week 48, each brolucizumab arm demonstrated non-inferiority to aflibercept in BCVA change from baseline; $P < 0.001$ for each comparison. The Panel noted that Beovu was found to be non-inferior to aflibercept in both studies. This primary endpoint result was not referred to in the advertisement at issue.

The Panel noted that additional secondary efficacy end points included, *inter alia*, the status of SRF (subretinal fluid)/IRF (intraretinal fluid) and sub-RPE (retinal pigment epithelium) fluid, and presence of disease activity at Week 16. In both studies, patients received a complete ophthalmic examination (including BCVA and anatomic assessments [IRF/SRF /sub-RPE fluid and CST]) and were evaluated for adverse events every 4 weeks.

The Panel noted that Dugel *et al* stated that each of the 4 BCVA-related non-inferiority hypotheses of HAWK reached statistical significance (1-sided $P < 0.025$) and therefore additional confirmatory superiority testing was conducted in HAWK to assess the superiority of

brolucizumab regarding, *inter alia*, presence of IRF and/or SRF. The study authors stated that this additional confirmatory superiority testing of brolucizumab versus aflibercept was prespecified in HAWK (based on HARRIER learnings). Dugel *et al* stated that superior anatomic outcomes regarding retinal fluid and retinal thickness with brolucizumab 6 mg versus aflibercept could be concluded from HAWK and HARRIER at Weeks 16 and 48 in both studies. Formal demonstration of statistical superiority versus aflibercept was only demonstrated in HAWK.

The Panel considered that it was not necessarily unacceptable to include secondary endpoint data in promotional material without reference to the primary endpoint from a non-inferiority trial so long as such references complied with the Code and were not otherwise misleading.

The Panel noted that section 5.1 of the Beovu SPC referred to the percentage difference in patients with IRF and/or SRF fluid for Beovu versus aflibercept in HAWK and HARRIER at Weeks 16 and 48 as statistically significant. There was no mention in the SPC that this data was secondary endpoint data, however, the secondary endpoint evidence, used to support the claim at issue, was referred to as exploratory in the Beovu EPAR which stated that it could not be the basis for claims in the product information. The Panel considered that the content of the EPAR was relevant, particularly in relation to the requirement in the Code for claims to be balanced and reflect all the evidence. In the Panel's view, whilst it might not be unacceptable to refer to exploratory analyses in promotional material, the context was an important consideration and it questioned whether such data should be used as the basis for a robust comparison of medicines.
The Panel noted that Beovu was a new product at the time the advertisement was published and in that regard health professionals reading a specialist eye journal would be interested in the outcomes of its key registration studies, HAWK and HARRIER.

The Panel considered the immediate and overall impression to health professionals reading the advertisement. In the Panel's view, the bold claim at issue including the use of 'superior' and 'outperformed' would be the take home message and might imply that Beovu was overall clinically superior to aflibercept. The Panel was concerned that the impression of clinical superiority given by the claim was inconsistent with HAWK and HARRIER as reported in Dugel *et al* which concluded that Beovu was non-inferior to aflibercept in terms of its primary endpoint. The footnote which qualified the claim at issue by stating that it was based on a secondary endpoint was not sufficient to negate this misleading impression. Further the advertisement did not include the study outcome ie that Beovu was found to be non-inferior to aflibercept. The primary efficacy endpoint measure was included in another footnote, headed 'study design'.

The Panel noted its comments above and considered that the claim in question in the context of the advertisement at issue was misleading and the reader was not provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Beovu vs aflibercept. A breach of Clause 7.2 was ruled.

2 Presentation of emerging clinical and scientific debate

COMPLAINT

Bayer accepted that Beovu showed a formal statistically significant difference from Eylea (aflibercept) in terms of total retinal fluid resolution in one pivotal study, albeit that this was an exploratory, secondary endpoint. However, the claim 'Outperformed aflibercept with superior

retinal fluid resolution at Weeks 16 and 48**[1]' was alleged to be misleading because it implied that total retinal fluid resolution had an accepted clinical relevance, when in fact the differential effect of resolution in different fluid compartments was increasingly considered to be more pertinent (Sharma 2016; Jaffe 2019; Singer 2019; Sharma 2020).

During inter-company dialogue, Novartis acknowledged that there was ongoing clinical debate on the relative importance of the drying of fluid in different compartments of the retina, but stated in its letter of 18 June 2020, 'It is not, however, Novartis' position to tell clinicians how to engage in that debate. This responsibility falls on the prescriber who should decide whether the claims made are relevant to their clinical practice based on current evidence, clinical experience and guidelines'.

Bayer stated that prescribers could not decide on relevance if they were not aware of the debate. Bayer contended that the debate was ignored by the prominent broad claim of superiority in respect to total fluid resolution as the drying of total fluid was not presented in the context of the drying of fluid in different retinal compartments. In that regard, the claim did not present the area of emerging scientific opinion in a balanced manner.

Bayer submitted that it was not in question that retinal fluid was important in diagnosing and assessing neovascular AMD and in making associated treatment decisions; however current scientific opinion was split over the clinical relevance of different types of retinal fluid. All three studies that Novartis had conducted comparing Beovu with aflibercept showed that the difference between the two in terms of total fluid resolution was driven principally by one type of retinal fluid (sub-retinal fluid) (Dugal 2019 and Dugal 2017). There was also evidence that suggested that excessive drying of this type of fluid might even be associated with harm in the long term (Sharma *et al* 2020, Zarbin 2020 and Grunwald *et al* 2014).

When compared with aflibercept, Beovu had not been demonstrated to have a significantly greater impact on drying intra-retinal fluid (Dugal 2019 and Dugal 2017), the compartment that was increasingly recognized by clinical consensus to be the one most closely associated with poor visual outcomes.

Bayer stated that whilst it recognized that this was a complex and controversial area, the debate had not been resolved in favour of one generally accepted viewpoint. The claim presented the increased drying of total retinal fluid by Beovu as a definite clinical benefit in comparison with Eylea, and thereby indicated clinical 'outperformance' and 'superiority' to Eylea, whereas this had not been proven and was an area where scientific opinion was evolving. In that regard, Bayer noted that the supplementary information to Clause 7.2 stated clearly 'Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'. Since Novartis had failed to treat the issue of retinal fluid drying in a balanced manner, Bayer alleged the material was misleading, in breach of Clause 7.2.

RESPONSE

Novartis drew attention to Bayer's own assertion during inter-company dialogue that 'Retinal fluid is important in diagnosing and assessing wet age-related macular degeneration ("wet AMD") and in making associated treatment decisions'. Bayer had again now stated 'It is not in question that retinal fluid is important in diagnosing and assessing nAMD and in making

associated treatment decisions'. Novartis did not understand, therefore, why Bayer alleged a breach of Clause 7.2 when it had definitively confirmed that the claim was very relevant to current clinical practice.

Clearly there was a recognition that the claim was in line with current practice and this was further confirmed by treatment guidelines issued by the Royal College of Ophthalmologists (RCO) and the European Society of Retina Specialists (EURETINA) (copies provided). Additionally, market research conducted by Novartis consistently showed that retina specialists saw fluid management as an important factor in decision making around treatment (copy provided).

Novartis noted that Bayer acknowledged that there was some debate within the clinical community on the drying of *individual compartments*, and it was the pharmaceutical industry's responsibility to state the facts for clinicians to make their own decisions on the relative merits of the various sides to the debate.

Notwithstanding, no claim was made about specific compartments of fluid and Novartis was reassured that Bayer agreed that retinal fluid in general was important in diagnosing and assessing wet AMD and in making associated treatment decisions. It seemed clear that both Novartis and Bayer believed that there was significant clinical relevance to drying of fluid in the retina.

During inter-company dialogue, Novartis accepted there was ongoing debate around the drying of individual compartments of fluid. This was what was referred to in the text reproduced by Bayer's: 'It is not, however, Novartis' position to tell clinicians how to engage in that debate. This responsibility falls on the prescriber who should decide whether the claims made are relevant to their clinical practice based on current evidence, clinical experience and guidelines'. That text specifically referred to the debate around the different sub-compartments of fluid and, as noted above, the claim made no reference to that. There was minimal debate, if any, about the relevance of fluid in the retina in general and it was an accepted part of decision making in clinical practice, as acknowledged by Bayer.

Novartis, therefore, refuted the alleged breach of Clause 7.2.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2, emerging clinical or scientific opinion, 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 noted that Bayer was not questioning whether retinal fluid was important in diagnosing and assessing neovascular AMD and in making associated treatment decisions. The Panel noted that Bayer accepted that Beovu showed a statistically significant difference from Eylea (aflibercept) in terms of total retinal fluid resolution in one pivotal study (HAWK), albeit that this was an exploratory, secondary endpoint. Bayer alleged that the claim was misleading because it implied that total retinal fluid resolution had an accepted clinical relevance, when in fact the differential effect of resolution in different fluid compartments was increasingly considered to be more pertinent. Bayer was concerned that drying of total fluid was not presented in the context of the drying of fluid in different retinal compartments.

The Panel noted Bayer's submission that all three studies that Novartis had conducted comparing Beovu with aflibercept showed that the difference between the two in terms of total fluid resolution was driven principally by one type of retinal fluid (sub-retinal fluid) and there was evidence that suggested that excessive drying of this type of fluid might even be associated with harm in the long term. The Panel further noted Bayer's submission that when compared with aflibercept, Beovu had not been demonstrated to have a significantly greater impact on drying intra-retinal fluid, the compartment that was increasingly recognized by clinical consensus to be the one most closely associated with poor visual outcomes. The Panel noted that it appeared that Novartis accepted there was ongoing debate around the drying of individual compartments of fluid.

Section 5.1 of the Beovu SPC referred to the percentage difference in patients with IRF and/or SRF fluid for Beovu versus aflibercept in HAWK and HARRIER at Weeks 16 and 48 as statistically significant. The Panel considered that it was not necessarily unacceptable to include this secondary endpoint data in promotional material so long as it was not misleading in terms of the clinical benefits of one treatment compared to another.

The Panel considered that as noted in point 1 above the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48' might incorrectly imply that the results seen in the study directly translated into clinically meaningful benefits for Beovu over Eylea. In the Panel's view, the advertisement over-simplified the position in that it implied that Beovu clinically outperformed Elyea based on total fluid resolution when there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina.

The Panel noted its comments above and did not consider that the reader had been provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Beovu vs aflibercept in relation to its effect on retinal fluid resolution. A breach of Clause 7.2 was ruled. This ruling was appealed by Novartis.

APPEAL FROM NOVARTIS

Novartis noted that the Panel ruled that the advertisement implied that Beovu clinically outperformed Eylea based on total fluid resolution, over-simplifying the position, particularly when there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina. Novartis disagreed with the Panel's interpretation that there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina and its relevance to the management of wet age-related macular degeneration (wet AMD). While there was certainly debate on the relevance of drying different compartments on visual outcomes, Novartis submitted that it was nevertheless accepted by the clinical community (and evidenced by guidelines discussed further below), that drying different compartments of the eye was clinically relevant in making treatment decisions, in particular deciding treatment intervals, as it could determine the injection burden of a patient and healthcare system. This was supported by Bayer which submitted that retinal fluid levels were clinically relevant for making associated treatment decisions.

Novartis noted that the superiority claim made a comparison between Beovu and aflibercept on retinal drying outcomes, and not on visual outcomes. Novartis submitted that the drying claim was supported by Beovu's SPC and data from HAWK and HARRIER.

Novartis noted that Wet AMD was a chronic condition that was characterised by retinal fluid accumulation, causing damage to retinal structure and function, leading to sight loss if left untreated. In the context of wet AMD management, retinal fluid was pathological and a key aim of treatment was to dry the retina and maximise visual outcomes with the least number of injections possible (Wykoff *et al,* 2018). Drying the retina was a key treatment goal accepted by the clinical community.

Novartis noted that in the management of wet AMD patients, ophthalmologists aimed to preserve or improve vision as well as treat the underlying retinal fluid with anti-vascular endothelial growth factor (anti-VEGF) therapies. The clinical relevance of managing retinal fluid was a concept that was widely understood and accepted by the ophthalmology community. This was further supported by the fact that clinical studies involving anti-VEGF agents included fluid (anatomical) outcomes determining treatment interval extension and/or fluid resolution endpoints (CATT Research Group, 2011, Chakravarthy *et al*, 2012, Kodjikian et al, 2013, Busbee *et al*, 2013, Berg *et al*, 2015, Richard *et al*, 2015, Wykoff, *et al*, 2015, Kertes *et al,* 2019, Gillies *et al,* 2019, Dugel *et al*, 2020). This included the registration studies of Bayer's aflibercept, which was used as the comparator in the Beovu HAWK / HARRIER registration studies (Richard *et al*, 2015; Dugel *et al,* 2020).

In relation to Bayer's view that it was not in question that retinal fluid was important in making associated treatment decisions, Novartis submitted that the fluid status of the retina (anatomic status) had a significant role in determining the maximum treatment interval hence fluid resolution results were important for a clinician to understand the efficacy of an anti-VEGF. Lanzetta *et al* stated:

> *'*The interval between each visit was either increased or decreased according to the anatomic and VA status, to determine the maximum time between injections without disease recurrence'

Novartis submitted therefore, medicines that could dry the retina more effectively could extend the treatment interval and reduce treatment burden. Furthermore, the importance of fluid control and resolution and its relationship with treatment burden was evident in the SPC of all three licensed anti-VEGFs which had posologies describing the role of anatomical parameters (fluid status) in determining the extension of treatment intervals for patients after the loading phase. For example, the Eylea SPC stated:

> 'Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval might be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals were increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of two months during the first 12 months of treatment'.

Novartis noted that there was explicit mention of 'anatomic outcomes' in the SPC further reinforcing Novartis' position that the influence of fluid resolution on treatment intervals of anti-VEGF therapy was not an area of emerging science or debate but an established clinical outcome.

Novartis submitted that whilst there was some debate on the role of subretinal fluid (SRF) in terms of visual outcomes, it was accepted by the ophthalmology community that the presence of

SRF impacts the clinician's ability to extend the treatment interval. This was further confirmed by treatment guidelines issued by the Royal College of Ophthalmologists (RCOphth) which also explicitly referred to SRF. The 2013 the RCOphth guidelines for the management of wet AMD stated the following criteria for 'Continuation of Treatment' stated:

> 'Disease activity was denoted by retinal, subretinal or sub-RPE fluid...'; the guidelines went on to state 'Where there was recurrence of CNV activity, treatment was reinstated...".

Novartis submitted that additionally, the 2014 European Society of Retina Specialists (EURETINA) guidelines for the management of wet AMD (Schmidt-Erfuth *et al*, 2014) stated:

> 'IRC, SRF and RPE detachments were important signs of disease activity... all these features were usually considered as criteria for reinjection of anti-VEGF substances'

Therefore, Novartis submitted that products that could effectively resolve SRF could extend treatment intervals. Novartis data demonstrated that Beovu was equally effective in drying intraretinal fluid (IRF) and more effective in drying subretinal fluid (SRF) compared to aflibercept (Dugel *et al*, 2019).

Novartis submitted that both UK and European academic society guidelines explicitly called out the role of SRF in the criteria for reinjection with anti-VEGF. The guidelines were from 2013 and 2014, respectively, demonstrating that the concept had been well established and could not be considered areas of emerging science. This was further supported by guidelines, recently, released in 2019 from the American Academy of Ophthalmology (AAO) which stated:

> 'Treatment was based on the presence or absence of subretinal or intraretinal fluid.'

Novartis submitted the guidelines from AAO continue to demonstrate that this area of science was well established, and no new information has warranted a change of thinking or approach from academic societies from around the world. This was supported by a Bayer sponsored publication titled 'Recommendations by a UK expert panel on an aflibercept treat-and-extend pathway for the treatment of neovascular age-related macular degeneration' published in the Eye journal in January 2020 (Ross *et al*, 2020). The publication indicated that one of the reasons for extending the treatment interval was the absence of fluid on Optical Coherence Tomography (OCT) scan at the clinic visit. Further to this, it stated:

> 'The expert panel recommends treating SRF to stability. The aim should be to achieve dryness...[ ]... The treatment interval should be reduced with new SRF, worsening SRF over time.'

Novartis submitted that this publication, in conjunction with the RCOphth, EURETINA and AAO clinical guidelines, made it clear that resolving SRF was key to extending treatment intervals and was reflective of the view of the scientific community.

Novartis submitted that the claim 'outperformed aflibercept with superior fluid resolution' stated that for this clinically relevant parameter of fluid control, Beovu outperformed aflibercept – ie Beovu was a better drying agent than Eylea – and this was demonstrated by the statistically significant difference between the two medicines' drying abilities in HAWK and HARRIER trials.

There was no reference to visual outcomes, the claim focussed on the medicines ability to dry the retina, which was clinically meaningful.

Furthermore, Beovu was the only licensed anti-VEGF that allowed extension to 12 weekly dosing intervals immediately after the loading phase (SPC); Eylea could only extend to 8 weeks immediately after the loading phase (SPC). This difference was due to Beovu's superior fluid resolution compared with aflibercept, as demonstrated in the HAWK and HARRIER trials (Dugal *et al*, 2020). The clinical relevance of superior drying was clear: it could determine a lower injection burden for both patients and the healthcare system.

For the reasons outlined above, Novartis submitted the demonstrable clinical merit of fluid resolution and clarified the significance of drying the different compartments of the retina, including SRF. Furthermore, drying SRF to determine treatment intervals was not an area of emerging science; this was an accepted fact by UK and international guidelines. Accordingly, in the context of non-inferior visual acuity gains, the claim was meaningful for prescribers, patients and the healthcare system in terms of treatment intervals/burden, regardless of which sub-compartment of fluid was driving the superiority. In that regard, Novartis submitted that it was not an over-simplification and the reader had sufficient information to properly assess the claim and form his/her opinion of the therapeutic value of Beovu vs aflibercept in relation to its effect on retinal fluid resolution.

RESPONSE TO APPEAL FROM BAYER

Bayer agreed that the Panel interpreted the evidence correctly in this matter. Bayer's response to Novartis' appeal was as follows.

Background to the case

Bayer noted that Neovascular (wet) age-related macular degeneration ('nAMD') was a common, sight-threatening condition affecting mainly older people.

Bayer noted that there were currently three licensed medicines available in the UK for the treatment of nAMD: ranibizumab (Lucentis), launched by Novartis in 2007; aflibercept (Eylea), launched by Bayer in 2012; and brolucizumab (Beovu), launched by Novartis in February 2020. All were biological anti-angiogenic therapies administered by injection into the eye and all act by inhibiting vascular endothelial growth factor (anti-VEGF).

Bayer noted that vascular endothelial growth factor was a naturally occurring protein that became overexpressed in nAMD causing abnormal new blood vessels to develop under the light-sensitive tissues at the back of the eye (the retina). These new blood vessels were fragile and might leak fluid and blood both into and under the retina, causing damage to the retina. However, leaking of fluid was not the only way in which damage was caused to the retina in nAMD. Over time the most sensitive part of the retina, the macula, might become thin and damaged; an irreversible process known as macular atrophy.

Bayer noted that the relationship between fluid occurring in different areas (compartments) of the retina, the development of macular atrophy, and the impact of a medicine's treatment on vision in nAMD (arguably the most important outcome from the patient's perspective) was complex and not yet completely understood. This area was therefore the subject of much ongoing research and debate amongst ophthalmologists.

Original complaint

Bayer noted that in or around March 2020, Novartis approved promotional materials for brolucizumab that were published as an advertisement in Eye News in April 2020 ('Advertisement'). Bayer complained to the Authority about the advertisement in July 2020, following unsuccessful intercompany dialogue. The advertisement contained the following promotional claim in relation to brolucizumab:

'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48[**1]'

The claim appeared as one of two prominent headlines to the advertisement, printed in large dark pink typeface. Two breaches of Clause 7.2 were ruled by the Panel in relation to this statement. Novartis now sought to appeal the breach of Clause 7.2 of the Code pertaining to the presentation of emerging clinical and scientific debate.

Original Panel decision and Novartis appeal

Bayer noted in its ruling the Panel noted that the supplementary information to Clause 7.2, emerging clinical or scientific opinion, 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 agreed with Bayer and considered that the claim might incorrectly imply that the results seen in the study directly translated into clinically meaningful benefits for brolucizumab over aflibercept. The Panel decided that the advertisement over-simplified the position in that it implied that brolucizumab clinically outperformed aflibercept based on total fluid resolution when there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina. The Panel did not consider that the reader had been provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of brolucizumab versus aflibercept in relation to its effect on retinal fluid resolution. The Panel ruled a breach of Clause 7.2.

Bayer noted that Novartis in its appeal stated that it disagreed with the Panel's interpretation that there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina and its relevance to the management of wet age-related macular degeneration (wet AMD).

Bayer noted that Novartis agreed that there was debate on the relevance of drying different compartments on visual outcomes but stated that it was accepted by the clinical community (and evidenced by guidelines), that drying different compartments of the eye was clinically relevant in making treatment decisions, in particular deciding treatment intervals, as it could determine the injection burden of a patient and healthcare system.

Bayer response to Novartis appeal

Bayer alleged from the outset that Novartis had inaccurately represented the Panel's decision. Bayer's original complaint was that the claim presented the increased drying of total retinal fluid by brolucizumab as a definite clinical benefit in comparison with aflibercept, and thereby indicated clinical 'outperformance' and 'superiority' to aflibercept, whereas this had not been proven and was an area where scientific opinion was evolving. Accordingly, and quite

appropriately, the Panel did not decide the case on the relevance of retinal drying to the management of nAMD. The Panel's ruling was based on the interpretation that Novartis over-simplified the position by implying that brolucizumab clinically outperformed aflibercept based on total fluid resolution when there was emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina. Bayer contended that the Panel was entirely correct in both its assessment of the evidence originally provided by both parties and its ruling on this point.

Bayer restated and alleged that the data in question related to an area of evolving scientific and clinical debate (and so was captured by the supplementary information to Clause 7.2 of the Code) and that the claim ('Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48**[1]) was misleading contrary to Clause 7.2.

Area of emerging clinical or scientific opinion

Bayer noted that there were two principal types of retinal fluid occurring in nAMD, which differed in their location within the layers of the retina, and which might have different effects on disease progression and might be differentially impacted by anti-VEGF treatments; sub-retinal fluid ('SRF'), which occurred under the retina, and intra-retinal fluid ('IRF'), which occurred within the retina. 'Total retinal fluid' was the sum of fluid occurring in all retinal compartments.

The presence of retinal fluid was widely used as a marker for disease activity in nAMD and was referred to in clinical guidelines and the SPCs of both brolucizumab and aflibercept. Bayer and Novartis agreed that retinal fluid was important in diagnosing and assessing nAMD and in deciding whether to treat.

However, Bayer alleged that using a difference in total fluid resolution alone to claim a definite clinical advantage of one anti-VEGF treatment over another was misleading if there was no recognition of the context and controversies within this complex area. In accordance with the supplementary information to Clause 7.2 of the Code, claims of clinical superiority relating to total retinal fluid reduction **in isolation** should therefore not be used in promotional material without sufficient information being provided to enable the reader to make a proper assessment of clinical relevance in light of the ongoing uncertainty.

Bayer noted that resolution of total fluid was not the primary outcome of the studies used to substantiate the claims in the advertisement; the primary endpoint was best-corrected visual acuity (BCVA), a standard measure of vision. The BCVA outcomes for both aflibercept and brolucizumab over the course of 48 weeks were not statistically or clinically different (ie were 'non-inferior'). Indeed, the visual acuity in the aflibercept group was numerically better at 48 weeks than that achieved with brolucizumab in both the HAWK and HARRIER trials, and this difference persisted to 96 weeks in the HARRIER trial. HAWK/HARRIER 48 week data: (least squares [LS] mean, +6.6 [6 mg] and +6.1 [3 mg] letters with brolucizumab vs. +6.8 letters with aflibercept [HAWK]; +6.9 [brolucizumab 6 mg] vs. +7.6 [aflibercept] letters [HARRIER]; P < 0.001 for each comparison); 96 week data: Mean change (least squares [LS] mean ± standard error) in BCVA from baseline to 96w in HAWK was 5.6±0.79 letters for brolucizumab 3 mg, 5.90±0.78 letters for brolucizumab 6 mg, and 5.3±0.78 letters for aflibercept and in HARRIER was 6.1±0.73 letters for brolucizumab 6 mg and 6.6 ± 0.73 letters for aflibercept] (Dugel *et al* 2020, Dugel *et al* 2021).

Bayer accepted that brolucizumab showed a statistically significant difference from aflibercept in terms of total retinal fluid resolution in the HAWK and HARRIER pivotal studies. However, Bayer alleged that this was an **exploratory**, secondary endpoint, which in the view of the European Medicines Agency (EMA) European Public Assessment Report (EPAR) for brolucizumab (page 88) *'*cannot be the basis for claims in the product information'.

Bayer alleged that current scientific opinion was undecided over the clinical relevance of the different types of retinal fluid. IRF was the fluid type increasingly recognised by clinical consensus to be the one most closely associated with structural damage leading to poor visual outcomes in nAMD; SRF less so, especially if stable. Indeed, there was evidence that suggested excessive drying of SRF might lead to worse vision outcomes for patients in the long term and that stable SRF might offer an element of protection against the development of macular atrophy, a currently untreatable consequence of longstanding nAMD (Zarbin, 2020, Grunwald *et al,* 2014).

Bayer alleged that all three studies that Novartis had conducted comparing brolucizumab with aflibercept in nAMD showed that the difference between the two medicines in terms of total fluid resolution was driven principally by reducing one type of retinal fluid, SRF, rather than by reducing IRF (Dugal, 2019, Dugal *et al*, 2017). Novartis stated in its appeal that brolucizumab reduced IRF in a similar manner to aflibercept but was more effective in reducing SRF confirming that the difference in total fluid resolution observed in the brolucizumab pivotal studies was driven entirely by reduction in SRF.

Novartis referenced a Bayer sponsored publication titled 'Recommendations by a UK expert panel on an aflibercept treat-and-extend pathway for the treatment of neovascular age-related macular degeneration' published in the Eye journal in January 2020 (Ross, *et al*). The publication indicated that one of the reasons for extending the treatment interval was the absence of fluid on Optical Coherence Tomography (OCT) scan at the clinic visit. Novartis provided the following quote from this publication in its appeal:

> 'The expert panel recommended treating SRF to stability. The aim should be to achieve dryness ... . The treatment interval should be reduced with new SRF, worsening SRF over time.'

Bayer alleged that this was a very selective quotation by Novartis that omitted important contextual information. The full statement from the original reference document read as follows (text omitted by Novartis was in bold):

> 'The expert panel recommends treating SRF to stability. The aim should be to achieve dryness; **however, in certain circumstances the treatment interval may be maintained or extended with SRF present, provided there are no other signs of disease activity on OCT. Treatment interval maintenance or extension may be appropriate when SRF is persistent and stable despite frequent treatment, or when there is a trend towards improvement over time. The volume of SRF that may be tolerated should be determined by the treating physician.**
>
> **The treatment interval should always be reduced when persistent SRF is accompanied by new haemorrhage or additional signs of disease activity on OCT, such as new choroidal neovascularisation (CNV) complex, subretinal hyperreflective material (SHRM) or pigment epithelial detachment (PED), as shown**

> **in Fig. 2.** The treatment interval should **also** be reduced with new SRF, worsening SRF over time **or significant visual loss (≥5 ETDRS letters) that is thought to be due to disease activity and cannot be explained by comorbidities'.** (Ross *et al*,).

Bayer alleged that the expert panel in this publication was therefore in agreement with the position now held by many ophthalmologists that continued treatment with the aim of reducing or eliminating stable SRF might not necessarily confer a clinical advantage. In addition, the publication presented and discussed considerable independent published evidence (none of which was referred to in the Novartis appeal) to support the position that IRF was of greater clinical relevance than SRF (Jaffe *et al,* 2013, Jaffe *et al*, 2019, Wickremasinghe *et al*, 2012, Waldstein et al, 2016), and concluded that there might be advantages to service capacity by tolerating some stable SRF, with no detriment to clinical outcomes.

Bayer also noted that The Royal College of Ophthalmologists' publication 'Age-related macular degeneration: Guidelines for Management', quoted by Novartis in its appeal dated from 2013. This publication had now been archived by the College. Understanding of the role of total fluid, IRF and SRF in making treatment decisions had evolved substantially since 2013. Not least with the recent improvements in retinal imaging technologies and the availability of newer data suggesting that whilst IRF could be considered a biomarker of disease activity, some stable SRF could be tolerated whilst maintaining good visual outcomes.

Bayer alleged that although not referenced in its appeal, Novartis' own randomised, controlled study, FLUID, (Guymer *et al*, 2018) demonstrated that for patients treated with the anti-VEGF ranibizumab for 2 years, some SRF could be tolerated whilst allowing patients to achieve visual acuity comparable to more intensive treatment regimens, with the benefits of fewer treatments and hospital visits and lower costs.

Bayer stated that it did not dispute that there were differing opinions on this point. However, the Panel's original ruling in this case was correct based on the fact that there was not a settled view that elimination of stable SRF (which, when present, forms part of total retinal fluid) was always in the best interests of the patient. SRF resolution did not necessarily translate into superior outcomes for patients in terms of vision. This was demonstrated by the findings of the HAWK and HARRIER studies where the visual acuity results at 48 and 96 weeks with aflibercept were equally as good as those achieved with brolucizumab (Dugel *et al*, 2019, Dugel *et al*, 2020). It was therefore appropriate for the Panel to conclude that it was an over-simplification to base promotional claims of definitive clinical superiority and outperformance of brolucizumab over aflibercept purely upon this exploratory secondary endpoint, with no additional context.

<u>Misleading promotion</u>

Bayer alleged that the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48[**1]' was misleading because it implied that differences shown between treatments in total retinal fluid resolution seen in HAWK and HARRIER were of definite and conclusive benefit, when in fact fluid resolution in different retinal compartments was increasingly considered to be more pertinent to clinical outcomes (Jaffe *at al* 2019, Sharma *et al*, 2016, Singer 2019, Sharma *et al*, 2020). These other points were not presented in the advertisement to allow a balanced appreciation of the context of the broad and prominent promotional claim.

During inter-company dialogue, Novartis acknowledged that there was ongoing clinical debate on the relative importance of the drying of fluid in different compartments of the retina, but stated in its letter of 18 June 2020:

> 'It was not, however, Novartis' position to tell clinicians how to engage in that debate. This responsibility fell on the prescriber who should decide whether the claims made were relevant to their clinical practice based on current evidence, clinical experience and guidelines'.

Bayer's position remained that prescribers could not decide on the relevance of a promotional claim if they were not made aware of the debate and the other evidence that existed; this was also apparently accepted by the Panel in its ruling and was an established principle of the Code. Bayer contended that the existence of any debate was ignored by the prominent broad claim of superiority of brolucizumab over aflibercept, based only on total fluid resolution, because the drying of total fluid was not presented in the context of the drying of fluid in different retinal compartments and the controversy over the relative clinical impact of total fluid, SRF and IRF.

Bayer alleged that the claim did not present this area of emerging scientific opinion in a balanced manner and thus gave an over-simplified view that a statistically significant difference in resolution of total retinal fluid was sufficient evidence on its own that brolucizumab 'outperformed' and was clinically 'superior' to aflibercept, despite the fact that the observed difference was driven by a difference in resolving SRF, with the effect on IRF being similar between the products (Dugal, 2019, Dugal *et al,* 2017).
Novartis now appeared to suggest that the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48**1' was not misleading because 'drying different compartments of the eye was clinically relevant in making treatment decisions, in particular deciding treatment intervals, as it could determine the injection burden of a patient and healthcare system'. Such a suggestion was not apparent from the advertisement nor would a reader naturally assume such an interpretation. Importantly, this proposed interpretation was not supported by the reference to the HAWK and HARRIER clinical trials given in the advertisement as these studies were not designed to examine differences in injection frequency, but rather to test whether brolucizumab was non-inferior to aflibercept in terms of visual acuity (primary endpoint).

Novartis also stated that brolucizumab was the only licensed anti-VEGF that allowed extension to 12 weekly dosing intervals immediately after the loading phase and went on to state that this 'difference was due to Beovu's superior fluid resolution compared with aflibercept, as demonstrated in the HAWK and HARRIER trials... The clinical relevance of superior drying was clear: it could determine a lower injection burden for both patients and the healthcare system.' Bayer alleged that this argument was misleading.

Bayer noted that the licensed posology of brolucizumab was based upon the HAWK/HARRIER pivotal trial design, which permitted immediate extension of brolucizumab to 12 weeks after the loading doses but did not allow extension of the comparator aflibercept in a similar manner. The studies were not designed to test the maximum dosing intervals achievable with each product. Bayer alleged that it was not aware of any other evidence to support claims that aflibercept was more limited than brolucizumab in terms of achieving long injection intervals based on a difference in total fluid resolution.

Bayer noted that in the HAWK and HARRIER studies, aflibercept was administered in a dosing regimen of 3 initial monthly loading doses followed by fixed 8 weekly dosing, with no potential for extension of dosing intervals beyond 8 weeks. Aflibercept dosing frequency was therefore driven entirely by the study protocols and not by change in total fluid. This study regimen did not fully reflect the current licensed posology of aflibercept, which after 3 monthly loading doses and then one dose interval of 8 weeks, could be extended by intervals of 2 or 4 weeks up to a maximum interval of 16 weeks, an interval potentially achievable in year one of treatment.

Bayer noted that licensed posology was typically a reflection of pivotal trial design. For example, the aflibercept SPC specifically mentions potential extension of treatment intervals up to 16 weeks (4 months) as part of a treat and extend regimen, whereas the brolucizumab SPC did not. Aflibercept had published evidence from two separate studies to support extension of treatment interval to 16 weeks (Ohji M *et al* 2020, Mitchell, *et al* 2021), whilst Bayer was not aware of any data providing outcomes from a 16-week extension with brolucizumab.

In summary, Bayer submitted that

(i) if the claim at issue related to clinical benefit, then using a difference in total fluid resolution **alone** to claim a definite clinical advantage of one treatment over another, without any recognition of the context and controversies within this complex area, was misleading: and

(ii) if the superiority claimed in the claim related to the opportunity for less frequent treatment (as suggested in Novartis' appeal), this was neither apparent nor the obvious inference of the advertisement and also could not be substantiated either by the data referenced in the claim, or any other data of which Bayer was aware, and so was misleading.

Conclusion

Bayer alleged that the Panel was correct in its ruling that the claim in the advertisement for brolucizumab was in breach of Clause 7.2 of the Code by failing to acknowledge the emerging clinical/scientific opinion on the clinical relevance of the drying of fluid occurring in different compartments of the retina. In doing so, the advertisement was misleading. Bayer alleged that:

- The claim in the advertisement over-simplified the claimed clinical benefits of brolucizumab compared to aflibercept, based on one exploratory, secondary endpoint in isolation, and did not present a balanced view of emerging clinical and scientific opinion relevant to the interpretation of that endpoint.
- The claim was based on resolution of total fluid, an exploratory secondary endpoint in the HAWK and HARRIER pivotal studies, which in the view of the EMA 'could not be the basis for claims in the product information' for brolucizumab.
- There was ongoing debate and controversy in ophthalmology around the clinical relevance of different fluid compartments to clinical outcomes in nAMD and the claim did not place the claim in this context. Clinicians were therefore unable to reach their own conclusion based on a balanced presentation of all the evidence.
- Specifically, there was a growing body of data to suggest that total fluid might be less important to treatment outcomes in nAMD than the differential effect of treatment on fluid in different retina compartments. Stable SRF might even offer some protection against vision loss caused by macular atrophy. Available evidence suggested that the observed

difference in total fluid resolution between aflibercept and brolucizumab was driven by reductions in SRF rather than IRF. None of this was presented in the claim or elsewhere in the advertisement.

- By failing to present sufficient information representing the emerging clinical/scientific debate to enable readers to be aware of the uncertainties and to draw their own conclusions, the claim of clinical superiority was misleading.
- Novartis submitted in its appeal that the claim related to logistical advantages around treatment intervals, however this was not apparent from the advertisement, would not be the obvious interpretation to readers and was not capable of substantiation by the references given nor by any other evidence of which Bayer was aware. On this basis, the claim was misleading.
- Novartis also attempted to link differences in the licensed posologies of brolucizumab and aflibercept directly to differences in the action of the two medicines on total retinal fluid. This claim was incorrect, misleading and not capable of substantiation.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48**[1]' was based on a secondary, exploratory endpoint (resolution of total retinal fluid) of two non-inferiority studies (Dugal *et al* 2020).
The explanation for the asterisks, **to the claim at issue, was given in the fourth line of the footnote text which stated: 'Secondary endpoint in HAWK and HARRIER, confirmatory analysis in HAWK only (1-sided *p* values for superiority of Beovu)'. One sentence, in the seventh and eighth lines of the footnote, was bold and stated: 'The primary efficacy endpoint in both studies was non-inferiority in mean BCVA [best corrected visual acuity] change from baseline to Week 48 as measured by ETDRS'.

The Appeal Board noted Bayer's submission that there were two principal types of retinal fluid occurring in neovascular AMD: sub-retinal fluid (SRF) and intra-retinal fluid (IRF). 'Total retinal fluid' was the sum of fluid occurring in all retinal compartments. Retinal fluid was important in diagnosing and assessing neovascular AMD and in making treatment decisions.

The Appeal Board noted Novartis' submission that Beovu was equally effective in drying IRF and more effective in drying SRF compared to Eylea (Dugel *et al*, 2019).

Section 5.1 of the Beovu SPC referred to the percentage difference in patients with IRF and/or SRF fluid for Beovu versus aflibercept in HAWK and HARRIER at Weeks 16 and 48 as statistically significant. There was no mention in the SPC that this data was secondary endpoint data, however, the secondary endpoint evidence, used to support the claim at issue, was referred to as exploratory in the Beovu EPAR which stated that it could not be the basis for claims in the product information.

The Appeal Board considered that it was not necessarily unacceptable to include the exploratory secondary endpoint data in promotional material as long as it complied with the Code including that it was not misleading in terms of the clinical benefits of one treatment compared to another.

The Appeal Board noted Bayer's view that current scientific opinion was undecided over the clinical relevance of the different types of retinal fluid, noting that there was evidence that

suggested excessive drying of SRF might lead to worse vision outcomes for patients in the long term and that stable SRF might offer an element of protection.

The Appeal Board noted that the clinically important outcome for neovascular AMD patients was the maintenance or improvement of their vision.

In response to a question, the representatives from Novartis stated that assessment of the fluid in the eye helped the clinician decide how to prescribe and that the absence of relevant information in the NICE guideline did not mean that drying the retina was not clinically relevant.

The Appeal Board noted Novartis' submission that the claim at issue was meaningful for prescribers, patients and the healthcare system in terms of treatment intervals/burden, regardless of which sub-compartment of retinal fluid was driving the difference. The Appeal Board considered that that was not clear from the advertisement at issue. The supporting references were not designed to examine differences in treatment intervals between Beovu and Eylea.

The Appeal Board considered that the claim at issue incorrectly implied that the results seen in the study directly translated into clinically meaningful benefits for Beovu compared to Eylea. The Appeal Board considered that the advertisement oversimplified a complex area and it implied Beovu clinically outperformed Elyea based on total fluid resolution when there appeared to be emerging clinical/scientific opinion on the clinical relevance of the drying of the different compartments of the retina.

The Appeal Board did not consider that the reader had been provided with sufficient information to properly assess the claim and form his/her own opinion of the therapeutic value of Beovu vs Eylea in relation to its effect on retinal fluid resolution. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

3 Alleged misleading comparison re safety profiles

COMPLAINT

Bayer alleged that the promotional approach in the advertisement did not provide readers with all the facts necessary to interpret the claim objectively, because it did not discuss the differences between the safety profiles of the two products shown in the same studies. The advertisement not only misleadingly stated that Beovu 'outperformed' Eylea (aflibercept) based on an exploratory, secondary endpoint in non-inferiority studies, it also failed to acknowledge that a safety difference was identified during these same studies. The misleading nature of the advertisement was of concern to patient welfare as, when the advertisement was approved, the pivotal studies referenced had shown increased rates of intraocular inflammation and retinal artery occlusion with Beovu compared with Eylea (Dugal 2020). These safety concerns (specifically retinal artery occlusive events) with Beovu were specifically highlighted by the EMA in the summary of the initial CHMP opinion and retinal artery occlusion appeared in the Beovu SPC, but not in the Eylea SPC.

Bayer stated that the clinical importance of that initial observation had been highlighted by further events. Within a few months following the October 2019 launch of Beovu in the US, Novartis confirmed a new safety signal had been identified for retinal vasculitis and/or retinal

vascular occlusion, typically associated with intraocular inflammation, which might result in severe vision loss (links to websites provided).

Retinal artery occlusion (listed in the SPC) was a subset of retinal vascular occlusion (identified in the safety signal). Therefore, this new signal was directly related to the adverse events seen more frequently with Beovu in the pivotal trials. Subsequent re-examination of the pivotal trial data by a safety review committee appointed by Novartis had recently confirmed that 50 Beovu treated patients in the studies showed evidence of intraocular inflammation or retinal vasculitis or retinal vascular occlusion (4.6%) of which 36 (3.3%) had retinal vasculitis with or without vascular occlusion. This compared with 8 patients with Eylea (1.1%) showing evidence of intraocular inflammation or retinal vasculitis or retinal vascular occlusion. Novartis had not disclosed how many of those 8 Eylea treated patients had intraocular inflammation (a known side effect of all licensed anti-VEGF medicines) in isolation (website link provided).

As a direct result, Beovu was currently subject to investigation of a new safety signal and was in the process of an update to its global prescribing information. In June 2020, some 8 months after first launch, the US label for Beovu was the subject of safety amendments to its label in the US, Australia and Switzerland (website link provided). Bayer understood discussions were ongoing with the European regulators regarding a similar change to the Beovu SPC (website links provided).

Bayer submitted that that safety signal had not been recognised with any other licensed product for neovascular AMD, despite those other products having had far wider population exposure than Beovu, comprising many years and tens of millions of doses; the signal appeared to be unique to Beovu. Novartis was still conducting investigations into the possible cause(s) of the new safety signal, whether any particular groups of patients were at greater risk from these safety events, whether anything could be done to lower the incidence and how these events should be treated (website link provided).

In Novartis' post-marketing assessment of the new safety signal, retinal vasculitis, retinal vascular occlusion or retinal vasculitis and retinal vascular occlusion were seen at rate of 8.65 events per 10,000 injections (website link provided). In Bayer's assessment of the aflibercept safety database, the same events had been observed at a rate of 0.03 events per 10,000 injections (Eylea data on file).

Whilst Bayer accepted that the safety signal was confirmed only after the advertisement was first approved, the advertisement's publication in April 2020 occurred after the first emergence of potential post marketing safety concerns in February 2020, and when it was already clear from the pivotal study that adverse events of direct relevance to the new safety signal occurred far more frequently with Beovu compared with Eylea (Dugal 2020). To compare the two products in the advertisement without presenting comparative differences in safety data between them from the pivotal studies, when an advantage based on an exploratory, secondary endpoint from the same studies was claimed, was therefore a misleading comparison by omission. Bayer alleged a breach of Clause 7.3.

Bayer also submitted that these safety concerns remained relevant when it came to the general promotional approach for Beovu given that it was a newly launched medicine where post marketing safety experience was still evolving and there remained many uncertainties related to causation, risk factors, incidence and optimal treatment of adverse events. Bayer had presented evidence in inter-company dialogue of the same or similar promotional approach

continuing to be used by Novartis in other promotional launch materials. Given the evolving nature of the safety concerns associated with Beovu, Bayer was concerned that Novartis did not agree during inter-company dialogue to present a specific overview of the comparative safety differences between the two products (rather than simply rely on the prescribing information) in the context of making a superiority claim based on an exploratory, secondary endpoint from non-inferiority studies. On that basis, Bayer alleged that the ongoing promotional approach, typified by the advertisement, was a breach of Clause 7.2 because it was neither balanced, nor objective, nor did it reflect a clear and up to date evaluation of all the evidence.

RESPONSE

Novartis noted that Paragraph 5 of the Constitution and Procedure stated that: 'A complaint from a pharmaceutical company will only be accepted if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter but that this offer was refused or dialogue proved unsuccessful'. As acknowledged by Bayer in a copy of correspondence provided, the issue of the safety signal was resolved during inter-company dialogue, Novartis did therefore not understand why it had been reintroduced at this juncture. As this matter had been resolved in inter-company dialogue, Novartis did not believe that the matter should be considered by the Panel nor should it make a ruling on this matter.

For clarity, the resolution was included in the summary inter-company email of 9 July that was seen and confirmed by Bayer's country medical director. It would have been more appropriate to bring up that area of dispute when that email was written and, in fact, Bayer's country medical director did make amends to the text of the email where he was unsatisfied with the original proposed wording. Novartis had reproduced the relevant paragraph from the email, below:

> 'Bayer and Novartis agreed that the points already resolved in intercompany dialogue were:
>
> > ……The emerging safety data was not relevant to the journal advert at the time of its publication as it emerged after and was not reflected in the SPC at the time of the advertisement (and it still isn't at this time). Novartis committed to appropriately representing all safety data as required by the Code in future material. How that is done would depend on the nature of the future information about the emerging safety data and on the nature of future material; and so Novartis would not commit to specific wording.'

That issue was discussed during initial inter-company dialogue and Bayer accepted that Novartis could not have adjusted promotional material prior to the confirmation of a signal. The issue was later reintroduced by Bayer in its letter to Novartis of 4 June 2020 (copy provided) and again discussed in the final call between the two companies, which was summarised in emails of 9/10 July (copy provided). Novartis stated that it had engaged in good faith during proceedings and had considered that aspect resolved but the issue continued to be raised despite acceptance by Bayer that it would have been impossible to include information in the advertisement at issue on a matter that had not yet occurred.

Notwithstanding the prior resolution of this topic, in the interest of transparency, Novartis outlined its position below.

Novartis acknowledged the emergence of a safety signal subsequent to the publication of the advertisement in question. However, that signal was only confirmed after publication and was, therefore, not relevant to the discussion around this specific journal advertisement. Clause 7.9 states: 'Information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience'. When the advertisement went to print, those requirements were met. The signal was confirmed on 6 April 2020, the material was certified on 16 March 2020 and went to print the same month for publication in the April issue. It would not be reasonable to expect Novartis to predict the future confirmation of a safety signal and include it in promotional material.

Novartis acknowledged that there were initial reports communicated by the American Society of Retinal Specialists (ASRS) earlier in the year. Novartis, like all pharmaceutical companies, was bound by regulatory and pharmacovigilance laws and processes and could not make decisions based on initial reports. Novartis had already initiated a thorough investigation and the signal was confirmed in April. Throughout this process appropriate steps were taken to communicate with relevant health professionals (details provided).

Additionally, while some discussions with regulators had completed, the consultation with the EMA was ongoing and the new safety information had not yet been introduced into the SPC at time of writing. Clause 3.2 of the Code stated 'The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics'. Novartis submitted that when it was published and at the time of writing (6 August 2020), the journal advertisement complied with that aspect of the Code. However, since the emergence of the safety reports and subsequent confirmation of the signal, Novartis took additional steps to ensure it appropriately communicated with relevant stakeholders and continued to do so (details provided). Novartis understood that it would be inappropriate to continue to promote based on the existing SPC without informing relevant stakeholders of the safety signal. However, the situation was still evolving, with no update to the SPC so the information that was shared was tailored to the situation. For example, whilst the safety information was proactively introduced during promotional calls, it was the medical team who followed up to provide full detail.

Novartis noted the use of post-marketing safety data in Bayer's complaint. Novartis had already demonstrated that the signal was only confirmed subsequent to the publication of the journal advertisement. The safety review committee's preliminary report based on its *post hoc* analysis was published on 4 June 2020 (copy provided). Evidently, that information could not have been included in the journal advertisement. Novartis noted that that was the same date that Novartis received the letter from Bayer detailing it allegations.

However, Novartis noted the omission of the following statement from Bayer's summary of the safety review committee's findings:

> 'Of note, despite the vision loss associated with increased incidences of IOI, retinal vasculitis and/or retinal vascular occlusion associated with brolucizumab, the overall rates of at least moderate vision loss (≥15 ETDRS letter loss) are similar between the brolucizumab and aflibercept treatment arms: 7.4% or 81/1088 in brolucizumab and 7.7% or 56/729 in aflibercept.'

Novartis stated that even with the emergence of the signal, this was independent acknowledgement that the overall rates of vision loss, the most important potential adverse event with the use of these medicines, were almost identical between the two. This was pertinent when considering the overall safety profiles of each medicine.

Novartis reiterated that when it was published the advertisement reflected the available information and the understanding of the comparative safety profiles of the two medicines.

The second part of Clause 7.2 stated 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. Novartis believed that the prescribing information, which occupied approximately half the space of the material, was sufficient to complete a single page advertisement. The prescribing information was designed to contain the most relevant safety information for a physician to make an informed decision. In the context of a single page advertisement and a single comparative claim, Novartis considered that this was sufficiently complete for readers.

The Code neither stipulated that comparative information must be provided in relation to every aspect of a medicine and its features, nor did it state that a safety statement must be included alongside every claim.

Of relevance, Novartis noted the significant, very common undesirable effects of using aflibercept. According to the Eylea SPC (copy provided), visual acuity loss, conjunctival haemorrhage and eye pain were more common with aflibercept than with Beovu. Novartis raised this point to demonstrate that no two medicines had identical safety profiles but, overall, two medicines' safety profiles could be considered broadly similar despite differences in individual aspects of the risk/benefit profiles. When the advertisement was published, the overall safety profiles of the two medicines were considered comparable even if there were numerical differences in the studies between individual adverse events.

Reassuringly, the authors of the peer-reviewed manuscript relating to the pivotal studies, (Dugal *et al* 2020), stated that 'Overall safety of [Beovu] was similar to [Eylea] and consistent with other anti–VEGF-A agents approved for nAMD treatment'. Novartis acknowledged that although author comments did not automatically permit for their use as promotional claims, it had included this information as supporting evidence.

Similarly, the Beovu EPAR contained the following reassuring language:

> 'Overall, AE incidence was similar between [Beovu] 6mg and [Eylea] 2mg groups in both safety databases (48.8% vs 47.3% and 89.7% vs 89.6% respectively).'
>
> 'SAE in the study eye leading to permanent discontinuation of study drug or to permanent discontinuation of the study occurred in ≤ 1% of subjects in all treatment groups.'
>
> 'The incidence of deaths, SAE, and AE leading to permanent discontinuation of study drug or of the study was similar across treatment groups.'

Again, Novartis acknowledged that the EPAR was not the reference document for promotional material but it was reassured by the regulatory authority's remarks with regards to the safety.

Given the general acceptance between clinical and regulatory experts that the safety profiles of the two medicines were broadly similar at the time of authorization, Novartis did not consider that the numerical differences in a single category of adverse event required highlighting. Accordingly, it would be inappropriate to highlight adverse events seen with numerically higher rates in the Eylea SPC (as previously described) or in the aflibercept arm of the pivotal studies; for example, visual acuity reduced and cataract formation. Novartis noted that a retinal artery occlusion was seen with aflibercept in the studies but, again, it would not consider highlighting that as significant at this stage given it was not contained in the SPC.

In light of the above, when the advertisement was certified and published, there was no specific area that required highlighting to prescribers, and, as such, the prescribing information (which took up approximately half the content of the material) was sufficient for a single page advertisement that contained a single, accurate, comparative claim. Novartis acknowledged that the prescribing information alone would not be sufficient for a more substantial piece of material and, as always, it would create and certify material based on its individual merits in line with the Code.

Novartis noted Bayer's request for a future commitment on the way in which Novartis communicated safety information. However, as mentioned during inter-company dialogue and above, any future material would be certified based on the merits of the individual piece. Additionally, Novartis could not commit to any undertaking for future specific wording on the safety signal, as requested by Bayer during inter-company dialogue, because the SPC was yet to be updated and knowledge was still emerging during investigations. Novartis could not predict what the SPC would eventually say.

It was Novartis' responsibility to continue to appropriately communicate this information to relevant stakeholders. Novartis had provided details of its current approach to emerging safety signals and, once from the EMA had confirmed the wording in the SPC, Novartis would introduce more detail into promotional materials, as appropriate. Novartis noted that Bayer had taken a screenshot of a single page of a current promotional website to 'represent' Novartis' ongoing approach to safety and in that regard had chosen a page that focused on efficacy to 'demonstrate' Novartis' approach to safety. The link to the more appropriate page of the website was clearly signposted in the screenshot. The side bar showed the prominence of the 'Safety profile' of Beovu, which was given its own section on the website and came before the efficacy results. Novartis provided a PDF copy of, and a link to, the 'Safety profile' page of the website. The page clearly presented the eye disorders in the registration studies and contained a statement regarding the new safety signal. However, given the new safety information was not yet included in the SPC and knowledge was evolving, the decision was made to ask physicians to refer to the medical team for more information should it be required.

For the reasons outlined above, Novartis refuted the allegations of breaches of Clauses 7.2 and 7.3. Furthermore, Novartis did not consider that the PMCPA should accept or rule on the aspect of the complaint which was discussed and resolved, with regard to the journal advertisement at issue, during inter-company dialogue.

PANEL RULING

The Panel noted that it was agreed during inter-company dialogue that the emerging safety data was not relevant to the journal advertisement at the time of its publication as it had emerged after and was not reflected in the SPC at the time of the advertisement. Novartis had committed

to appropriately representing all safety data as required by the Code in future material. Novartis would not commit to specific wording; how it would be done would depend on the nature of the future information about the emerging safety data and on the nature of future material. The Panel noted that this matter had thus been settled and therefore it would make no rulings in that regard.

The Panel noted, however, that during inter-company dialogue Bayer had also raised concerns that the claim comparing efficacy should only have been made if a comparison of safety data was also provided. Bayer alleged that not doing so misled as to the overall clinical comparison between the medicines and was the allegation upon which the Panel would make its ruling.

The Panel noted that it was not necessarily unacceptable to include comparative efficacy data without including comparative safety data as long as the material complied with the Code and was not misleading in this regard. Material must not be inconsistent with the particulars in a medicine's current SPC.

The Panel noted that the advertisement in question did not directly compare the safety of Beovu with aflibercept but that such a comparison might be indirectly implied by the use of the term 'outperformed' and 'superior' as used in the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48'. As noted in Point 1 above, the Panel considered that the headline claim might be misinterpreted as Beovu outperforming aflibercept overall. The implication might be read as including a comparison of the medicines' safety profiles which was not so. The Panel noted Bayer's concern that the promotional approach in the advertisement did not provide readers with all the facts necessary to interpret the claim objectively, because it did not discuss the differences between the safety profiles of the two products shown in the studies. According to Bayer when the advertisement was approved, the pivotal studies referenced had shown increased rates of intraocular inflammation and retinal artery occlusion with Beovu compared with Eylea (Dugal 2020).

The Panel noted Novartis' submission that when it was published the advertisement reflected the available information and the understanding of the comparative safety profiles of the two medicines. The Panel noted that Dugel *et al* stated that brolucizumab was generally well tolerated; overall ocular and non-ocular adverse event rates were similar to those with aflibercept within each trial. The Panel further noted Novartis' submission that given the general acceptance between clinical and regulatory experts that the safety profiles of the two medicines were broadly similar at the time of authorization, Novartis did not consider that the numerical differences in a single category of adverse event required highlighting.

The Panel noted that both medicines would only be administered by ophthalmologists experienced in intravitreal injections; this was a specialist area. Such health professionals, in the Panel's view, on the balance of probabilities, would not be misled that the claim 'Outperformed aflibercept with superior retinal fluid resolution at Weeks 16 and 48' included a comparison of safety profiles.

The Panel did not consider that Bayer had shown, on the balance of probabilities, that presenting efficacy data from HAWK and HARRIER without presenting the comparative differences in safety data between Beovu and aflibercept was misleading by omission as alleged. No breach of Clauses 7.2 and 7.3 were ruled.

Complaint received	**17 July 2020**
Case completed	**17 May 2021**