CASE AUTH/2748/2/15

BAYER v NOVARTIS

Promotion of Lucentis

Bayer plc submitted a complaint about claims made by Novartis Pharmaceuticals UK at two symposia which Novartis Pharma AG had sponsored at a European ophthalmology congress held in the UK in 2014. The claims related to the comparative safety profiles of Bayer's product Eylea (aflibercept) vs Novartis' product Lucentis (ranibizumab).

Eylea and Lucentis were intravitreal injections indicated, *inter alia*, for the treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular oedema (DME).

The detailed response from Novartis Pharmaceuticals UK is given below.

Bayer noted that the first symposium in question was entitled 'Forging the future in nAMD [neovascular age-related macular degeneration]: The role of anti-VEGF [anti-vascular endothelial growth factor] and novel therapeutic targets' and submitted that in inter-company dialogue, Novartis had acknowledged the promotional intent of this symposium.

Data from two studies were presented to claim a statistically, significantly increased risk of endophthalmitis following injection of Eylea compared with injection of Lucentis (Kelly *et al* 2014 and Kiss *et al* 2014). However, the conclusions were based on a retrospective analysis of insurance claims. Neither study was a scientifically valid retrospective cohort study, nor did either try to obtain clinical data to confirm the alleged incidents of endophthalmitis. No standardised definition of endophthalmitis was applied so the events could not be validated as truly inflammatory in nature. Given the heterogenicity of these data, the confidence intervals and p-value reported in slides 44 and 47 clearly lacked scientific validity and did not represent the balance of the evidence for the two medicines.

Bayer alleged that Novartis did not try to balance the discussion of data from Kelly *et al* and Kiss *et al* (and the conclusions it drew from them) with data from the large, robust, randomised and double-masked phase 3 studies (VIEW 1 and VIEW 2) which compared Eylea and Lucentis in the treatment of wet AMD (Heier *et al* 2012). These studies concluded that Eylea was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to that for Lucentis. The results at 52 and 96 weeks of follow-up showed no difference in rates of endophthalmitis between Lucentis and Eylea (Heier *et al*, Schmidt-Erfurth *et al* 2014). Relevant sections (4.4 and 4.8) of the Eylea summary of product characteristics (SPC) did not mention any difference in risk of endophthalmitis compared with Lucentis; it just stated that endophthalmitis was a known risk with all intravitreal injections.

Bayer submitted that there was selective presentation of data of weak scientific validity in the absence of data from robust, large, randomised controlled trials with follow-up to 2 years, which showed a very different conclusion. In addition, it was not disclosed in the symposium that Kiss *et al* was funded and co-authored by Genentech, the manufacturer of Lucentis and a business partner of Novartis. Bayer alleged that the overall representation of the safety profile of Eylea at this promotional symposium was unbalanced, inaccurate, misleading and did not fairly represent the totality of available evidence, in breach of the Code.

The Panel noted that the presentation at issue focussed on endophthalmitis which was described as a rare but feared complication of intraocular surgery and intravitreal injection, its pathogenesis, management and new data on safety signals. The new data were from two database studies, Kelly *et al* (VERO) and Kiss *et al* which looked at retrospective analysis of insurance claims taken from two different US payor claims databases. The studies were based on two separate databases although slide 44 stated, as did the speaker, that the database source data would overlap so that the same injection data might be included in both analyses. The Panel noted slide 43 was headed '"Big data" is of merit to explore safety signals'.

The Panel noted Novartis' submission that the presentation made it clear that it was difficult to obtain robust information on endophthalmitis as pivotal studies such as VIEW 1 and 2 were not powered to detect differences in the frequency of such rare adverse events; this information could only be provided by very large data sets. A point not covered within the slides although stated by the speaker. In this regard, however, the Panel also noted Novartis' submission that although data from patient populations which were broader than those in phase 3 studies could be better for evaluating rare events, such data was not as confirmatory as phase 3 data. The Panel thus queried the claim '*Robust* information on rare safety events can only be provided by very large data sets' (emphasis added).

The Panel noted the limitations of the retrospective study of insurance claims. In the conclusion of his presentation the speaker noted that such data might show a difference between the treatments but 'that without doubt' clinical studies were needed to confirm such differences. The speaker stressed that the data in Kelly *et al* and Kiss *et al* was based on claims, payments and requests for payments; it was not clinical data. The Panel noted that Kelly *et*

al concluded that all sensitivity analysis undertaken also supported the differences and that data from this retrospective analysis should be interpreted with caution, because of the inherent limitations of this type of study and limited understanding of mechanisms to explain the apparent difference in endophthalmitis risk with Eylea. Additional studies would be required to further explore the implications for clinical practice.

The Panel noted the potential benefit and limitations of Kelly *et al* and Kiss *et al*. However the presentation did not contextualise the results presented for Kelly *et al* and Kiss *et al* with the limitations of that data, the clinical data on endophthalmitis or the frequency of endophthalmitis documented in each medicine's SPC. In that regard the presentation was not sufficiently complete to enable the delegates to form their own opinion of the therapeutic value of the medicines. A breach of the Code was ruled. The comparison of the two products was misleading. A breach of the Code was ruled. The Panel noted the limitations of the retrospective analysis of insurance claims taken from US payor claims databases including the possible variability of potential disease coding and physician experience. It did not consider that the presentation reflected all the available evidence. A breach of the Code was ruled.

Bayer alleged that slide 13 significantly overstated the dosing flexibility permitted by the new Lucentis label; it implied that physicians could use Lucentis as they pleased with no restrictions with regard to treatment intervals or follow-up/monitoring requirements. Bayer stated that the Lucentis SPC clearly stated that treatment must be initiated with one injection a month until maximum visual acuity was achieved and/or there were no signs of disease activity, and specified that there was also a minimum treatment interval. A treat-and-extend regimen could only be followed when monthly treatment was established, and the patient stabilised, but even then the SPC gave clear guidance on the degree of flexibility permitted, with extensions for wet AMD limited to two weeks at a time.

The Panel noted the Lucentis SPC only permitted flexibility in monitoring and treatment intervals once maximum visual acuity was achieved and/or there were no signs of disease activity. The Panel considered that this was not clear from slide 13. A breach of the Code was ruled.

Bayer alleged that the claim on slide 13 that Lucentis dosing was: 'Personalized' 'Physicians determine monitoring and treatment intervals* for optimal outcomes ....' was in conflict with the Lucentis SPC as regards its flexibility. In addition the claim that the new posology would deliver 'optimal outcomes' was a superlative which could not be substantiated. The claim of 'optimal outcomes' was a hanging comparison and thus the exact comparison made by Novartis was unclear, but there was no evidence that the current Lucentis posology offered clinical outcomes which were optimal compared with either proactive treatment with Eylea or reactive use of Lucentis with monthly monitoring (as per the previous Lucentis SPC).

The Panel noted the claim 'optimal outcomes' was part of the first stab point on slide 13 under the heading 'Introducing the new ranibizumab EU label, which supports a personalized treatment approach'. The Panel did not consider that the claim at issue was a superlative as alleged. In that regard the Panel noted that the claim at issue did not exclude the possibility that other treatment regimens could also provide optimal outcomes. The changes to the Lucentis SPC enabled prescribers to determine monitoring and treatment intervals such as to optimise treatment with Lucentis. In that regard the Panel did not consider that the claim was a hanging comparison as alleged. It was substantiated by the Lucentis SPC. The Panel ruled no breach of the Code.

Bayer stated that with regard to the retrospective US health insurance data, slide 13 clearly stated that Kelly *et al*, (the VERO study) was sponsored by Novartis; this implied that the other retrospective study (Kiss *et al*) was independent. However, Kiss *et al* was supported by Genentech, the company which manufactured Lucentis and marketed it in the US. Further, from the abstract it appeared that one author was employed by Genentech Inc. Genentech was in commercial partnership with Novartis, which marketed Lucentis on its behalf outside the US. The disclosure was therefore incomplete and misleading about the independence of the data presented at the meeting. Bayer did not accept Novartis' assertion that it was reasonable to only disclose that it had supported Kelly *et al* as the author was also the presenter. Bayer stated that this was a promotional symposium, sponsored by Novartis, in which Novartis claimed comparatively greater safety for Lucentis vs Eylea based wholly on two studies which were both funded by companies which marketed Lucentis in their respective territories. This information would have been highly relevant to the audience in assessing any potential bias in these data. Accordingly, it was not acceptable for the funding details of both studies not to be made transparent; simply referencing the studies on the slide deck was insufficient. Bayer alleged a breach of the Code.

The Panel noted that the presenter was involved with one of the studies, which was mentioned on the disclosures made at the beginning of his presentation (slide 38) which included 'VERO study was sponsored by Novartis'. When presenting this he stated that as he was going to be talking about this study and it was a Novartis event, his involvement should be made clear.

The Panel noted that the second of the studies, Kiss *et al*, was sponsored by Genentech which marketed Lucentis in the US. The Panel noted that these two studies of US medical claims databases were used by the presenter to compare the event rate of endophthalmitis/severe intraocular inflammation for Lucentis and Eylea. The Panel considered that disclosing that VERO was sponsored by Novartis but remaining silent about Kiss *et al* might lead

the audience to assume that Kiss *et al* was not sponsored by a commercially interested party. This was not so. The Panel considered the presentation was misleading in this regard. A breach of the Code was ruled.

Bayer alleged that the second symposium in question, entitled 'Optimizing benefits and risks in DME [diabetic macular oedema]', built a picture of a worse adverse event profile for Eylea vs Lucentis in diabetic macular oedema (DME); many of the most contentious statements were made by presenters rather than on the slides.

Bayer alleged that data were presented selectively from published studies to minimise the apparent risk of arterio-thrombotic events with Lucentis and to support the incorrect assertion that Eylea had a worse safety profile than Lucentis in DME. Overall, the symposium misrepresented the safety profile of Eylea compared with Lucentis. Given the 'take-home' impact on the audience, Bayer, alleged that the impression given about the safety profile of Eylea in DME was in breach of the Code.

The Panel noted that Bayer complained about the overall impression created of the safety profile of Eylea in diabetic macular oedema. In that regard, although the symposium had consisted of three presentations and a question and answer session, the Panel considered the symposium as a whole and not each of its component parts separately.

The Panel noted that both Lucentis and Eylea were antineovascularisation agents, they prevented endothelial cell proliferation and the formation of microvascular vessels as well as vascular leakage, all of which were thought to contribute, *inter alia*, to diabetic macular oedema. The medicines did this by inhibiting vascular endothelial growth factor (VEGF). Lucentis inhibited VEGF A whilst Eylea inhibited VEGF A and the related placental growth factor (PlGF). Slide 30 compared the products. Eylea was a larger molecule than Lucentis and its structure contained an Fc (fragment crystallisable) fragment of a human immunoglobulin. Lucentis had no Fc fragment. The potential side-effect of systemic administration of anti-VEGF treatment in oncology patients was discussed. From the SPCs for Lucentis and Eylea (both administered intravitreally) it appeared that systemic effects from the inhibition of VEGF was a possibility. In a question and answer session the Panel noted that speakers stressed that ideally an anti-VEGF agent which would stay in the eye, and thus not cause systemic side-effects, would be one without an Fc portion ie Lucentis and not Eylea. The speakers also referred to the fact that there was 5 year data for Lucentis but only 2 year data for Eylea.

The Panel noted the data presented and that there was longer term data for Lucentis as it was available before Eylea. The Panel considered that much had been made of the differences between the molecules and the impression was given that this might impact on safety. This difference was not set in the context of the information in the SPC which was similar for Eylea and Lucentis.

Overall, the Panel considered that the take home message was, as alleged, that the safety profile for Lucentis was more favourable than that for Eylea and that real differences in that regard would be seen in the clinic. On balance that Panel considered that there was insufficient data to show that this was so and that the symposium overall was misleading in that regard. A breach of the Code was ruled. The comparison of the two medicines was thus misleading and a breach of the Code was ruled. The impression of a significant clinical difference between Eylea and Lucentis could not be substantiated and breaches of the Code were ruled.

In summary, Bayer was concerned that two Novartis-sponsored symposia at the ophthalmology congress misleadingly compared the safety profiles of Lucentis and Eylea. In the first symposium the misrepresentation of safety occurred in the context of superlative promotional claims which related to the efficacy of Lucentis and exaggerated claims about the flexibility of its new posology. In the second symposium implications based upon data irrelevant to the dosages and indications under discussion, verbal comment and the misleading presentation of Lucentis safety data combined to build a false picture of the comparative safety of Eylea vs Lucentis and to raise unfounded concerns in the minds of prescribers about the safety of Eylea in its newest indication.

In addition, Bayer considered that there was clear evidence in the examples given above of repeated, serious misrepresentations of safety data and disregard for the Code, such that Novartis had failed to maintain high standards and had brought the industry into disrepute. Taking everything into consideration, Bayer alleged breaches of the Code including Clause 2.

The Panel noted its rulings above. It considered that the misleading presentation of the data meant that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted that the supplementary information to Clause 2 referred to examples of activities likely to be in breach of Clause 2 and these included prejudicing patient safety. The Panel noted that although it considered that the symposium had presented a misleading impression of the comparative safety profiles of Lucentis and Eylea, patient safety would not have been put at risk. The Panel noted its rulings above but nonetheless did not consider that its rulings of breaches of the Code in this case amounted to a breach of Clause 2 and no breach was ruled.

Bayer plc complained about claims made by Novartis Pharmaceuticals UK Ltd at two symposia which Novartis Pharma AG had sponsored as part of the EURetina Ophthalmology congress in London, 11-14 September 2014. The claims related to the comparative safety profiles of Bayer's product Eylea (aflibercept) vs Novartis' product Lucentis (ranibizumab).

Eylea and Lucentis were intravitreal injections (ie into the eye). Both products were indicated, *inter alia*,

for the treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular oedema (DME).

A recording of the symposium was provided by Novartis. The slide numbering used in this case was as provided by Novartis. Bayer's numbering has been changed to Novartis' numbering. There were a couple of instances where the photographs provided by Bayer provided more details than the slides provided by Novartis and this was noted in the minute.

The case was considered under the 2014 Code using the 2015 Constitution and Procedure.

A Symposium 'Forging the future in nAMD [neovascular age-related macular degeneration]: The role of anti-VEGF [anti-vascular endothelial growth factor] and novel therapeutic targets' 13 September 2014, 1-2pm, attended by 965 conference delegates

1 Use of insurance claims data

COMPLAINT

Bayer submitted that in inter-company dialogue, Novartis had acknowledged the promotional intent of this symposium.

Data from two studies were presented to claim a statistically, significantly increased risk of endophthalmitis following injection of Eylea compared with injection of Lucentis (Kelly *et al* 2014 and Kiss *et al* 2014). However, the conclusions were based solely on retrospective analysis of insurance claims. Neither study was a scientifically valid retrospective cohort study, nor did either try to obtain clinical data to confirm the alleged incidents of endophthalmitis. No standardised definition of endophthalmitis was applied to the data so the events could not be validated as truly inflammatory in nature. Given the heterogenicity of these data, the confidence intervals and p-value reported in slides 44 and 47 of the presentation clearly lacked scientific validity and did not represent the balance of the evidence for these two medicines.

Bayer acknowledged that large datasets based on uncontrolled observation might sometimes provide relevant information regarding the post-marketing safety profile of medicines. However, the Code required that promotional, comparative safety claims must present an evaluation of all the evidence and must not mislead either directly or implicitly. Thus, when claims were based on uncontrolled observational data it was important to present the limitations of such datasets, including any potential sources of bias (such as study funding – see Point A3 below) and also to present any relevant data from large, randomised, controlled studies. This last point was especially important if the results of the controlled and uncontrolled data differed.

Bayer alleged that Novartis did not try to balance the discussion of data from Kelly *et al* and Kiss *et al* (and the conclusions it drew from them) with data from the large, robust, randomised and double-masked phase 3 studies (VIEW 1 and VIEW 2) which compared Eylea and Lucentis in the treatment of wet AMD (Heier *et al* 2012). These studies (n=2,419) concluded that 'Intravitreal [Eylea] was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to those for monthly [Lucentis]'. The results at 52 and 96 weeks of follow-up showed no difference in rates of endophthalmitis between Lucentis and Eylea (Heier *et al*, Schmidt-Erfurth *et al* 2014). Neither Sections 4.4 (special warnings and precautions for use) nor 4.8 (undesirable effects) of the Eylea summary of product characteristics (SPC) mentioned any difference in risk of endophthalmitis compared with Lucentis; it just stated that endophthalmitis was a known risk with all intravitreal injections.

In the Novartis wet AMD symposium there was selective presentation of data of weak scientific validity in the absence of data from robust, large, randomised controlled trials with follow-up to 2 years, which showed a very different conclusion. In addition, it was not disclosed in the symposium that Kiss *et al* was funded and co-authored by Genentech, the manufacturer of Lucentis and a business partner of Novartis (see Point 4 below).

Bayer alleged that the overall representation of the safety profile of Eylea at this promotional symposium was unbalanced, inaccurate, misleading and did not fairly represent the totality of available evidence, in breach of Clauses 7.2, 7.3 and 7.9.

RESPONSE

Novartis submitted that the aim of the presentation was to present new data on an important single aspect of ocular safety – endophthalmitis, which was accepted as a known potential, but fortunately rare, complication of intravitreal injection. This data was of interest to the audience at EURetina as there had been a cluster of endophthalmitis cases in the US which prompted the Therapeutic Surveillance Subcommittee of the American Society of Retinal Specialists (ASRS) to publish by way of a letter and associated tables on this particular adverse event (Hahn *et al*, 2013).

The presentation made it clear that it was difficult to obtain robust information on safety events such as endophthalmitis since even the pivotal, randomized, controlled, comparative studies in ophthalmology, such as VIEW 1 and 2, were not powered to detect differences in the frequency of such rare events (slide 43). Therefore, numbers for these adverse events could only be provided by very large data sets. Novartis noted that the VIEW studies involved 2,419 patients whereas the database studies referred to in the symposia involved 431,518 (VERO study, slide 45) and 339,046 (slide 47 and Kiss *et al*) injections.

Retrospective database studies were standard research tools that allowed medical evidence from the real world to be evaluated using pre-specified protocols; the retrospective nature of the data and the study were acknowledged several times during the symposium. The data was based on a specific actual event (endophthalmitis) which

occurred and resulted in a claim for treatment or a claim for time for that adverse event. The data came from independent insurance claims and not claims submitted to either pharmaceutical company, which eliminated any possibility of bias. With regard to Bayer's allegation that there was no standardised definition of endophthalmitis applied to the data Novartis noted that in the VERO study the definitions of endophthalmitis were pre-specified and agreed with clinicians in an unbiased way, prior to conducting the analyses; the algorithms to identify diagnoses of endophthalmitis were applied consistently and independently of Novartis (by IMS). Kiss *et al* used a standardised diagnostic code for endophthalmitis, ICD-9-CM, which was the current medical coding standard used in US hospitals.

Novartis submitted that database studies were standard tools to use to understand treatment and effects in real world use, away from the strict protocols of phase 3 studies which might exclude many patients by focusing on naive patients. It was accepted that broader and more representative populations than phase 3 studies, were better to evaluate rare events (Stein 2014 and Hess 2004) but of course not as confirmatory as phase 3 studies, just additional evidence generation. Stein specifically mentioned 'Large sample sizes can be particularly useful for studying uncommon conditions, such as endophthalmitis. For example, 424 enrolees in one of these databases received a diagnosis of endophthalmitis in a single year, providing a potential sample size that is considerably larger than those of most other studies of endophthalmitis'.

Novartis noted that rofecoxib was a well recognised example of where only the use of large claims and managed care databases provided the necessary power to show adverse events ie the increased risk of acute myocardial infarction and sudden cardiac death

Novartis submitted that the symposium was consistent with the Eylea and Lucentis SPCs which clearly documented that endophthalmitis was an uncommon complication of each medicine. The symposium demonstrated additional data in keeping with the adverse event profile which reflected that there might be a difference in the real world incidence of these adverse events between the products.

For the VERO and Kiss *et al* analyses which were presented, the limitations were clearly defined as being obtained from data taken from US payor claims databases, which were one source of such large datasets. The limitations of such data were made explicit both by the speaker and on the slides several times throughout the presentation:

- 18.45 – These are database studies of claims following claims for endophthalmitis or severe intra ocular inflammation for patients with neovascular AMD in the US who received ranibizumab or aflibercept

- 19.05 – the definition of a claim is a medical care use for treatment or time spent associated with the payment information which is the bill or the payment that comes out. So you might send the bill in and you might get the cheque out by a number of different sources of payment

After an event of a claim for intravitreal anti-VEGF injection with either of the two licensed agents where in another claim for payment for treatment for the same patient for an eye condition for endophthalmitis or severe intraocular inflammation follows the first injection

- 20.56 – I stress these are not actually patients these are statements of claims being submitted to the IMS database for payments.'

In addition to the statements above the concluding slide (slide 48) stated 'Further studies and additional data are required to better understand inflammation following anti-VEGF injections' and the speaker discussed the following:

- 24.10 – and without a doubt given that safety is paramount further studies are needed to try and get to the bottom of this and find out what's going wrong or what the issues are because this is only a study of claims, payments and request for payments. This is not clinically confirmed information and we need clinical data to ascertain if there is something happening or not following anti-VEGF injections.'

Novartis thus rejected Bayer's claim that the overall representation of the safety profile of Eylea at the symposium was unbalanced, inaccurate, misleading and did not represent the totality of available evidence and therefore there was no breach of Clauses 7.2, 7.3, and 7.9.

PANEL RULING

The Panel noted that the symposium in question was entitled 'Forging the future in nAMD: the role of anti-VEGF and novel therapeutic targets'. The welcome and introduction slides included slide 6 which stated 'This symposium will seek to answer the following questions: What evidence supports flexible dosing of ranibizumab for a personalized treatment approach? What are the current data on ocular safety and endophthalmitis with anti-VEGF therapies? What is the evidence supporting the efficacy of ranibizumab in nAMD patients with PED [pigment epithelial detachment]? How can we build on the success of ranibizumab therapy for nAMD?' The following slide provided the symposium flow which consisted of five presentations; 'Evidence for flexible dosing of ranibizumab in neovascular AMD', 'New data on ocular safety', 'PEDs: evidence for the best anatomical outcome', 'Mapping the future with novel pathways' and 'Closing statements and conclusions'. The Panel considered that the symposium promoted Lucentis.

The Panel noted the section of the symposium at issue was 'New data on ocular safety' (slides 37-48). Novartis' rationale for this section was in part due to the audience's interest in the topic since there had been a cluster of endophthalmitis cases in the US which had prompted the Therapeutic Surveillance Subcommittee of the American Society

of Retinal Specialists (ASRS) to publish a letter and associated tables on this particular adverse event. This letter published in May 2013 (16 months before the symposium at issue) was headed 'Aflibercept-Related Sterile Inflammation'. The Panel noted that the final paragraph stated *inter alia* 'Small sample size, clinical variation, and the limitations of voluntary reporting preclude definitive conclusions. Subgroup analysis did not detect any variables significantly affecting visual outcome or number of days to resolution'. It further stated that the frequency of the sterile inflammation reported by the manufacturer in the reporting period (approximately 30,000 injections administered, corresponding to a sterile inflammation rate of approximately 0.05%) was 'within the range documented by pivotal, prospective trials for aflibercept and other intravitreal agents and by retrospective analysis'.

The presentation at issue focussed on endophthalmitis which was described as a rare but feared complication of intraocular surgery and intravitreal injection, its pathogenesis, management and new data on safety signals. The new data were from two database studies, Kelly *et al* (VERO) and Kiss *et al* which looked at retrospective analysis of insurance claims taken from two different US payor claims databases. The studies were based on two separate databases although slide 44 stated, as did the speaker, that the database source data would overlap so that the same injection data might be included in both analyses. The Panel noted slide 43 was headed '"Big data" is of merit to explore safety signals'. Followed by:

- Cases of endophthalmitis have been reported following intravitreal anti-VEGF therapy in clinical practice
- Robust information on rare safety events can only be provided by very large data sets
- Two retrospective, database studies compared endophthalmitis/severe intraocular inflammation claims for patients with nAMD who received ranibizumab or aflibercept in the US
- Claim definition: medical care use (treatment or time spent) and associated payment information used for adjudication of payment by payers.

The Panel noted Novartis' submission that the presentation made it clear that it was difficult to obtain robust information on rare safety events such as endophthalmitis as pivotal, randomized, controlled, comparative studies in ophthalmology, such as VIEW 1 and 2, were not powered to detect differences in the frequency of such rare adverse events; this information could only be provided by very large data sets. A point not covered within the slides although stated by the speaker. In this regard, however, the Panel also noted Novartis' submission that although data from patient populations which were broader than those in phase 3 studies could be better for evaluating rare events, such data was not as confirmatory as phase 3 data. The Panel thus queried the claim '*Robust* information on rare safety events can only be provided by very large data sets' (emphasis added) above.

Slides 44-47 set out the objectives and timelines of both studies and provided an analysis of the of endophthalmitis/severe intraocular inflammation claims for Lucentis and Eylea in Kelly *et al* (VERO) and Kiss *et al* and event rates were shown. Slide 45 was headed 'VERO: endophthalmitis/severe intraocular inflammation claims from the US IMS Health retrospective database and was followed by a graphical representation of the results. The graph stated that the number of Lucentis injections administered was 252,864; the number of Eylea injections administered was 178,654. The event rate per 1,000 injections for Lucentis was 0.64 (1 in 1,561 injections) and for Eylea it was 1.06 (1 in 945 injections); the adjusted relative risk was 1.65 ($p<0.0001$). Slide 47 was headed 'WK data': endophthalmitis/severe intraocular inflammation claims from the WK retrospective US database' and set out the results from Kiss *et al*. In this study the number of Lucentis injections administered was 202,225; the number of Eylea injections was 136,821. The event rate per 1,000 injections in this study for Lucentis was 0.8 (1 in 1,279 injections) and 1.7 (1 in 575 injections) for Eylea; the odds ratio was 2.7 ($p<0.001$). Novartis submitted the symposium was consistent with the SPCs of both medicines.

The Panel noted the SPC for both Lucentis and Eylea listed endophthalmitis as an uncommon adverse reaction (frequency of ≥1/1000 to <1/100). The Lucentis SPC stated that adverse reactions were defined as adverse events (in at least 0.5 percentage points of patients) which occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with Lucentis than those receiving control treatment. The Panel noted that no reference appeared on the slides or was mentioned by the speaker to remind the audience of the frequency of endophthalmitis for each medicine as set out in the respective SPCs and demonstrated in clinical studies. The Panel queried Novartis' submission that these data were consistent with the SPCs for the medicines given that the data in slides 45 and 47 showed a statistically significant difference for Lucentis compared with Eylea. Further it appeared that the event rate for endophthalmitis/severe intraocular inflammation for Lucentis (0.64 and 0.8 per 1,000 injections) was lower than in the range specified in the SPC for an uncommon adverse event and in that respect suggested that the reaction was rare (> 1/10,000 to < 1/1,000). It was not entirely clear whether the event rates in the SPCs were per injection or per patient.

Slide 48 conclusions included that 'Further studies and additional data are required to better understand inflammation following anti-VEGF injections'.

The Panel examined the two references provided by Novartis to support the use of the data analysis from retrospective analysis of insurance claims taken from US payor claims. Stein 2014 stated that:

> 'Large sample sizes can be particularly useful for studying uncommon conditions, such as endophthalmitis'

and that

> 'randomised controlled trials allow researchers to identify causal relationships between 2 variables

of interest while controlling for known and unknown confounding factors. Although a well-designed randomized trial is undoubtedly more informative than other types of study designs, including retrospective analyses using claims data, such clinical trials can be prohibitively expensive, can take years to recruit adequate numbers… to answer the research question… Before investing considerable resources…to provide a more definitive answer… researchers may find it valuable to first perform initial analyses to test their hypothesis using claims data'.

Stein also stated that:

'…because claims data exist primarily for billing and reimbursement purposes, some of the data may incompletely capture the conditions and outcomes documented in the medical records' and 'When interpreting analyses using claims data, one must consider that multiple providers with different levels of experience and expertise are contributing patient data'.

The Panel noted the limitations of this type of retrospective study of insurance claims. In conclusion of his presentation the speaker noted that such data might show a difference between the treatments but 'that without doubt' clinical studies were needed to confirm such differences. The speaker stressed that the data in Kelly *et al* and Kiss *et al* was based on claims, payments and requests for payments; it was not clinical data. The Panel noted that Kelly *et al* concluded that all sensitivity analysis undertaken also supported the differences and that data from this retrospective analysis should be interpreted with caution, because of the inherent limitations of this type of study and limited understanding of mechanisms to explain the apparent difference in endophthalmitis risk with Eylea. Additional studies would be required to further explore the differences in risk of endophthalmitis identified by this study and the implications for clinical practice.

The Panel considered the information above and noted the potential benefit and limitations of Kelly *et al* and Kiss *et al*. However the presentation did not contextualise the results presented for Kelly *et al* and Kiss *et al* with the limitations of that data, the clinical data on endophthalmitis or the frequency of endophthalmitis documented in each medicine's SPC. In that regard the presentation was not sufficiently complete to enable the delegates to form their own opinion of the therapeutic value of the medicines. A breach of Clause 7.2 was ruled. The comparison of the two products was misleading. A breach of Clause 7.3 was ruled. The Panel noted the limitations of the retrospective analysis of insurance claims taken from US payor claims databases including the possible variability of potential disease coding and physician experience. It did not consider that the presentation reflected all the available evidence. A breach of Clause 7.9 was ruled.

2 Claims alleged to be inconsistent with the SPC

The introductory section of the symposium, slide 13 was headed 'Introducing the new ranibizumab EU [European] label, which supports a personalized treatment approach'. This slide stated that the new regimen was:

'Personalized treatment	*Physicians determine monitoring and intervals* for optimal outcomes…'; and*
Flexible	*Mandatory monthly monitoring no longer required; now based on clinical need.*
Right treatment, right time	*Retreatment decisions based on [visual acuity] and/or anatomical parameters [optical coherence tomography or fluorescein angiography] help avoid under or overtreatment.*

**Interval between two doses injected in the same eye should be at least four weeks.'*

COMPLAINT

Bayer alleged that slide 13 significantly overstated the dosing flexibility permitted by the new Lucentis label; it implied that physicians could use Lucentis as they pleased with no restrictions with regard to treatment intervals or follow-up/monitoring requirements.

The Lucentis SPC stated:

'The recommended dose for Lucentis is 0.5mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05ml. The interval between two doses injected into the same eye should be at least four weeks.

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity ie no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (eg optical coherence tomography or fluorescein angiography).

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly.

In the treatment of visual impairment due to CNV secondary to PM, many patients may only need one or two injections during the first year, while some patients may need more frequent treatment.'

Bayer stated that the Lucentis SPC therefore clearly stated that treatment must be initiated with one injection a month until maximum visual acuity was achieved and/or there were no signs of disease activity, and specified that there was also a minimum treatment interval. A treat-and-extend regimen could only be followed when monthly treatment was established, and the patient stabilised, but even then the SPC gave clear guidance on the degree of flexibility permitted, with extensions for wet AMD limited to two weeks at a time.

In inter-company dialogue Novartis submitted that the slide did not provide full details of the new posology because this was stated in the prescribing information available at the meeting. Bayer, however, submitted that pharmaceutical companies could not make claims in the body of promotional material which might mislead the prescriber as to the precise requirements of the SPC and rely on the prescribing information as a disclaimer in the event of a complaint.

The Lucentis SPC did not permit total flexibility in monitoring and treatment intervals and thus Bayer alleged a breach of Clause 3.2.

RESPONSE

Novartis submitted that slide 13 was intended to communicate the very recent changes to the Lucentis EU dosing posology from mandatory monthly monitoring to physician-led assessment, rather than to provide an in-depth description of the posology in its entirety. The requirement for initial monthly dosing had not changed.

Rather, as the key changes to the posology referred to the maintenance phase of treatment this was the area of focus, the minimum treatment interval was clearly described on the slide. It was clearly stated in the opening disclaimer slide (slide 4) that local labels might differ and that for complete information the local label should be consulted.

Novartis did not accept that slide 13 overstated the dosing flexibility of the new Lucentis label. As Lucentis had been on the market since 2007, it was incongruous to suggest that clinicians were unaware of the need for initial monthly dosing. Novartis thus denied a breach of Clause 3.2.

PANEL RULING

The Panel examined slide 13 and noted that the same slide was used at the end of the symposium during the summary and conclusions section (slide 79).

The Panel noted Novartis' submission that as the key changes to the posology referred to the maintenance phase of treatment this was the area of focus, and that the minimum treatment interval was clearly described on the slide. In that regard the Panel noted that the statement referring to a minimum treatment interval was included as a footnote in small print on slide 13 and was not referred to by the speaker. The Panel noted the Lucentis SPC, Section 4.2 (posology and method of administration) stated 'Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity' and that 'In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed'. The SPC further stated: 'The treatment interval should be extended by no more than two weeks at a time for wet AMD ...'. Slide 13 did not make it clear that the personalized treatment approach was only in relation to the maintenance phase of treatment and not its initiation.

The Panel did not agree with Novartis' submission that as Lucentis had been available since 2007, all clinicians would know about the need for initial monthly dosing. Slide 13 referred to a new EU label with no reference to the fact that the difference in dosing from that previously used was only in the maintenance phase.

The Panel noted Clause 3.2 required the promotion of a medicine to be in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in its SPC. The Lucentis SPC only permitted flexibility in monitoring and treatment intervals once maximum visual acuity was achieved and/or there were no signs of disease activity. The Panel considered that this was not clear from slide 13. A breach of Clause 3.2 was ruled.

The Panel noted Novartis' submission that clear information had been provided at the beginning of the symposium, slide 4, which was headed 'Disclaimer' which included the statement 'These presentations are intended for educational purposes only and are based on the EU SmPC. Product registrations may vary country to country, so please check your local label for complete information'. The next bullet point on the slide was 'The recently

updated ranibizumab abbreviated UK prescribing information has been inserted into your abstract book for information'. The Panel noted that Clause 7.2 required material to be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. Relying on other materials to provide context and balance was not sufficient to correct an otherwise misleading impression. The Panel requested that Novartis be advised of its views.

3 Alleged superlative claim

COMPLAINT

Bayer alleged that the claim on slide 13 that Lucentis dosing was: 'Personalized' 'Physicians determine monitoring and treatment intervals* for optimal outcomes ....' was in conflict with the exact terms of the Lucentis SPC as regards its flexibility. In addition the claim that the new posology would deliver 'optimal outcomes' was a superlative which could not be substantiated. In inter-company dialogue, Novartis stated that it meant optimal in terms of individualizing treatment to ensure the best chance of achieving optimal outcomes in that specific patient, but Bayer stated that the slide appeared to claim that the personalized treatment strategy would in itself deliver outcomes which were optimal. The claim of 'optimal outcomes' was a hanging comparison and thus the exact comparison made by Novartis was unclear, but there was no evidence that the current Lucentis posology offered clinical outcomes which were optimal compared with either proactive treatment with Eylea or reactive use of Lucentis with monthly monitoring (as per the previous Lucentis SPC).

Bayer alleged that the use of the superlative 'optimal' in a promotional symposium, without substantiation, was in breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Novartis submitted that the phrase 'optimal outcomes' on slide 13 referred to the label supporting the ability of the physician to determine the treatment and monitoring frequency on a patient-by-patient-basis, dependent on their disease activity. Thus the physician could tailor treatment to an individual rather than treat all patients with a single approach. Giving physicians this flexibility ensured the best chance of optimal outcomes for patients.

Novartis submitted that 'optimal outcomes' was not a superlative. No comparisons were drawn between Lucentis or any other product on the slide; the slide encouraged the rational use of Lucentis by presenting it objectively without exaggerating any properties. Novartis thus denied that slide 13 breached Clauses 7.2, 7.4 or 7.10.

PANEL RULING

The Panel noted the claim 'optimal outcomes' was part of the first stab point on slide 13 under the heading 'Introducing the new ranibizumab EU label, which supports a personalized treatment approach'. The Panel considered that the claim at issue was not a superlative as alleged by Bayer. The supplementary information to Clause 7.10 Superlatives was clear that superlatives were grammatical expressions of the highest quality or degree such as best, strongest etc. In that regard the Panel noted that the claim at issue did not exclude the possibility that other treatment regimens could also provide optimal outcomes. The changes to the Lucentis SPC enabled prescribers of Lucentis to determine monitoring and treatment intervals such as to optimise treatment with Lucentis. In that regard the Panel did not consider that the claim was a hanging comparison as alleged. It was substantiated by the Lucentis SPC. The Panel therefore ruled no breach of Clauses 7.2, 7.4 and 7.10.

4 Slide 38 – disclosures and alleged misleading source data

Slide 38 was part of a presentation headed 'Disclosures' and stated 'Advisory board/consultant to Bayer and Novartis', 'Speaker fees: Novartis' and 'Conference and travel: Alcon, Bayer and Novartis'. Slide 38 also stated that a hospital was involved in research supported by Allergan, Bayer and Novartis and the final bullet point was 'VERO study was sponsored by Novartis'.

COMPLAINT

Bayer noted that, as stated above, the symposium included a section presented on 'New data on ocular safety' (slides 37-48) which discussed the relative risks of Lucentis and Eylea in causing endophthalmitis and severe intraocular inflammation, based solely on data from two retrospective studies of data collated in US health insurance databases.

Bayer stated that it was clear from slide 13 that Kelly *et al*, (the VERO study) was sponsored by Novartis; this implied that the other retrospective study (Kiss *et al*) was independent. However, Kiss *et al* was supported by Genentech, the company which manufactured Lucentis and marketed it in the US. Further, from the abstract it appeared that one author was employed by Genentech Inc. Genentech was in commercial partnership with Novartis, which marketed Lucentis on its behalf outside the US. The disclosure was therefore incomplete and misleading about the independence of the data presented at the meeting.

Bayer did not accept Novartis' assertion that it was reasonable to only disclose that it had supported Kelly *et al*, as one of the authors was also a presenter. Bayer stated that this was a promotional symposium, sponsored by Novartis, in which Novartis claimed comparatively greater safety for Lucentis vs Eylea based wholly on two studies which were both funded by companies which marketed Lucentis in their respective territories. This information would have been highly relevant to the audience in assessing any potential bias in these data. Accordingly, it was not acceptable in these circumstances for the funding details of both studies

not to be made transparent; simply referencing the studies on the slide deck was insufficient. Bayer alleged a breach of Clause 7.2.

RESPONSE

Novartis submitted that in keeping with Clause 23.1 that 'in their written contracts or agreements with consultants, companies must include provisions regarding the obligation of the consultant to declare that he/she is a consultant to the company whenever he speaks in public about a matter that is the subject of the agreement', the speaker disclosed that he was involved with the VERO study and that this was a Novartis sponsored study.

Novartis submitted that as the speaker was not involved in Kiss *et al* there was no need for him to declare this to the audience. The speaker disclosed that VERO was a Novartis sponsored study in order to be transparent that he was also the author of a poster on VERO at the same meeting where the symposium was being held. Therefore this was the basis for this specific disclosure on his slide rather than any other intention as implied by Bayer.

Kiss *et al* was presented at the Association for Research in Vision and Ophthalmology (ARVO) conference in 2014 and Novartis had no access to additional data beyond that which was in the public domain. The ARVO conference was a scientific conference of high regard and as such all ARVO data was peer reviewed and then published in the Investigative Ophthalmology & Visual Science (IOVS) journal.

The reference for this study was clearly cited on slides 43, 44, 47 and 48 all of which referred to Kiss *et al*. Novartis therefore refuted the allegation that there was an intention to mislead the audience about the level of disclosure and it denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the presenter was involved with one of the studies, which was mentioned on the disclosures made at the beginning of his presentation (slide 38) which included 'VERO study was sponsored by Novartis'. The presenter stated that as he was going to be talking about this study and it was a Novartis event, his involvement should be made clear.

The Panel noted that the second of the studies, Kiss *et al*, was sponsored by Genentech Inc. which marketed Lucentis in the US. The Panel noted that these two studies of US medical claims databases were used by the presenter to compare the event rate of endophthalmitis/severe intraocular inflammation for Lucentis and Eylea. The Panel considered that disclosing that VERO was sponsored by Novartis but remaining silent about Kiss *et al* might lead the audience to assume that Kiss *et al* was not sponsored by a commercially interested party. This was not so. The Panel considered the presentation was misleading in this regard. A breach of Clause 7.2 was ruled.

B Symposium 'Optimizing benefits and risks in DME [diabetic macular oedema]' 11 September 2014, 1-2pm, attended by 633 conference delegates

Alleged misleading, unbalanced and inaccurate claims

COMPLAINT

Bayer stated that this symposium was carefully designed by Novartis to build a picture of a worse adverse event profile for Eylea vs Lucentis in diabetic macular oedema (DME); many of the most contentious statements were made by presenters rather than on the slides.

Bayer stated there was no proven link to an increased risk of vascular adverse events (arterio-thrombotic events) with Eylea compared with Lucentis at the doses used intravitreally in any indication, and yet the overall construction of the symposium deliberately questioned the safety record of Eylea compared with Lucentis in DME. Of particular concern was that many of the alleged safety issues were raised indirectly and were implied by reference to different medicines administered in different indications, at vastly different doses and by a different route, without recourse to any clinical data to support the propositions.

The first presentation set out the high risk of cardiovascular complications in diabetic patients as a result of their disease, and the dangers of systemic inhibition of growth factors such as vascular endothelial growth factors A and B (VEGF A and B) and placental growth factor (PlGF). Bayer noted that Eylea inhibited VEGF A, B and PlGF whereas Lucentis only bound to VEGF A. Particular emphasis was placed on the potential protective effect of VEGF B and PlGF in vascular disease (slide 25) and the dangers of inhibiting these factors, particularly PlGF inhibition in pregnancy – an irrelevant statement as Eylea, like other anti-VEGF therapies, was not recommended in pregnancy. In inter-company dialogue, Novartis denied that its symposium included information on the risks of PlGF inhibition in pregnancy, based on the fact that nothing about pregnancy was on any of the slides, but Bayer stated that the recording confirmed that this denial was not true. PlGF was discussed starting from time point 14.07 minutes in the recording, and at 14.47 the presenter noted the risks of 'severe disregulation' in pregnancy and an increased risk of eclampsia and pre-eclampsia in pregnancy related to PlGF inhibition.

The second presenter then presented on the risks of systemic VEGF inhibition (slides 29-45). Bayer stated this was based mainly on evidence from use of high dose intravenous anti-VEGF agents in oncology, as opposed to intravitreal use (ie Lucentis and Eylea) from which systemic circulation was minimal. Bayer noted that Novartis included a disclaimer relating to difference in dose and side-effect profile on this slide, but the overall impression was of a high risk of serious adverse events related to systemic availability of the medicine. Slide 28 summarised that 'systemic VEGF inhibition could lead to serious side effects' and slide 30 illustrated differences in

molecular structure between different anti-VEGF agents, including Lucentis and Eylea.

The presenter then discussed the theoretical relationship between molecular structure and safety profile for anti-VEGF medicines. The molecular differences highlighted on Slide 30, most notably the presence of an Fc fragment in Eylea, were used to imply a greater risk of systemic availability of Eylea vs Lucentis, with the further suggestion that this might increase the risk in DME patients of the kinds of systemic adverse events seen in cancer patients. There were no data presented to support this contention, as none existed – the argument was built entirely on implication. The observed 2 year death rate for Lucentis 0.5mg in its phase 3 studies RISE and RIDE was 4% and 4.8% respectively (Nguyen *et al* 2012) which were very similar values (indeed numerically slightly higher) than the death rates of 3.7% and 3.9% seen at 100 weeks with Eylea in the phase 3 DME studies, VIVID/VISTA, respectively. The Eylea and Lucentis SPCs did not differ with respect to their use in diabetic patients at risk of vascular disease, nor in any other respect regarding the risk of systemic vascular adverse events in any licensed indication. Indeed, although not applicable in the EU, Section 6 of the US prescribing information for Lucentis carried a specific warning of 'fatal events in DME patients', whereas Section 6 of the US prescribing information for Eylea had no such warning. Within the US, Lucentis was licensed at a lower dose (0.3mg) in DME than its licensed dose in other US indications or any indications in the EU (0.5mg) because of concerns over the risk-benefit profile of the 0.5mg dose in diabetic patients.

Bayer alleged that data in this section were presented selectively from published studies to minimise the apparent risk of arterio-thrombotic events with Lucentis, and to support the incorrect assertion that Eylea had a worse safety profile than Lucentis in DME. Specifically:

- Pooled arterio-thrombotic events safety data were presented from the RESOLVE, RESTORE and RETAIN studies, which used a flexible dosing regimen of Lucentis (slides 37-39). However, non-myocardial arterio-thrombotic events and myocardial arterio-thrombotic events from the RISE/RIDE phase 3 studies of Lucentis in DME were presented separately (slides 33/34), which made the total numbers of arterio-thrombotic events with the 0.5mg dose of Lucentis look smaller in these studies (5.2% and 2.8%) than was actually the case (8%). Myocardial infarction was not even labelled as an arterio-thrombotic event on slide 33, when it clearly was such an event.

- Following the discussion of the long-term safety profile of Lucentis, week 100 safety data from Bayer's VIVID/VISTA trials (slide 41) were shown to imply that questions remained around relevance of higher death rates in Eylea arms compared with laser. And this was also implied by the speaker (time point 26.20) ie 'results for Eylea demonstrating differences in number, particularly concerning deaths…and we look forward to seeing the 5 year data where we can conclude even more definitely if this is relevant to our treatments'. This built up to a comparison of the length of safety data available in DME for Lucentis (5 years) vs Eylea (2 years) on slide 42, a comparison made by the speaker at time point 26.54 of the recording used the trade names of both products: 'So again not only are efficacy data available for 5 years….and also the safety data available now for 5 years for Lucentis and 2 years for Eylea…'.

Bayer stated that in the final section of this symposium, from time point 50.30 to 54.00 in the recording, there was a discussion and question and answer session during which the speakers made strong promotional statements for Lucentis none of which were based in evidence. It was stated that there was 'a real big difference' in systemic exposure related to presence of an Fc portion, a statement for which there was no evidence and in addition a series of statements were made to the effect that only Lucentis and not Eylea should be used in eye disease. Specifically, the third presenter stated:

> 'Yes you are right, I think the size of the molecule matters. What really matters is the Fc portion… recirculation maximises the amount of drug exposure systemically. So if you think about that, if you want a drug which maximises the amount of systemic exposure, you want the Fc portion – like a cancer drug, like Avastin - but if you want a drug that's only going to go to the eye and nowhere else, and not be exposed to systemic circulation, then you do not want an Fc portion. So if you are looking for an eye drug that goes in the eye but doesn't go anywhere else, then you really want to look for a drug without an Fc portion and that's what Lucentis, Lucentis, does have, it has no Fc portion at all, unlike Eylea and unlike Avastin, and that's an important point.'

Bayer stated that Eylea was the only medicine licensed in ophthalmology which had an Fc portion in its molecule, and so the closing message of the Novartis symposium effectively recommended that Eylea not be used because of its Fc portion, based on unproven allegations of safety risks relating to increased systemic circulation. Indeed it appeared that the entire symposium was designed to build up to this message. Bayer repeated that there were no data to support increased adverse events, or any risk arising specifically from an Fc portion, in patients treated with Eylea compared with Lucentis, in any of its licensed indications.

Although a couple of slides were included elsewhere in the symposium which correctly stated that Lucentis and Eylea had 'well documented' safety profiles, slides 42 and 44 (Bayer incorrectly referred to slide 45 in its complaint as this was a slide of the third speaker) and there was an additional correct comment on slide 42 that no new safety concerns had been identified with Eylea, the inclusion of these comments did not mitigate the overwhelming promotional take-home message that there were serious questions over the vascular safety of Eylea, particularly in the DME population at high risk of vascular events, and that Eylea was unsafe to use and only Lucentis should be considered in this population.

Bayer alleged that the cumulative effect of the symposium misrepresented the safety profile of Eylea compared with Lucentis. Given the 'take-home' impact on the audience, Bayer, alleged that the overall impression given by this symposium about the safety profile of Eylea in DME breached Clauses 7.2, 7.3, 7.4 and 7.9.

RESPONSE

Novartis noted that Bayer included a video recording of the symposium with its complaint. Slide 5 (Novartis incorrectly referred to slide 2 as this was a welcome slide) of the symposium presentation clearly requested that the symposium not be videoed and that it would be available as a live stream. Novartis further noted that Clause 10.3 stated that symposia were 'private occasions' and advised companies that quotations from such activities must not be used without the formal permission of the speaker. Novartis stated that in making the video Bayer had not fully respected the professional standing of the speakers (Clauses 9.1 and 9.2).

Novartis also noted that Bayer had decided not to include the symposium slide entitled 'Housekeeping' (slide 5) which contained the following information:

- This symposium is being broadcast live on the EURETINA website
- Please mute mobile phones
- Videoing the symposium is not permitted
- Questions to the audience will be asked throughout – please respond using the keypads provided
- A Q&A session will be held at the end of the session – please use the question card provided in your abstract book to submit a question
- Please return completed evaluation forms before you leave. Forms can be found in the back of the program book
- Please do participate!'

Novartis stated that it had provided the full slide deck for the presentation – to highlight the omission of some slides by Bayer and aid legibility of the ones provided to the PMCPA; there were thus differences in the slide numbering as referenced by Novartis. (This case used Novartis' numbering). In addition, Novartis noted that Bayer sometimes incorrectly referenced slides even in accordance with the reference material it had provided.

Novartis refuted Bayer's assertion that the symposium was designed to build a picture of a worse adverse event profile for Eylea vs Lucentis in diabetic macular oedema (DMO also known as DME). The symposium was designed to look at the very valid considerations that an ophthalmologist might face when treating diabetics with DMO and also the additional possible comorbidities. It reviewed the current data available for all the anti-VEGF inhibitors which might be used to treat DMO.

Novartis submitted that the SPC excerpts presented below demonstrated a well recognised theoretical risk associated with the use of anti-VEGF inhibitors. As a VEGF inhibitor and a medicine used off-licence, bevacizumab (Avastin) was a valid molecule to include in this scientific debate. The content of the symposium was of interest to the audience and warranted legitimate scientific debate on the theoretical impact of VEGF on arterial thromboembolic events. It was therefore consistent with the information contained within both SPCs:

Eylea SPC	**Lucentis SPC**
Section 4.4 **Systemic effects**	**Section 4.4** **Systemic effects following intravitreal use**
Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with CRVO or DME with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.	Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. There are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients (see Section 4.8).
Section 4.8 **Description of selected adverse reactions**	**Section 4.8** **Product-class-related adverse reactions**
Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.	There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors.

Section 5.1 Mechanism of action	Section 5.1
Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PIGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.	Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (eg VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO.

Novartis submitted that the symposium was therefore clearly designed to enable debate to enhance the current scientific knowledge in this area. As with all treatments for a condition the clinician was required to weigh up the risks and benefits of treatment when making decisions and in line with the title of the symposium the benefits and risks of medicines were reviewed.

Novartis stated that speaker 1 was a world renowned expert in his field as a diabetologist and also a researcher into microcirculation. His presentation was entitled 'The importance of systemic safety in patients with DME: a diabetologist's viewpoint'. He was therefore well positioned to lead such a debate on the microvascular and macrovascular complications associated with hyperglycaemia and also the additional cardiovascular risk seen in such patients.

Novartis stated that Bayer first raised a concern that this speaker had made a statement about placental growth factor in its letter of 10 December when it stated that 'the speaker drew attention to potential problems with inhibition of placental growth factor (PIGF), notably pregnancy'. However, no further details were provided unlike the level of detail provided in the letter to the PMCPA. Novartis responded to this complaint based on the information made available by Bayer at the time.

This speaker in slides 22-25 generally spoke about the VEGF family which included PIGF. He talked about what was known about the VEGF family in general and therefore Novartis could not understand how the statements he made about PIGF were derogatory to Eylea. In addition, there was no link made for any anti-VEGF inhibitors (including PIGF) in treatment of DMO. Further, Novartis agreed with Bayer that anti-VEGF inhibitors were not recommended in pregnancy but it did not consider that the contribution to the debate as provided by this speaker was negative as suggested by Bayer. Novartis referred to this speaker's transcript in relation to his comments for PIGF below to demonstrate that Bayer had cherry picked phrases which suggested the speaker spoke solely about the negative effects of PIGF on pregnancy:

> '14.42 - Placental Growth Factor (PIGF) is actually one of the most interesting. Until very recently we thought PIGF was nothing more than a decoy. PIGF will bind to the decoy receptor and therefore make your VEGF-A more responsive.
>
> 15.00 - We've recently demonstrated however that PIGF is its own endothelial stimulant. In HUVEC cells, it promotes nitrous oxide dependent vasodilatation. It appears to have protective properties.
>
> 15.15 - We know that if the absence of placental growth factor pregnancy is severely deregulated we know that low placental growth factor is very strongly associated with preeclampsia and eclampsia in pregnancy.

A lot of what we know comes from administration of VEGF receptor antagonists or VEGF inhibition. Before I go on I want to emphasise that most the data, these data I'm showing here come from systemic administration of VEGF. This is when VEGF inhibitors were used to treat cancers and clearly in cancer where the alternative is dying, then a slight increase in vascular risk is something that can be accepted.'

Novartis stated that confusingly Bayer attributed parts of speaker 1's presentation to speaker 2. Novartis noted that slides 26 and 28 were presented by speaker 1; slide 28 (Bayer reference 2) was his last slide. Novartis reiterated that speaker 1 spoke from his experience as a diabetologist and his understanding from his research of the impact of VEGF inhibition. The theoretical risk of VEGF inhibition for systemic adverse events including arterial thromboembolic events was clearly documented as it was included in the SPC. Therefore the statement highlighted by Bayer 'Systemic VEGF suppression could potentially lead to serious side effects' (Slide 28) was in keeping with the SPCs for the products.

Novartis refuted Bayer's assertion as modified in the reference material it provided to the PMCPA that slide 28 was 'immediately' followed by a slide illustrating differences in molecular structure between different anti-VEGF agents (slide 30).

Slide 30 was actually presented by speaker 2 and separated by an introductory slide, slide 29.

Speaker 2 then spoke about 'Balancing efficacy with safety considerations in DME'. The slide (Novartis stated slide 20 but this was incorrect; the relevant slide appeared to be slide 30, slide 20 was presented by speaker 1 not speaker 2) presented by this speaker looked at the molecular and pharmacodynamic properties of the three medicines which might be used to treat DMO. Novartis disagreed with Bayer's assertion that this speaker specifically drew attention to the Fc fragment as a cause for a greater risk of systemic availability with a further suggestion that this might increase the risk in DMO patients of the kind of systemic adverse events seen in cancer patients.

Novartis submitted that this speaker therefore legitimately looked at the differing elements of the different products, including Avastin and the first slide focused on the legitimate place for the use of anti-VEGF inhibitors in DMO by showing the wealth of evidence supporting the efficacy of anti-VEGF treatments.

Further slides then looked at the systemic safety of anti-VEGF agents. This then focused on the safety analyses of arterial thromboembolic events from available clinical trial data which, as Bayer highlighted, showed data for vascular events from RISE/RIDE, RESOLVE/RESTORE/RETAIN. There were several slides which presented the data for Lucentis but this was because there were more clinical data available for Lucentis than for Eylea – studies VISTA/VIVID.

Novartis considered that the US labelling for Lucentis in the area of DMO, as referred to by Bayer, was not relevant to the European market to which this congress was specifically focused and therefore it did not accept that cherry picking statements from the US labelling for these products was relevant where there was specific European labelling.

Novartis did not accept that the data presented in this section minimised the apparent risk of arterial thromboembolic events with one medicine over another nor did it understand Bayer's point that myocardial infarction was not labelled as an arterial thromboembolic event on slide 33. Novartis submitted that the material was appropriately labelled and suitable for the specialist audience who would know that a myocardial infarction was an arterial thromboembolic event.

Novartis further noted that Bayer raised the fact that a speaker referred to trade names of products. Novartis did not ask the speaker to refer to products by brand name, but considered that the speaker used language and terms that he was at ease with. Novartis submitted that the speaker was balanced and fair in his use of brand names such that he did not refer to Bayer's product generically but by brand name for Novartis' product. The speaker also reflected the availability of amount of safety data accurately and reported that there were 5 year data for Lucentis and 2 year data for Eylea.

The speaker acknowledged that there was a difference in perception for the RISE and RIDE data vs data collected from studies in non-US populations. As there had been some debate in the scientific community on whether these studies showed a dose dependent safety profile it was decided that this was entirely relevant to look at in some more detail. Therefore the speaker looked at the safety profile as seen in these studies. Slide 35 showed the two-year incidence of vascular deaths with Lucentis 0.3/0.5 mg in RISE and RIDE. Deaths during the 24-month study period in RISE/RIDE had shown overall deaths as 11 (4.2%) at the 0.5mg dose group vs 7 (2.8%) at the 0.3mg dose group and 3 (1.2%) in the sham (placebo) group.

Slide 35 was headed 'Two year incidence of vascular deaths with ranibizumab 0.3/0.5mg in RISE and RIDE' and was referenced to Nguyen *et al* (2012).

Deaths during the 24-month study period	**[Placebo] (n = 250)**	**[Lucentis] 0.3 mg (n = 250)**	**[Lucentis] 0.5 mg (n = 250)**
Overall, n (%)	3 (1.2)	7 (2.8)	11 (4.2)
Vascular	3 (1.2)	5 (2.0)	6 (2.4)
Non-vascular	0	2 (0.8)	4 (1.6)
Unknown cause	0	0	1 (0.4)

Novartis submitted that it was relevant to the debate to reflect that the total numbers had come from both vascular and non-vascular deaths. However when the vascular deaths were looked at specifically there was a difference between the two doses.

Novartis noted Bayer's reference to comments that were made in the discussion and question and answer section at the end of the symposium. Answers given by the panelists were their personal view, understanding and expertise in this area. To highlight the differences in what was said, Novartis provided a more detailed transcript as opposed to the cherry-picked transcript presented by Bayer:

> 'Q: What determines the PK in the blood stream with different anti-VEGF agents?'
>
> 'A: Actually it's difficult to say because we don't know all the answers to this but there are various properties of different substances which all end up in different behaviour in the body and one of this different behaviour is the systemic concentration over time actually and one of the aspects may well be size of the molecule; smaller molecules are eliminated from the systemic circulation very fast, larger molecules need some more time and this may be part of the explanation why there is a real big difference in systemic exposure of the different drugs.'

This was the 'real big difference' statement that Bayer incorrectly attributed to having been linked to the presence of an Fc portion. As demonstrated by the transcript from the presentation there clearly was no such statement which linked the statement 'real big difference' to the Fc portion.

Speaker 3 who led the question and answer session then followed up with his perspective and related the differences in size to the Fc portion. This text had been provided by Bayer and, other than a few minor words, Novartis submitted it accurately reflected the follow-up answer given by speaker 3 to the question and answer session.

Novartis stated that the presence of an Fc portion was clearly a key difference between the medicines as highlighted on slide 30 which showed their various molecular and pharmacokinetic attributes. This was a statement made by speaker 3 in relation to possible reasons for a longer systemic exposure. Novartis did not accept that responses to a question and answer session supported Bayer's allegation that the entire symposium had been designed to build up to this message. As acknowledged by Bayer there were multiple safety profile slides which clearly gave a balanced view of the safety data available for the medicines.

Novartis vigorously rejected Bayer's assertion that the 'take-home' message of this symposium was that Eylea had a poor safety profile because:

- The symposium was set up to invite debate on the factors which might be taken into account when treating diabetes patients with macular oedema
- The factor relating to the active medicinal ingredient and the pharmacodynamic factors were all presented in a balanced and factual manner
- The theoretical risks in relation to systemic effect were recognised and outlined in the SPCs of the two licensed medicines
- The presentation looked at the practical considerations for the three products which might be used in this condition – one of which could be used as an unlicensed treatment
- All data presented was presented in full and with balance where available
- It was clearly presented that there was a potential class effect which was relevant for all the medicines discussed
- The data presented was for the registration trials on the products which had a licence and reflected the comparators used in those trials.
- There were no promotional claims made in the symposium about any licensed indication nor were specific efficacy claims made for Lucentis.

Novartis denied the allegation that the symposium was set up to present a poorer safety profile for Eylea vs Lucentis and noted that summary slides after presenting the available data from clinical studies clearly reflected that both had good safety profiles by the statement 'There is a well-documented safety profile in DMO for [Eylea] (2 years) and [Lucentis] (5 years)', so Novartis did not accept that an overall negative 'take-home' impression was created. Novartis accepted that the data reflected that there was 5 year safety data for Lucentis which was longer than that shown for Eylea but this was a statement of fact and an accurate evaluation of the current data.

Novartis refuted a breach of Clause 7.9 in that information and claims about adverse events must reflect the available evidence or be capable of substantiation by clinical experience.

As Novartis disagreed that the symposium was promotional in nature or that it was set up to make comparisons of the adverse events data for arterial thromboembolic events and that as such it was misleading – it did not therefore accept that this was in breach of Clause 7.3.

The company considered that the data presented under this scientific symposium was accurate, balanced, fair and objective. That it did not mislead directly or by implication, by distortion, exaggeration or undue emphasis and that consequently it was not in breach of Clause 7.2 nor Clause 7.4.

PANEL RULING

The Panel noted that Bayer complained about the overall impression created of the safety profile of Eylea in diabetic macular oedema (DME) by the symposium. In that regard, although the symposium had consisted of three presentations and a question and answer session, the Panel considered the symposium as a whole and not each of its component parts separately. The symposium was organised by Novartis and referred in detail to its medicine. The Panel considered that the symposium promoted Lucentis.

The Panel noted that both Lucentis and Eylea were antineovascularisation agents, they prevented endothelial cell proliferation and the formation of microvascular vessels as well as vascular leakage, all of which were thought to contribute, *inter alia*, to diabetic macular oedema. The medicines did this by inhibiting vascular endothelial growth factor (VEGF). Lucentis inhibited VEGF A whilst Eylea inhibited VEGF A and the related placental growth factor (PlGF). Slide 30 compared the products. Eylea was a larger molecule than Lucentis and its structure contained an Fc (fragment crystallisable) fragment of a human immunoglobulin. Lucentis had no Fc fragment.

The symposium in question was entitled 'Optimizing benefits and risks in DME management'. In that regard the Panel considered that attendees would expect the presentations to be about the practical and clinical aspects of managing DME. The first section of the symposium was about systemic safety in DME patients. The speaker set out the complications associated with diabetes and in particular that diabetic patients with DME had an even greater risk of co-morbid complications than those without DME. The presentation then focussed on the role of the VEGF family of growth factors and the beneficial effects of VEGF A, VEGF B and PlGF in animal studies. Slide 25 was entitled 'The role of VEGF-B and PlGF has been explored in animal studies' and stated that PlGF had protective properties in preclinical models of heart, retinal and neural diseases. The following slide (26) was headed 'Potential side-effects of systemic administration of anti-VEGF treatment in oncology patients'. Such side effects included hypertension, thromboembolic events and cardiac dysfunction. Slide 26 included 'The dosage, route of administration and side effect profile of anti-VEGF therapies in oncology patients are different to those in ophthalmology patients'. The next slide (27) was headed 'audience participation' and was blank. The slide set provided by Bayer gave the detail (page 21 of Bayer's pdf) which made it clear that participants were asked to use voting buttons to answer the question 'Do you think that systemic VEGF inhibition is clinically relevant in patients with DME?'; Almost 69% thought yes, 22% thought no and 9% did not know. The concluding slide to this section of the symposium ended with the statement that 'Systemic VEGF suppression could potentially lead to serious side effects'.

The Panel noted that Section 5.2, pharmacokinetic properties, of the Lucentis SPC stated that following monthly intravitreal administration of the medicine, serum concentrations of ranibizumab were generally low, with maximum levels generally below those needed to inhibit the biological activity of VEGF by 50% as assessed in an in vitro assay. The Eylea SPC stated in Section 5.2 that aflibercept was slowly absorbed from the eye into the systemic circulation after intravitreal administration, predominantly as an inactive, stable complex with VEGF; only free Eylea was able to bind with endogenous VEGF. The mean maximum plasma concentration of free aflibercept was approximately 50 to 500 times below that required to inhibit systemic VEGF by 50% in animal models. Section 4.4 of both SPCs stated that systemic adverse events, including non-ocular haemorrhages and arterial thromboembolic events, had been reported following intravitreal injection of VEGF inhibitors. Similarly both SPCs advised that caution should be exercised when treating patients with a history of stroke or transient ischaemic attacks or myocardial infarction. Section 4.8 of both SPCs stated that there was a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction following intravitreal use of VEGF inhibitors. It thus appeared for both medicines, that systemic effects from the inhibition of VEGF was a possibility. There was five year data for Lucentis and two year data for Eylea.

The second part of the symposium was entitled 'Balancing efficacy with safety considerations in DME'. The speaker started by explaining that 'there are various substances we have available for treating our patients with DME and the other disease that responds to anti-VEGF treatment. However all these substances are not all exactly the same'. They might have different efficacy, risks and side effects. The first slide in this section (slide 30) compared the molecular weight, structure etc of Lucentis, Eylea and Avastin. It was noted on the slide that Eylea and Avastin unlike Lucentis, contained an Fc portion. The speaker drew attention to the differences in systemic elimination half-life (around 2 hours for Lucentis, 5-6 days for Eylea and 20 days for Avastin) and mean serum exposure after one injection (area under curve, days nM) after one injection (0.2, 3.3 and 14.1 for Lucentis, Eylea and Avastin respectively). The speaker continued by talking about 'Systemic safety of anti-VEGF agents' and explained there had been extensive discussions in the US with respect to the differences in various doses of Lucentis particularly 0.3 and 0.5mg and that he would summarise why this was not seen as such an issue in Europe. He presented seven slides relating to arterio-thrombotic events (ATEs) for Lucentis and concluded, (slide 40), *inter alia*, that 'No differences in event rates of MIs, non-myocardial ATEs (including cerebrovascular events) and vascular deaths were observed…' and 'Based on currently available data there is no evidence to suggest differences in safety between Lucentis 0.5mg, 0.3mg and control'. Data on the safety of Eylea was then presented (slide 41). The speaker referred to 'similar results' for Eylea but pointed to 'differences in number particularly concerning death'. The speaker noted that the data shown was 2 year data and that 'we will be happy to see the 5 year results where we can conclude even more definitely if this is of any relevance for our treatments'.

The speaker summarised the data for Lucentis and Eylea with slide 42, entitled 'Consistent and well-documented long-term safety profile of anti-VEGF agents in DME', beneath which was the statement: 'Incidences of ocular and non-ocular events similar across groups, and similar to previous trials in other indications; no new safety findings or increased safety concerns reported'. At the end of this section of the symposium slide 43 (page 37 of Bayer's pdf which had the detail) asked delegates whether molecular and pharmacokinetic differences influenced their choice of anti-VEGF agent (for DME patients); 63% voted yes and 33% voted

no (3.6% did not know). The speaker concluded (slide 44) by noting that there were molecular and pharmacokinetic differences between anti-VEGF agents, repeating that there was a well documented safety profile in DME for Eylea (2 years) and Lucentis (5 years) and that treatment considerations should balance the benefits of treatment and the risk and severity of adverse effects.

In the closing comments the speaker presented two slides (82 and 83) to conclude. Slide 82 stated, 'Anti-VEGF therapy provides similar VA [visual acuity] scores in patients with DME at 12 months, regardless of the agent or dosing regimen used. Both agents provide sustained VA gains – aflibercept (2 years) and ranibizumab (5 years)' and that there was a wealth of phase 3 data to support the safety of anti-VEGF agents in DME and that Lucentis had a consistent, well-documented long-term safety profile in this indication. With regard to the question and answer session the Panel noted that the speakers stressed that ideally an anti-VEGF agent which would stay in the eye and thus not cause systemic side effects would be one without an Fc portion ie Lucentis and not Eylea or Avastin. One speaker stated that a medicine without an Fc portion ie Lucentis would enable him to give his patients the best vision possible as safely as possible.

The Panel noted the data presented and that there was longer term data for Lucentis as it was available before Eylea. The Panel considered that much had been made of the differences between the molecules and the impression was given that this might impact on safety. This difference was not set in the context of the information in the SPC which was similar for Eylea and Lucentis. In considering the data as a whole the Panel noted that according to Bayer there were differences between the US labelling for Lucentis in DME which referred to fatal events in DME. This was not in the Lucentis SPC. The Panel also noted Novartis' submission that this was not relevant in Europe.

Overall, the Panel considered that the take home message was, as alleged, that the safety profile for Lucentis was more favourable than that for Eylea and that real differences in that regard would be seen in the clinic. On balance that Panel considered that there was insufficient data to show that this was so and that the symposium overall was misleading in that regard. A breach of Clause 7.2 was ruled. The comparison of the two medicines was thus misleading and a breach of Clause 7.3 was ruled. The impression of a significant clinical difference between Eylea and Lucentis could not be substantiated and breaches of Clause 7.4 and 7.9 were ruled.

C Summary

COMPLAINT

Bayer stated that it was gravely concerned that two Novartis-sponsored symposia at the London EURetina congress misleadingly compared the safety profiles of Lucentis and Eylea.

In the case of the wet AMD symposium, (A above), the misrepresentation of safety occurred in the context of superlative promotional claims which related to the efficacy of Lucentis and exaggerated claims about the flexibility of its new posology. In the case of the DME symposium, (B above), implication based upon data irrelevant to the dosages and indications under discussion, verbal comment and misleading presentation of Lucentis safety data combined to build a false picture of the comparative safety of Eylea vs Lucentis and to raise unfounded concerns in the minds of prescribers about the safety of Eylea in its newest indication.

In addition, Bayer considered that there was clear evidence in the examples given above of repeated, serious misrepresentations of safety data and disregard for the Code, such that Novartis had failed to maintain high standards and had brought the industry into disrepute. Taking all of Novartis' activities at EURetina into consideration, Bayer alleged breaches of Clauses 9.1 and 2.

RESPONSE

Novartis submitted that Bayer had not proven its allegations as set out in its complaint which contained multiple inaccuracies of fact and misrepresented the content of the symposium by selectively presenting slides or by misrepresenting the order of slides used in the presentation. Furthermore, Bayer repeated this with inaccuracies of quotations, which could be easily disproven, or selective use of those sections of speaker statements which supported its argument of imbalance without presentation or use of the full statement in context.

As clearly outlined above the symposia took place in the context of debate to further scientific knowledge; neither symposium misrepresented the overall safety profiles for the two medicines as alleged either favourably for Lucentis or negatively for Eylea.

Finally, Novartis did not accept that Bayer had, provided clear evidence in the examples given in its complaint of repeated, serious misrepresentation of safety data and disregard for the Code such that Novartis had failed to maintain high standards and had brought the industry into disrepute. Consequently, Novartis did not consider that there had been a failure to maintain high standards such as to warrant a breach of Clause 9.1 nor that it had brought the industry into disrepute such as to warrant a breach of Clause 2.

PANEL RULING

The Panel noted its rulings in Points A and B above. It considered that the misleading presentation of the data meant that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. The Panel noted that the supplementary information to Clause 2 referred to examples of activities likely to be in

breach of Clause 2 and these included prejudicing patient safety. The Panel noted that although it considered that the symposium had presented a misleading impression of the comparative safety profiles of Lucentis and Eylea, patient safety would not have been put at risk. The Panel noted its rulings above but nonetheless did not consider that its rulings of breaches of the Code in this case amounted to a breach of Clause 2 and no breach was ruled.

Complaint received **12 February 2015**

Case completed **24 June 2015**
