CASE AUTH/2709/4/14

GLAXOSMITHKLINE v ACTELION

Presentation of composite endpoints

GlaxoSmithKline complained about the promotion if Opsumit (macitentan) by Actelion. Opsumit was indicated in the long-term treatment of certain patients with pulmonary arterial hypertension (PAH). The summary of product characteristics (SPC) stated that treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

GlaxoSmithKline was concerned about the presentation of endpoints from Pulido *et al* (2013) in a detail aid and leavepiece. GlaxoSmithKline did not refute that the composite primary end point of morbidity-mortality or the secondary composite endpoint of PAH related death or hospitalisation was achieved in Pulido *et al* or was mentioned in the Opsumit SPC. However, in GlaxoSmithKline's view, the promotional use of such composite endpoints must clearly show which components of that composite endpoint were statistically achieved, particularly as a mortality benefit had not been demonstrated. Claims which used arbitrarily titled endpoints (even if specified in clinical studies or the SPC) were misleading if they implied that all components of the endpoint had been achieved.

The detailed response from Actelion is given below.

GlaxoSmithKline alleged that use of 'reducing morbidity-mortality' in the claim in the detail aid that 'Opsumit helps redefine the future for patients with PAH by reducing morbidity – mortality', was misleading as it implied a mortality benefit whereas only the morbidity component of the endpiont was significant. GlaxoSmithKline was similarly concerned about the claim that Pulido *et al* had demonstrated morbidity-mortality in stable patients. The claim appeared on a graph which showed, over the course of three years, the percentage of placebo and Opsumit patients who were event free (49% vs 63% respectively).

The Panel noted that this was a specialist area. The composite endpoint was the time from initiation of treatment to the first event related to the worsening of PAH or death from any cause up to the end of treatment. Pulido *et al* reported that Opsumit significantly reduced morbidity and mortality but that the treatment effect for the primary outcome was driven mainly by differences in the rates of worsening PAH. When death was considered alone, there was a positive treatment effect for Opsumit but the difference compared with placebo was not statistically significant. Given that PAH was a progressive disease and clinical deterioration was likely to precede death the authors were not surprised that death from any cause or from PAH was rarely the first recorded event. The study was not powered to show an effect on mortality alone and concluded that Opsumit significantly reduced morbidity and mortality and benefits were shown for patients with no previous treatment and for those receiving therapy for PAH at study entry. The SPC gave the outcome endpoints including data on the composite morbidity-mortality endpoint and estimates of the first morbidity-mortality event. The summary of outcome events showed that for the composite endpoint 53% of patients in the placebo group had an event vs 37% in the Opsumit 10mg treatment group ($p<0.0001$). However when this was broken down into its component parts the data showed that 7.6% of patients in the placebo group died vs 5.8% in the treatment group ($p=0.2$) and that 37.2% of patients in the placebo group experienced a worsening of their PAH vs 24.4% in the treatment group ($p<0.0001$).

The Panel noted that the detail aid was entitled 'Help her write future chapters'. The claim that 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality' appeared on page 2 under the heading 'It's time to challenge outcomes for your patients today and tomorrow'. The page in question did not include the additional data provided in either the study (to which it was referenced) or the SPC. The Panel considered that the meaning of the phrase morbidity-mortality was not necessarily clear in the detail aid. There was no reference to it being a composite endpoint ie the first occurrence of a morbidity or mortality event; given the references in the detail aid to the future and to tomorrow the Panel considered that it was not unreasonable that some readers would assume that Opsumit therapy significantly reduced not only morbidity but also mortality. This was not so. In the Panel's view insufficient information had been given about the primary endpoint results such that readers would not appreciate that the reduction in the primary outcome in the Opsumit treatment group was driven by a reduction in morbidity. The material was not sufficiently complete such that a health professional could form his/her own opinion about the full therapeutic value of the medicine. The Panel considered that the claim was misleading in that regard and ruled a breach of the Code. The Panel similarly ruled a breach with regard to the claim on the graph that Pulido *et al* had demonstrated morbidity-mortality in stable patients.

GlaxoSmithKline alleged that the risk reduction in the claim 'Sustained risk reduction from the start of therapy', which appeared within a graph, was not clear. As the title to the graph included 'reducing morbidity-mortality', it implied morbidity and mortality which was misleading as it was not clear that there was no significant effect on mortality.

The Panel noted its comments above and considered that they were relevant here. The Panel considered that the detail aid had not provided the reader

with sufficient information about the morbidity-mortality endpoint such that he/she would be able to readily appreciate the full therapeutic value of Opsumit. The Panel noted Actelion's submission that the graph had been taken from the SPC. In contrast with the SPC, however, readers were not provided with sufficient information such that they could appreciate that the reduction in the primary endpoint in the treatment group was driven by a reduction in morbidity. The Panel considered that, in that regard, the graph with its claim for a 'Sustained risk reduction from the start of therapy' was misleading. A breach of the Code was ruled. The Panel considered that in the context in which they were presented, the graph and the claim exaggerated the therapeutic value of Opsumit; a breach of the Code was ruled.

GlaxoSmithKline alleged that the claim 'Reduced risk of PAH-related death or hospitalisations' was misleading as it implied a reduction in death rates whilst the composite secondary endpoint was driven by reductions in hospitalisation with no significant reduction in mortality.

The Panel noted that Pulido *et al* included a secondary endpoint of death due to PAH or hospitalisation for PAH up to the end of treatment. A statistically significant treatment effect was observed with respect to this composite endpoint driven by lower rates of hospitalisation in the treatment group. There was no significant difference between the placebo group and the treatment group in the rates of death as a component of the composite endpoint. The Panel noted its comments about the context of the presentation of results relating to the composite endpoint above and considered that they were relevant here. The Panel considered that in the context of the detail aid the reader had not been presented with sufficient information such that he/she would appreciate that the reduction in the endpoint was driven by lower rates of hospitalisation. The Panel considered that in this regard the claim was misleading. A breach of the Code was ruled.

GlaxoSmithKline stated that substantiation was needed for the claims regarding the reduction of mortality, which it alleged were misleading and submitted that use of the terms morbidity-mortality and death or hospitalisation as quotations from Pulido *et al* had breached the Code.

The Panel considered that the impression of reduced mortality given by the claims at issue could not be substantiated and in that regard high standards had not been maintained. A breach of the Code was ruled. The Panel noted that in inter-company dialogue, Actelion had failed to provide substantiation for the implied mortality claims. A breach of the Code was ruled. The Panel noted that although the detail aid had featured the outcome of the study no actual quotations from the paper had been included. In that regard there could be no breach of the Code and the Panel ruled accordingly.

GlaxoSmithKline alleged that the claim 'In stable patients already receiving PAH-specific therapies, Opsumit offered a 38% reduction in relative risk reduction in morbidity-mortality at 3 years (p=0.009 [ARR 14%])' used within the leavepiece was misleading as there was no statistically significant mortality benefit shown in Pulido *et al* or in the Opsumit SPC.

The Panel noted its comments and rulings above with regard to the presentation of the composite endpoint. The Panel noted that the context in which the claim appeared in the leavepiece was different to the detail aid as it did not refer to 'tomorrow' or the 'future'. The Panel noted, however, that the claim appeared immediately after a claim about 'the first long-term event-driven outcome trial'. As above, the Panel considered that without the additional information provided in the study or in the SPC, it was not clear that the treatment effect for the primary event-driven outcome (morbidity-mortality) was driven by a decrease in morbidity, not mortality. In the Panel's view, the reader had not been given sufficient information upon which to make a fully informed decision about the therapeutic value of Opsumit. The Panel considered that the claim in the leavepiece was misleading. A breach of the Code was ruled.

GlaxoSmithKline UK Ltd complained about a detail aid (ref OPS 13/0038) and a leavepiece (ref OPS 13/0039) for Opsumit (macitentan) issued by Actelion Pharmaceuticals UK Ltd. Opsumit was indicated as monotherapy or in combination for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of world health organization (WHO) functional class (FC) II to III. Efficacy had been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease. Both pieces of material were for use with health professionals within specialist PAH centres and those who referred PAH patients to specialist centres.

GlaxoSmithKline marketed Volibris (ambrisentan) indicated for the treatment of adult patients with PAH classified as WHO functional class II and III, to improve exercise capacity. Efficacy had been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

General Comments from GlaxoSmithKline

At issue in this case was the way in which the primary and secondary composite endpoints from Pulido *et al* (2013) had been presented in the detail aid and leavepiece. GlaxoSmithKline did not refute that the composite primary end point of morbidity-mortality or the secondary endpoint of PAH related death or hospitalisation was achieved in Pulido *et al* or was mentioned in the Opsumit summary of product characteristics (SPC). However, in GlaxoSmithKline's view, the promotional use of such composite endpoints must clearly show what components of that composite endpoint were statistically achieved, particularly as a mortality

benefit had not been demonstrated. Claims which used arbitrarily titled endpoints (even if specified in clinical studies or the SPC) were misleading if they implied that all components of the endpoint had been achieved.

Background from Actelion

Actelion noted that GlaxoSmithKline considered that its use of the phrase 'reducing morbidity-mortality' implied a mortality benefit claim. Actelion submitted however, that there was an underlying misinterpretation in GlaxoSmithKline's complaint and in that regard Actelion explained the origins of 'morbidity-mortality' to put into context how the phrase was used in the specialist literature, the SPC and the detail aid and leavepiece at issue.

Actelion stated that the traditional endpoints in PAH studies, and used for licensing, were short-term symptomatic measures such as the change in six minute walk distance (6MWD). Studies were typically conducted over 12-24 weeks. Bosentan (Tracleer), an Actelion medicine licensed for use in PAH in 2002, and ambrisentan, GlaxoSmithKline's Volibris licensed in 2008, were investigated using this endpoint. However, 6MWD did not correlate with long-term outcomes in PAH and offered limited information on disease progression. The world PAH community set up an expert task force in 2008 to look for better correlates of long-term outcomes which would more accurately measure disease progression. This task force focused on endpoints and clinical trial design and met at the 4th World Symposium on Pulmonary Hypertension (WSPH) in 2008. It recommended including a primary composite endpoint to accurately reflect clinical worsening and independent and blinded adjudication of events to minimize bias.

This primary endpoint should be a composite endpoint which reflected clinical worsening (morbidity or time to clinical worsening [TTCW]) and mortality. The adjudication of events by an independent and blinded panel would reduce the inconsistencies between event classification by sites and investigators.

The use of such a composite primary endpoint was subsequently recommended by the *European Medicines Agency* (EMA) as more relevant than change in 6MWD. The EMA recognized that measurement of mortality in such a rare disease in which effective therapies were already available would be challenging.

In 2009 the EMA published new guidelines for investigating medicines in PAH and recommended an event-driven design with mortality and morbidity as a composite endpoint. A 2009 review of the history and design of PAH studies by McLaughlin *et al* provided a summary of this recommendation. The Opsumit phase III study, (Pulido *et al*), the source of the data used in the materials at issue, provided a clear picture of disease progression by taking into account all of the events recommended by the task force and the EMA (a long-term, event-driven study with an adjudication of events). Pulido *et al* had time to the first occurrence of a morbidity or mortality event as its composite primary endpoint.

The use of this event-driven morbidity-mortality endpoint directly and accurately reflected disease progression in PAH. The task force for the 5th WSPH in 2013 also recognised the robust nature of the evidence for only two products, Opsumit and epoprostenol. These were the only two treatments highlighted in the treatment algorithm for PAH with a level 1 recommendation based on the demonstration of morbidity and mortality as a primary endpoint or the reduction in all-cause mortality as a pre-specified endpoint.

Actelion noted that composite endpoints had been used in other studies and that its reference to morbidity-mortality was in line with such studies. Actelion cited in particular a number of cardiovascular studies.

Actelion submitted that in its view 'morbidity-mortality'referred to a composite endpoint with several components of mortality and morbidity. The approved wording in the SPC was carefully considered by national agencies. Section 5.1 of the Opsumit SPC used the hyphenated term 'morbidity-mortality' to describe the positive outcome of the composite primary endpoint of Pulido *et al* in figure 1 and table 1. In addition, all core materials had been pre-vetted by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Actelion submitted that it had clarified the endpoints above and throughout inter-company dialogue with GlaxoSmithKline. It seemed that GlaxoSmithKline was reluctant to acknowledge that guidelines now supported event-driven studies with complex composite endpoints, the SPC described the positive outcome of the composite primary endpoint of Pulido *et al* as morbidity-mortality, and the scientific community discussed outcomes from these studies as morbidity-mortality with the understanding that this meant the combination of all-cause mortality plus PAH-related morbidity events.

In summary, Actelion submitted that morbidity-mortality was not a misleading term, it was widely understood to mean 'morbidity plus mortality events, together'. It did not imply reduction in both components individually. This was reflected in the SPC and was also in line with expert opinion.

A Detail aid (ref OPS 13/0038)

The first page of the detail aid referred to the treatment of PAH and included the main claim 'Help her write future chapters' above an illustration of attending and graduating from university. Page two was headed 'It's time to challenge outcomes for your patients today and tomorrow' followed by a claim 'Opsumit helps redefine the future for patients with PAH by reducing morbidity–mortality' referenced to Pulido *et al*. A graph (adapted from Pulido *et al*) showed the sustained risk reduction from the start of therapy and referred to the percentage of patients that were event free. At three years 63% of Opsumit patients were without an event vs 47% of placebo

patients. A claim to the left of the graph stated 'Opsumit 10mg significantly reduced the overall risk of a morbidity-mortality event compared with placebo (63% versus 47%; p<0.001). The graph also included a claim '45%RRR 16% ARR p<0.001'.

1 Claim 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality'

This claim appeared as the sub-heading to page 2 and was referenced to Pulido *et al*.

COMPLAINT

GlaxoSmithKline alleged that use of 'reducing morbidity-mortality' was misleading in breach of Clause 7.2. The claim implied a mortality benefit whereas despite having a primary composite endpoint of time to first event of morbidity or mortality only the morbidity component was significant in table 2 of Pulido *et al* and table 1 of the Opsumit SPC. Pulido *et al* stated that the 'treatment effect for the primary endpoint was driven mainly by differences in the rates of worsening of pulmonary arterial hypertension'. GlaxoSmithKline stated that hyphenating morbidity-mortality into one word implied reductions in both components. Section 5.1 of the Opsumit SPC also stated 'The number of deaths of all causes up to [end of study] on macitentan 10mg was 35 versus 44 on placebo (HR 0.77; 97.5% CI: 0.46 to 1.28)', which was not statistically significant. GlaxoSmithKline alleged that using mortality as a claim in a promotional context was misleading in breach of Clause 7.2.

RESPONSE

Actelion submitted that the statement 'reducing morbidity-mortality' was widely understood to mean 'reducing mortality plus morbidity events' in the event-driven study. As discussed above, hyphenating the term did not imply a reduction in both components (in fact there were at least five components). There was no requirement in the Code to expand a composite primary endpoint into its components. Moreover, the hyphenated term was also used in the SPC. Actelion refuted that use of this term was in breach of Clause 7.2.

PANEL RULING

In considering all the allegations the Panel bore in mind that this was a specialist area. The SPC stated that treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

The Panel noted that Pulido *et al* was a long-term term trial to assess the efficacy of Opsumit using a primary composite endpoint of morbidity and mortality. The composite endpoint was the time from initiation of treatment to the first event related to the worsening of PAH or death from any cause up to the end of treatment. All endpoints were independently adjudicated. The authors reported that Opsumit significantly reduced morbidity and mortality but that the treatment effect for the primary outcome was driven mainly by differences in the rates of worsening PAH. When death was considered alone, there was a positive treatment effect for Opsumit but the difference compared with placebo was not statistically significant. Given that PAH was a progressive disease and clinical deterioration was likely to precede death the authors were not surprised that death from any cause or from PAH was rarely the first recorded event. The authors noted that the study was not powered to show an effect on mortality alone.

One of the limitations of the study was stated to be that it did not address the efficacy of Opsumit compared with other approved oral therapies for PAH. The study concluded that Opsumit significantly reduced morbidity and mortality and benefits were shown for patients with no previous treatment and for those receiving therapy for PAH at study entry.

The SPC provided details of the primary endpoint as the time to first occurrence of a morbidity event, up to the end of double-blind treatment, as defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous or subcutaneous prostanoids, or other worsening of PAH. Other worsening of PAH was further defined in the SPC. Following this information, Section 5.1 of the SPC gave the outcome endpoints including data on the composite morbidity-mortality endpoint and estimates of the first morbidity-mortality event. The summary of outcome events showed that for the composite endpoint 53% of patients in the placebo group had an event vs 37% in the Opsumit 10mg treatment group (p<0.0001). However when this was broken down into its component parts the data showed that 7.6% of patients in the placebo group died vs 5.8% in the treatment group (p=0.2) and that 37.2% of patients in the placebo group experienced a worsening of their PAH vs 24.4% in the treatment group (p<0.0001).

The Panel agreed with Actelion that there was no requirement in the Code to extend a composite primary endpoint into its components. The question to be considered was whether the claim for the composite endpoint in the context of the material at issue met the requirements of the Code.

The Panel noted that the detail aid was entitled 'Help her write future chapters'. The claim at issue that 'Opsumit helps redefine the future for patients with PAH by reducing morbidity-mortality' appeared on page 2 under the heading 'It's time to challenge outcomes for your patients today and tomorrow'. The page in question did not include the additional data provided in either Pulido *et al* (to which it was referenced) or the SPC. The Panel considered that the meaning of the phrase morbidity-mortality was not necessarily clear in the detail aid. There was no reference to it being a composite endpoint ie the first occurrence of a morbidity or mortality event; given the references in the detail aid to the future and to tomorrow the Panel considered that it was not unreasonable that some readers would assume that Opsumit therapy significantly reduced not only morbidity but also mortality. This was not so. In the Panel's view insufficient information had been given about the primary endpoint results such that readers would not appreciate that the reduction in the primary outcome in the Opsumit treatment group

was driven by a reduction in morbidity. The material was not sufficiently complete such that a health professional could form his/her own opinion about the full therapeutic value of the medicine. The Panel considered that the claim was misleading in that regard and ruled a breach of Clause 7.2 of the Code.

2 Claim 'Sustained risk reduction from the start of therapy'

This claim appeared within the graph featured on page 2 which showed, over the course of three years, the percentage of patients taking either placebo or Opsumit 10mg who were event-free (47% vs 63% respectively p<0.001).

COMPLAINT

GlaxoSmithKline alleged that it was not clear what the risk reduction related to, implying morbidity and mortality as the phrase 'reducing morbidity-mortality' was used in the title to the graph. No statistically significant reduction in mortality could be claimed, therefore the artwork was misleading in breach of Clause 7.8. GlaxoSmithKline noted that Section 5.1 of the Opsumit SPC mentioned a 45% relative risk reduction of the 'composite morbidity-mortality' endpoint which was 'established early and sustained', however in a promotional context it was not clear that there was no significant effect on mortality which remained misleading in breach of Clause 7.8.

GlaxoSmithKline alleged that the overall appearance of page 2 implied a morbidity and mortality benefit which was not so. The evidence in the study and the SPC showed no significant reduction in mortality. GlaxoSmithKline alleged that the claim exaggerated the properties of Opsumit and implied special merit which had not been shown in breach of Clause 7.10.

GlaxoSmithKline further alleged that the material claimed a mortality benefit which had not been substantiated by the evidence provided and was in breach of Clause 7.5.

RESPONSE

Actelion submitted that the artwork was taken directly from Section 5.1 of the SPC. The company further submitted that morbidity-mortality was not a misleading term; it was widely understood to mean 'morbidity plus mortality events, together'. The term did not imply reduction in both components separately and Actelion did not claim mortality benefits in its promotional materials. In that regard the company denied a breach of Clause 7.8.

Actelion submitted that morbidity-mortality did not imply reduction in both components separately therefore there was no exaggerated claim. Mortality on its own was not suggested by Actelion. Expert, informed clinicians and scientists, who made up the prescribing and referring target group for this tertiary specialist area, understood that the graphics and data described the mortality plus morbidity events that were used to examine the efficacy of Opsumit in Pulido *et al*. Actelion submitted that the claim reflected the SPC and was not a breach of Clause 7.10.

Actelion submitted that in its view the alleged breach of Clause 7.5 related to the previous points already covered under Clauses 7.2, 7.8 and 7.10 above regarding morbidity-mortality. Actelion did not consider that it had made a specific mortality claim and thus denied a breach of Clause 7.5.

PANEL RULING

The Panel noted its comments and ruling in Point 1 above and considered that they were relevant here. The Panel considered that the detail aid had not provided the reader with sufficient information about the morbidity-mortality endpoint such that he/she would be able to readily appreciate the full therapeutic value of Opsumit. The Panel noted Actelion's submission that the graph had been taken from the SPC. In contrast with the SPC, however, readers were not provided with sufficient information such that they could appreciate that the reduction in the primary endpoint in the treatment group was driven by a reduction in morbidity. The Panel considered that, in that regard, the graph with its claim for a 'Sustained risk reduction from the start of therapy' was misleading. A breach of Clause 7.8 was ruled. The Panel considered that in the context in which they were presented, the graph and the claim exaggerated the therapeutic value of Opsumit; a breach of Clause 7.10 was ruled.

The Panel noted the alleged breach of Clause 7.5 which required that substantiation for any information, claim or comparison be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or appropriate administrative staff. The Panel noted that in inter-company dialogue, Actelion had failed to provide substantiation for the implied mortality claim. A breach of Clause 7.5 was ruled.

3 Claim '[Pulido *et al*] is the first study to demonstrate morbidity-mortality in stable PDE5i patients'

This claim appeared within the graph featured on page 3 of the detail aid which showed, over the course of three years, the percentage of placebo and Opsumit 10mg patients who were event-free (49% vs 63% respectively).

COMPLAINT

GlaxoSmithKline alleged that the claim was misleading, Pulido *et al* attempted to show a primary endpoint of reduction in morbidity or mortality. Whilst it met this endpoint it was driven exclusively by reductions in morbidity and not mortality which was not statistically significantly different between groups. A breach of Clause 7.2 was alleged.

RESPONSE

Actelion submitted that GlaxoSmithKline might have misinterpreted Pulido *et al*. The primary endpoint of the study was not mortality or morbidity, but

mortality plus morbidity events together. As noted above, morbidity-mortality was widely understood to mean mortality plus morbidity events and in this context, the claims on page three regarding outcomes in the PDE5i subgroup were not misleading. The majority of patients in the study at baseline were on PDE5 inhibitors and this pre-planned subgroup analysis used the same primary endpoint. Actelion submitted that the data presented was not misleading and it denied a breach of Clause 7.2.

PANEL RULING

The Panel noted its comments and rulings above and considered that they were relevant here. The SPC did not include the data on page 3 of the detail aid. It was provided in a supplementary appendix to Pulido *et al* which was provided by Actelion upon request of the Panel. In the Panel's view, in the context of the detail aid the reader had not been provided with sufficient information such that he/she would appreciate that the reduction in the primary endpoint had been driven by reductions in morbidity. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

4 Claim 'Reduced risk of PAH-related death or hospitalisations'

The claim, together with a prominent figure of 50%, appeared as a bullet point on page 4 of the Opsumit detail aid which was headed 'Plus improvements in other key patient parameters'. The claim related to the secondary outcome in Pulido *et al* and was referenced to Pulido *et al* and Channick *et al* (2013).

COMPLAINT

GlaxoSmithKline stated that the claim 'Reduced risk of PAH-related death or hospitalisations' was misleading as it implied a reduction in death rates. This composite secondary endpoint was driven by reductions in hospitalisation with no significant reduction in mortality. In the discussion of the results, Pulido *et al* stated that this 'was driven by lower rates of hospitalisation in the [Opsumit] groups'. A breach of Clause 7.2 was alleged.

RESPONSE

Actelion submitted that the word 'or' served the same purpose as the hyphen in the morbidity-mortality phrase. It did not mean PAH death or hospitalisation, separately. It was clearly a combined endpoint, again, consistent with other endpoints in the study. Importantly, use of 'or' in this context was exactly as used in the SPC: 'The risk of PAH related event or hospitalisation for PAH up to EOT [end of trial] was reduced by 50% ....'. Actelion refuted that the data presented was misleading and in breach of Clause 7.2.

PANEL RULING

The Panel noted that Pulido *et al* included a secondary endpoint of death due to PAH or hospitalisation for PAH up to the end of treatment. A statistically significant treatment effect was observed with respect to this composite endpoint driven by lower rates of hospitalisation in the treatment group. There was no significant difference between the placebo group and the treatment group in the rates of death as a component of the composite endpoint. The Panel noted its comments about the context of the presentation of results relating to the composite endpoint above and considered that they were relevant here. The Panel considered that in the context of the detail aid the reader had not been presented with sufficient information such that he/she would appreciate that the reduction in the endpoint was driven by lower rates of hospitalisation. The Panel considered that in this regard the claim was misleading. A breach of Clause 7.2 was ruled.

5 Overall

COMPLAINT

GlaxoSmithKline stated that substantiation was needed for the claims regarding the reduction of mortality, which it alleged were misleading in breach of Clause 7.5. GlaxoSmithKline submitted that use of the terms morbidity-mortality and death or hospitalisation as quotations from Pulido *et al* had not been used in a Code compliant manner; they should have been adapted and stated as such, and were therefore in breach of Clause 10.2. GlaxoSmithKline further alleged a breach of Clause 9.1 as high standards had not been maintained.

RESPONSE

Actelion submitted that the points relating to Clauses 7.5 and 10.2 were linked to points raised under Clauses 7.2 and 7.8, regarding how the morbidity-mortality data from Pulido *et al* had been represented. As discussed above, Actelion submitted that it had been consistent with the SPC. Actelion therefore refuted that it was in breach of any of the clauses. Subsequently, Actelion submitted that it had maintained high standards at all times and it denied a breach of Clause 9.1.

PANEL RULING

The Panel noted its comments and rulings above. The Panel considered that the impression of reduced mortality given by the claims at issue could not be substantiated and in that regard high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted the alleged breach of Clause 7.5 which required that substantiation for any information, claim or comparison be provided as soon as possible, and certainly within ten working days, at the request of members of the health professions or appropriate administrative staff. The Panel noted that in inter-company dialogue, Actelion had failed to provide substantiation for the implied mortality claim. A breach of Clause 7.5 was ruled.

The Panel noted that although the detail aid had featured the outcome of Pulido *et al* no actual

quotations from the paper had been included. In that regard there could be no breach of Clause 10.2 and the Panel ruled accordingly.

B Leavepiece (ref OPS 13/0039)

1 Claim 'In stable patients already receiving PAH-specific therapies, Opsumit offered a 38% reduction in relative risk reduction in morbidity-mortality at 3 years (p=0.009 [ARR 14%])'

This was a slim leavepiece which opened out to A5. The claim at issue appeared on page one of the material as the second claim beneath the headline 'Opsumit – proven to reduce morbidity-mortality in pulmonary arterial hypertension'. The first claim read, Opsumit is effective as monotherapy and in combination with PDE5i, as shown in the first long-term, event-driven outcome trial in PAH'.

COMPLAINT

GlaxoSmithKline alleged that the claim was misleading in breach of Clause 7.2 as there was no statistically significant mortality benefit shown in Pulido *et al* or in the Opsumit SPC.

RESPONSE

Actelion submitted that the claim at issue was consistent with the definition of the primary endpoint of Pulido *et al* and the SPC, which included the same hyphenated term. There was no requirement to examine the relative contribution of components making up the composite endpoint. Actelion denied a breach of Clause 7.2.

PANEL RULING

The Panel noted its comments and rulings above with regard to the presentation of the composite endpoint. The Panel noted that the context in which the claim appeared was different to the detail aid as the leavepiece did not refer to 'tomorrow' or the 'future'. The Panel noted, however, that the claim appeared immediately after a claim about 'the first long-term event-driven outcome trial' ie Pulido *et al*. As above, the Panel considered that without the additional information provided in Pulido *et al* or in the SPC, it was not clear that the treatment effect for the primary event-driven outcome (morbidity-mortality) was driven by a decrease in morbidity, not mortality. In the Panel's view, the reader had not been given sufficient information upon which to make a fully informed decision about the therapeutic value of Opsumit. The Panel considered that the claim was misleading in that regard. A breach of Clause 7.2 was ruled as alleged.

Complaint received **1 May 2014**

Case completed **2 July 2014**