CASE AUTH/3185/4/19

COMPLAINANT v MUNDIBIOPHARMA

Promotion of Invokana

A complainant who described him/herself as a concerned UK health professional, complained about the online promotion of Invokana (canagliflozin) and Vokanamet (canagliflozin and metformin) by Mundibiopharma. Invokana and Vokanamet were used as an adjunct to diet and exercise in certain adults with type 2 diabetes.

The complainant had received an email titled 'ISN-WCN [International Society of Nephrology – World Conference of Nephrology] Invokana (R) (canagliflozin) virtual booth: Get the latest data on SGLT2 [sodium-glucose transport protein 2]'. The ISN-WCN 2019 had taken place in Melbourne, Australia, 12-15 April.

The complainant alleged that the email linked to the summary of product characteristics (SPC) rather than prescribing information. The 'microsite' accessed from the email mentioned Vokanamet but there was no generic name or prescribing information.

Within the microsite the complainant referred to a presentation about renal outcomes in the CANVAS (canagliflozin cardiovascular assessment study) programme and alleged that the outcomes on a slide looked good because the y-axis was suppressed. The complainant added that prescribing information on the material was extremely difficult to read.

With regard to another presentation on the CANVAS programme the complainant alleged that three slides made the outcomes look very good because the y-axis was not correctly numbered which exaggerated the effect. Similarly, the y-axis was suppressed on another slide.

The complainant alleged that a claim on a slide that canagliflozin reduced the risk of cardiovascular death was misleading as the confidence interval crossed 1 and the information below the graph stated that this was a non-statistical, potentially random outcome. A similar allegation was made in relation to another slide which claimed that canagliflozin reduced the risk of mortality in both the intention to treat and left-truncated analyses. This was presented in the same way as information where the confidence intervals did not cross 1. The presentation included prescribing information but the complainant alleged that it was extremely difficult to read.

The complainant stated that he/she did not have time to look through all 114 slides, but he/she thought that the above illustrated that the material had not received the rigour required before being widely sent to health professionals.

The complainant alleged that links to two documents (Perkovic *et al* (2018) and Neal *et al* (2017)) should have been certified for use and should have included prescribing information.

The complainant alleged that high standards had not been maintained and, for the sake of completeness, alleged a breach of Clause 2.

The detailed response from Mundibiopharma is given below.

The Panel considered that the link to the Invokana SPC in the email did not fulfil all the requirements of the Code and the Panel therefore ruled a breach. The Panel also considered that the omission of the non-proprietary name for Vokanamet immediately adjacent to the brand name at its first appearance meant that Mundibiopharma had failed to maintain high standards and a breach was ruled.

In the Panel's view, it would not be sufficiently clear to a user of the virtual booth that he/she would have to download a slide-deck in order to view the Vokanamet prescribing information. However, the Panel noted the complainant's allegation that there was no prescribing information for Vokanamet on the microsite and that was not so. Based on the very narrow allegation, the Panel ruled no breach in this regard.

The Panel noted the complainant's allegation that slide 33 of a deck titled 'Time to protect the diabetic kidney: renal outcomes in the CANVAS program' had 'made the outcomes look good by suppressing the y axis'.

The Panel noted that the slide in question was headed 'Canagliflozin reduced the decline in eGFR compared with placebo' below which was the graph in question. The y-axis of the graph, adjusted mean eGFR, had a suppressed zero and went from 68 to 80 mL/min/1.73m^2. To the right of the graph was a prominent red box which stated that the canagliflozin vs placebo eGFR slope difference was 1.2 mL/min/1.73m^2 per year 95% CI [confidence interval] 1.0-1.4. The Panel noted Mundibiopharma's submission that the graph was a faithful copy from Perkovic *et al* 2018 and that Mundibiopharma had highlighted the suppressed zero on the y-axis which was not done in the publication. Irrespective of whether the graph was a faithful copy of Perkovic *et al* its use in promotional material had to comply with the Code. The Panel noted that the graph in Perkovic *et al* had a y-axis which went from 68 to 80 mL/min/1.73m^2 and that all plotted data in the two treatment arms were within this range. The Panel considered that the scale used in Perkovic *et al* and in the slide in question might aid the reader to analyse each data point on the graph. The Panel noted its comments above, including that the slope difference for canagliflozin vs placebo was prominently stated next to the graph within the slide in question and that the y-axis was clearly labelled, and considered that the complainant had not established that health professionals would be misled with regard to the difference between the treatment arms by virtue of a suppressed zero. No breach of the Code was ruled.

The Panel considered that the prescribing information for Invokana and Vokanamet on the slide-deck in question was legible and no breach was ruled.

The Panel noted that slides 14 to 16 featured 6 graphs which showed differences between canagliflozin and placebo in relation to various measurements such as HbA1c,

body weight, blood pressure, cholesterol etc. The graph on Slide 30 showed differences between canagliflozin and placebo in change in urine albumin-to-creatinine ratio (UACR). The Panel noted that the use of a suppressed zero was not limited to those graphs where the difference in treatment favoured canagliflozin; for example, the LDL cholesterol graph on slide 16 favoured placebo and the y-axis was from 82 to 100 mg/dl. The Panel considered that the use of a suppressed zero was not necessarily unacceptable. In each of the 7 graphs in question, the y-axis was clearly labelled, all data points were within the y-axis range and the mean difference between treatment arms and the 95% confidence interval was stated clearly within each slide. In the Panel's view, the scales used in the slides in question might aid the reader to analyse each data point on the graph. The Panel did not consider that the complainant had established, on the balance of probabilities, that the use of a suppressed zero in the graphs in question would mislead a health professional with regard to the difference between the treatment groups. The Panel therefore ruled no breach of the Code.

In relation to slide 22 the Panel noted that the primary outcome measure in the CANVAS program was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Secondary outcomes planned for sequential conditional hypothesis testing included death from any cause and death from cardiovascular causes. If sequential testing was not significant for all the outcomes specified, the remaining outcomes were scheduled for assessment as exploratory variables in the integrated data set. The Panel noted that the study authors stated that significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (the composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke): HR 0.86; 95% CI, 0.75 to 0.97; p<0.001 for non-inferiority, p=0.02 for superiority. The study authors stated that superiority was not shown for the first secondary outcome in the testing sequence (death from any cause; p=0.24) and hypothesis testing was discontinued. Therefore, estimates for the fatal secondary outcomes, including death from any cause (HR 0.87, 95% CI, 0.74 to 1.01) and death from cardiovascular causes (HR 0.87, 95% CI, 0.72 to 1.06) were not considered to be significant.

The Panel noted the headline claim on slide 22 stated 'Canagliflozin reduced risk of CV death'. The hazard ratio (0.87) and confidence interval (0.72 to 1.06) were stated. The footnote to the graph, in small font, stated, 'Intention-to-treat analysis, exploratory outcome, no p-value is reported due to hierarchical testing strategy, only nominal effect estimate is given'. The Panel noted Mundibiopharma's submission that this slide indicated that there was a non-significant reduction in cardiovascular death as the confidence interval was shown crossing unity. The Panel further noted that the authors of the paper stated, 'All three components of the primary outcome – death from cardiovascular causes, nonfatal myocardial infarction, and non-fatal stroke – showed point estimates of effect that suggested benefit, although the individual effects did not reach significance'.

The Panel noted the hazard ratio and Mundibiopharma's submission that the point estimate was to the left of 1, favouring canagliflozin as illustrated in figure 2 of the Invokana SPC. The Panel considered that presenting data which did not reach statistical significance was not necessarily unacceptable, however, the presentation of such data, including claims, must not be misleading in this regard.

The Panel considered the immediate and overall impression to a health professional. In the Panel's view, the headline claim 'Canagliflozin reduced risk of CV death', which was in prominent bold red font above the graph, implied that the difference between canagliflozin and placebo reached statistical significance which was not so. The 95% confidence interval stated within the slide and the footnote in small font below the graph did not negate the immediate misleading impression given by the headline claim. The Panel noted its comments above and considered that the claim was misleading and was a misleading comparison of canagliflozin compared with placebo in this regard. The Panel ruled breaches of the Code.

In the Panel's view, the headline claim to slide 23 'Canagliflozin reduced risk of mortality in both the intention-to-treat and left-truncated analyses' implied that the difference between canagliflozin and placebo reached statistical significance which was not so, and the inclusion of the 95% confidence intervals and p-value did not negate the immediate misleading impression given by the headline claim. The Panel therefore considered that the claim was misleading and was a misleading comparison of canagliflozin compared with placebo in this regard. The Panel ruled breaches of the Code.

The Panel considered that the prescribing information for Invokana and Vokanamet on the slide-deck in question was legible and no breach of the Code was ruled.

With regard to the allegation that there were two links to items that did not appear to be part of the microsite and that both items required prescribing information and certification, the Panel noted Mundibiopharma's submission that the links in question were accessed by clicking once on pillars 2 and 4 within the microsite which provided a copy of Perkovic *et al* and Neal *et al*, respectively. The Panel noted Mundibiopharma's submission that pillars 1 and 2 were linked, as were pillars 3 and 4, and that the articles accessed from pillars 2 and 4 were references to support the content within pillars 1 and 3, respectively. The Panel further noted that pillars 1 and 3 were certified and that the signatory had read Perkovic *et al* and Neal *et al* to check that the articles complied with the Code and were not inconsistent with the SPC.

The Panel disagreed with Mundibiopharma's submission that certification of the articles was not required as 'each possible combination does not need to be certified' in the context of digital material as per the supplementary information to Clause 14.1. The Panel noted that the supplementary information stated, *inter alia*, that as the final form of digital material might not be static, consideration needs to be given to the context in which it appears, but each possible combination does not need to be certified. In the Panel's view, all promotional material required certification and the supplementary information cited by Mundibiopharma pertained to navigation within digital material; it did not preclude any of the content from being certified. Pillars 2 and 4 were sections of the virtual booth designed to provide health professionals with access to Perkovic *et al* and Neal *et al*, respectively, and therefore the material should have been certified for such use. In the Panel's view, this was no different to a physical exhibition stand providing a reprint. The Panel ruled a breach of the Code.

In the Panel's view, the exemption for cost in the limited scenarios described in the Code did not apply to the microsite in question. The Panel considered that the link to the Invokana SPC did not fulfil all the requirements for prescribing information and therefore ruled a breach of the Code.

The Panel noted its rulings of breaches of the Code and considered that Mundibiopharma had failed to maintain high standards and ruled a breach of the Code.

In the particular circumstances of this case and noting that there was a link to the Invokana SPC on the microsite and that Invokana and Vokanamet prescribing information was available within two slide-decks on the microsite, the Panel ruled no breach of Clause 2.

A complainant who described him/herself as a concerned UK health professional, complained about the online promotion of Invokana (canagliflozin) and Vokanamet (canagliflozin and metformin) by Mundibiopharma. Invokana and Vokanamet were used as an adjunct to diet and exercise in certain adults with type 2 diabetes.

The complainant had received an email titled 'ISN-WCN [International Society of Nephrology – World Conference of Nephrology] Invokana (R) (canagliflozin) virtual booth: Get the latest data on SGLT2 [sodium-glucose transport protein 2]'. The ISN-WCN 2019 had taken place in Melbourne, Australia, 12-15 April.

COMPLAINT

The complainant stated that the email linked to the summary of product characteristics (SPC) rather than prescribing information in breach of Clause 4.1.

The complainant stated that he/she clicked through to the 'microsite'. This mentioned Vokanamet but there was no generic name or prescribing information.

The complainant referred to a presentation about renal outcomes in the CANVAS (canagliflozin cardiovascular assessment study) programme and alleged that the outcomes on slide 33 looked good because the y-axis was suppressed in breach of Clause 7.8. The complainant added that prescribing information on the material was extremely difficult to read, in breach of Clause 4.1.

With regard to another presentation on the CANVAS programme the complainant alleged that slides 14, 15 and 16 made the outcomes look very good because the y-axis was not correctly numbered which exaggerated the effect in breach of Clause 7.8. Similarly, the y-axis was suppressed on slide 30 in breach of Clause 7.8.

Slide 22 stated that canagliflozin reduced the risk of cardiovascular death. However, the confidence interval crossed 1 and the information below the graph stated that this was a non-statistical, potentially random outcome. The complainant alleged breaches of Clauses 7.2 and 7.3. Slide 23 stated that canagliflozin reduced the risk of mortality in both the intention to treat and left-truncated analyses in breach of Clauses 7.2 and 7.3. This was presented in the same way as the information on slide 27 where the confidence intervals did not cross 1. The presentation included prescribing information but it was extremely difficult to read in breach of Clause 4.1.

The complainant stated that he/she did not have time to look through all 114 slides, but he/she thought that the above illustrated that the material had not received the rigour required before being widely sent to health professionals.

The complainant noted that there were two links to separate pages with documents on them from websites that did not appear to be part of the microsite. The two documents were copies of Perkovic *et al* (2018) and Neal *et al* (2017). The complainant stated that as these were two separate items they should have been certified for use and have included prescribing information. The complainant alleged breaches of Clauses 4.1 and 14.1.

The complainant further alleged a breach of Clause 9.1 and, for the sake of completeness, a breach of Clause 2.

When writing to Mundibiopharma, the Authority asked it to consider the clauses cited by the complainant in relation to the 2016 Code.

RESPONSE

Mundibiopharma stated that the digital promotion was designed to be available online by way of a 'virtual promotional booth' rather than host an actual promotional booth at the ISN-WCN conference itself.

Mundibiopharma submitted that the emails were sent by a third party on behalf of Mundibiopharma to GPs, cardiologists, nephrologists, diabetologists and endocrinologists (who were all specialist physicians) in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Slovakia, Sweden and the UK. These specialist physicians had each pre-subscribed to a healthcare website and as part of that pre-subscription had confirmed that they would accept promotional materials from time-to-time. The email as provided by the complainant included a clear link of how to unsubscribe.

With regard to the complainant's comment that the email linked to the SPC rather than prescribing information, Mundibiopharma submitted that Clause 4.1 stated that *'the prescribing information must be positioned for ease of reference'*, and that *'The summary of product characteristics may be provided instead'*. The link to the summary of product characteristics (SPC) was provided as a single click (as allowed under Clause 4.4) and was prominent on both the email and the virtual booth. The legal classification (as per Clause 4.2) was included on the electronic medicines compendium (eMC) web-link above the SPC on the linked web-site.

Mundibiopharma submitted that the medicine cost was not provided because the emails promoting the virtual booth were distributed across 15 European countries as well as the UK and so there would be not one cost but several. Mundibiopharma further submitted that Clause 4.2 was also relevant as cost was not required when more than 15 per cent of the circulation was outside the UK. Mundibiopharma denied a breach of Clause 4.1.

With regard to the complainant's reference to the lack of generic name and prescribing information for Vokanamet, Mundibiopharma submitted that the layout of the virtual booth microsite was such that there were four vertical pillars to the right of the virtual booth. From left to right they were headed 'Find out about the latest renal data for SGLT2is' (pillar 1), 'Key renal outcome trials for Invokana' (pillar 2), 'Find out about the latest cardiovascular data for SGLT2is' (pillar 3) and 'Key cardiovascular outcome trials for Invokana and Vokanamet' (pillar 4). Mundibiopharma provided a copy of the virtual booth to show the layout.

Mundibiopharma submitted that although the virtual booth was almost entirely about Invokana, Vokanamet (metformin and canagliflozin) was first mentioned within the title of pillar 4.

Vokanamet was also named on slide 2 of both pillar 1 and pillar 3 downloadable as pdf slide decks respectively, along with a statement that 'Prescribing information for Invokana and Vokanamet can be found at the end of the document'.

Mundibiopharma apologised for the unintended omission of the generic name for Vokanamet as indicated by the complainant. Mundibiopharma noted that the complainant had not cited Clause 4.3, however, the location of the prescribing information was included within slide 2 of the digital material itself as per Clause 4.4 (Mundibiopharma noted that Clause 4.4 had not been referred to nor raised by the complainant) and the last 3 slides within the pdf documents for pillars 1 and 3. Mundibiopharma denied a breach of Clause 4.1.

With regard to slide 33 referred to by the complainant, Mundibiopharma submitted that that slide was one of a deck of 47 which explained renal data, and was minimally about canagliflozin. There was a total of 37 data slides, of which 8 (~22%) were about canagliflozin. Mundibiopharma submitted that the entire slide deck should be considered when judged against Clause 7. Of the data slides, the first 18 did not mention SGLT2is, being comprised of a 4-slide introduction to the burden of chronic kidney disease (slides 5-8), 5 slides on chronic kidney disease and long-term outcomes (slides 10-14), then 9-slides on the management of chronic kidney disease: data supporting the standard of care (slides 16-24). The final section presented 19 slides on the renal benefits of all SGLT2 inhibitors (slides 26-44), including 8 slides on canagliflozin. Six slides included data for dapagliflozin, 5 for empagliflozin and 1 for ertugliflozin.

Mundibiopharma submitted that whilst, as noted by the complainant, the y-axis of the graph on slide 33 was suppressed it was a faithful copy of the graph from Perkovic *et al* (2018), accessed from pillar 2 of the virtual booth. For clarity Mundibiopharma took particular attention to highlight the suppressed zero on the y-axis, which was not done in the publication, as well as highlighting the absolute difference within a bold red box. The x-axis had also been converted from weeks to years for increased clarity. Mundibiopharma submitted that the graph, as presented, gave a clear, fair, balanced view of the matter with which it dealt and did not mislead for example by its incompleteness or by use of a suppressed zero or unusual scales as set out in Clause 7.8 and its supplementary information. Mundibiopharma thus denied a breach of Clause 7.8.

Mundibiopharma submitted that as acknowledged by the complainant the presence and location of the prescribing information for Invokana and Vokanamet was highlighted on slide 2 and could be found on slides 45-47, (of the 47-slide document), on pillar 1 of the virtual booth. As this was digital material Clause 4.4 was also of relevance to its legibility, as the document was intended to be viewed online via a computer screen within an internet browser.

When viewed through an internet browser, regardless of which one was used (commonly Microsoft Internet Explorer or Google Chrome), at the default 100% zoom setting the prescribing information was easily legible. If a viewer required increased text size, this could be achieved by increasing the browser's zoom setting. Indeed, when launched within the Google Chrome browser the pdf document was viewed within the Adobe Acrobat Reader and there was clearly available zoom in ('+') and zoom out ('-') settings in the bottom right hand corner of the reader to control the magnification of the pdf document. Mundibiopharma did not consider that the prescribing information was 'extremely difficult to read' and thus in that regard, the company denied a breach of Clause 4.1.

With regard to slides 14, 15 and 16 in the 114 slide CANVAS programme slide deck within pillar 3, as referred to by the complainant, Mundibiopharma referred to its response above (a suppressed y-axis on slide 33 of pillar 1). Slides 14, 15, and 16 were exact copies from Neal *et al* (2017). The full publication was provided to be viewed by clicking on pillar 4 of the virtual booth. Mundibiopharma stated that the y-axis was correctly numbered and had not been adapted to exaggerate any effects. Indeed, additional clarity had been added by stating the mean differences between the active and placebo arm on the graphs. Mundibiopharma provided copies of the graphs as shown on the slides and as shown in Neal *et al*, for comparison. Mundibiopharma denied a breach of Clause 7.8.

With regard to slide 30, (within the 114 slide-deck), Mundibiopharma referred to its explanation above about an alleged suppressed y-axis on slide 33 of pillar 1. Slide 30 was an exact copy from the presentation of the CANVAS trial results at the American Diabetes Association (ADA) annual conference in 2017. It was clear that the y-axis had not been adapted to exaggerate the effect and so the company denied a breach of Clause 7.8. Mundibiopharma provided copies of the graphs as shown on the slide and as used in the ADA presentation for comparison.

Mundibiopharma noted that the complainant considered that because the data presented on slide 22 of pillar 3 did not reach statistical significance, it had been presented in such a way as to mislead. Mundibiopharma stated that to understand the presentation of the results on slide 22, it was important to consider the preceding slides, as they provided the background study design and statistical context of the result at issue from the canagliflozin cardiovascular outcomes trial, CANVAS. The preceding slides began by outlining the trial design (slides 3-5), and most importantly the statistical analysis plan (slides 8, 9). Mundibiopharma stated that it took particular care to provide this background so as not to mislead and to provide sufficiently complete information about the study design, so that readers could form their own opinion about the clinical data from the study, in order to be able to evaluate the therapeutic value of canagliflozin.

Mundibiopharma submitted that ideally, clinical trials should have a singular (non-composite) primary endpoint that captured the potential effect of investigational therapies. However, the use of singular end points required substantially larger trial sample sizes and/or longer follow-up to provide reliable statistical power. Composite end points were a pragmatic necessity: combining clinical outcomes that seemed to share common pathophysiological mechanisms into a composite endpoint that increased the numbers of events ascertained and thus statistical power and precision. The 3Point-Major Adverse Cardiac Events (3P-MACE) appeared to be the most appropriate endpoint for assessing cardiovascular (CV) outcomes in large cardiovascular outcome trials (CVOTs) with glucose-lowering medicines. Indeed, the cardiovascular working party of the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use expressed a preference for 3P-MACE. Nevertheless, 3P-MACE as a composite endpoint suffered from potential problems with heterogeneity of effects on the component outcomes, as the mechanism of action of a glucose-lowering medicine might differentially impact the three components of this endpoint. A single component of a composite endpoint might unduly affect the treatment outcome compared with the other components or it was possible that favourable effects on one component might offset negative effects of another. An example of this phenomenon occurred in the LEADER study, where the incidence of CV death was significantly reduced with liraglutide but not that of nonfatal myocardial infarction or nonfatal stroke. In the EMPA-REG OUTCOME study, CV death appeared to offset an increase in non-fatal stroke which appeared to manifest predominately late in the trial. For this reason, it was important to critically review the individual components of composite endpoints to determine if

treatment effects varied across different components and over time, as it stood to reason that different behaviours of components between primary composite endpoints could be interpreted differently, despite similar overall effects on 3P-MACE.

Mundibiopharma submitted that in CANVAS, there was no apparent heterogeneity in the components of the 3P-MACE and all three components contributed equally to the statistically significant primary composite endpoint. This was important information to take into consideration when assessing the potential clinical value of the impact on the primary composite endpoint. Indeed, this point was made within the Invokana SPC (Section 5.1 Cardiovascular outcomes): Slide 22 accurately captured the change in this component of the 3P-MACE over time and indicated that there was a non-significant reduction in CV death, as clearly demonstrated by the confidence interval which was shown crossing unity – as noted by the complainant. While attention could be focused on whether the prespecified measure of success for the primary outcome had been met and whether a p-value of less than 0.05 had been achieved for the difference in treatments; in reality, a more nuanced interpretation of composite primary endpoints required a thorough examination of the totality of the evidence, including secondary endpoints, safety issues, and the size and quality of the trial. The inclusion of this slide followed the recommendations that component outcomes should be analysed separately and appeared alongside the results for the overall composite endpoint to facilitate a rigorous evaluation of the results.

Mundibiopharma submitted that slide 8 clearly indicated that the CANVAS program followed a pre-specified statistical testing hierarchy, beginning with the primary composite endpoint, and slide 9 explained that because superiority for all-cause mortality was not met, that formal hypothesis testing of secondary endpoints below all-cause mortality in the testing hierarchy was discontinued from that point on. Thus, p-values were not recorded for the individual components of the primary composite endpoint and hence in slide 22 the data was presented with the confidence interval spanning unity, but no p-value was shown as a consequence of the halt to formal statistical testing.

Mundibiopharma submitted that every slide referred to the published study (Neal B *et al*, provided in full in pillar 4 of the virtual booth), if the reader wished to further understand the complete information. Exploratory outcomes were indicated beneath each graph when this was the case, as it was for slide 22 as well as the renal outcomes presented in slides 26-29. The discussion section of Neal *et al* stated: 'All three components of the primary outcome – death from– showed point estimates of effect that suggest benefit, although the individual effects did not reach significance'. Also, the concluding sentence of the paper stated: '… patients treated with canagliflozin had a significantly lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those who received placebo …'.

Mundibiopharma submitted that the data presented within the slides, including slide 22 were not inconsistent with that explained within the Invokana SPC (Section 5.1 Cardiovascular outcomes). Mundibiopharma reproduced figure 2 from Section 5.1 of the SPC.

In summary, Mundibiopharma submitted that the data provided, and in the table in the SPC, demonstrated that the point estimate was to the left of 1, favouring canagliflozin and supporting the conclusion that all the components of the primary endpoint, including CV death, contributed to the overall result. Mundibiopharma stated that it had taken great care to ensure that the statistical significance of the result was made clear and it considered, as evidenced by the complainant, that this had been done by clearly stating the confidence interval, not claiming

significance and including further explanatory notes below the graph. Mundibiopharma denied that slide 22 was in breach of Clause 7.2 or 7.3.

Mundibiopharma noted the complainant's allegations regarding slide 23 and submitted that the slide was not inconsistent with the Invokana SPC (Section 5.1 Cardiovascular outcomes): which stated:

> *'All-cause mortality*
> In the combined canagliflozin group, the hazard ratio for all-cause mortality versus placebo was 0.87 (0.74, 1.01).'

The all-cause mortality was also presented in slide 21 with sufficiently complete details on the graph that this represented 'Intention-to-treat analysis, exploratory outcome, no p-value is reported due to hierarchical testing strategy, only nominal effect estimate is given'. Mundibiopharma denied a breach of Clause 7.2 or 7.3.

Mundibiopharma noted the complainant's allegation about confidence intervals with regard to slide 27. The company submitted that as explained above, the statistical analysis plan of hierarchical testing had been provided in detail, in a consistent, fair, balanced, and non-misleading format.

Mundibiopharma asserted that it was not simply whether the confidence intervals crossed 1, but also considered the point estimate and the overall trial statistical analysis. In slide 27 this was reported beneath the graph as 'Intention-to-treat analysis. Exploratory outcome, no p-value is reported due to hierarchical testing strategy, only nominal effect estimate is given'. Mundibiopharma noted that the complainant did not state whether he/she considered the data contained within slide 27 was in breach of the Code.

With regard to the prescribing information included in the presentation, Mundibiopharma referred to its comments above about viewing the prescribing information as digital material on an internet browser. The prescribing information was not difficult to read and could easily be magnified using the zoom functions of an electronic device. The company denied a breach of Clause 4.1.

Mundibiopharma strongly disagreed with the complainant's assertion about lack of rigour and firmly believed that it had clearly demonstrated the attention and detail it took in developing the virtual booth materials in a compliant manner. The company had focussed on providing a fair, balanced and comprehensive presentation of the available information; hence the 47 slides in pillar 1, and the 114 slides within pillar 3. Furthermore, the online materials allowed specialist physicians adequate time to thoroughly read the data at their own pace and form their own opinion about it. Mundibiopharma considered that it had maintained high standards.

Mundibiopharma noted that the complainant appeared to be mainly focused on selected slides from the 114 slide-deck within pillar 3 of the virtual booth and in that regard the company noted that it was important to consider the virtual booth in its entirety, including the downloadable documents in pillars 1 and 3, which were provided in a locked pdf format and not Microsoft PowerPoint, ensuring that the content was viewed in its entirety with specific slides not able to be reproduced separately.

Mundibiopharma considered that it had demonstrated that it had paid full and due attention to both the spirit and the letter of the Code. The company denied breaches of Clause 9.1 and 2.

Mundibiopharma noted the complainant's comments to links to separate documents which he/she contended should have been certified for use and that each should have included prescribing information. In that regard, Mundibiopharma submitted that the virtual booth was a digital microsite intended to be viewed online through an internet browser. The complainant's points would be relevant in respect of hard copy printed materials eg those which might be presented by a representative during a call upon a health professional (as per Clause 4). However, the documents quoted, which were linked through pillars 2 and 4 were accessed only from within the microsite virtual booth by clicking once on each pillar. The link to the Invokana SPC (which might be provided instead of the prescribing information) on the virtual booth was clear and prominent via a direct single click. The company denied a breach of Clause 4.1 (or Clause 4.4). In addition, the materials were certified (copies of the certificates were provided) and so Mundibiopharma denied a breach of Clause 14.1.

Mundibiopharma submitted that in its response above, it had explained how it had maintained high standards at all times. The company did not consider that its activities had brought discredit upon, or reduced confidence in, the pharmaceutical industry. Mundibiopharma denied breaches of Clauses 9.1 and 2.

Following a request for further information, Mundibiopharma submitted that pillars 1 and 2 of the virtual booth were contextually linked, as were pillars 3 and 4. Mundibiopharma certified pillars 1 and 3 but did not separately certify pillars 2 and 4. Mundibiopharma noted that Clause 14.1 supplementary information stated 'Certifying Digital Material …consideration needs to be given to the context in which it appears but each possible combination does not need to be certified'.

The 'separate pages within documents' quoted by the complainant were links through pillars 2 and 4 accessed only from within the microsite virtual booth by clicking once on each pillar. Mundibiopharma submitted that it was important to consider the entire context of the microsite (the appearance of which was certified as MBL/INVK-19078c) which had a clear link to the Invokana SPC (which in Mundibiopharma's view might be provided instead of the prescribing information) via a clear and prominent direct single click. The prescribing information could be accessed within pillars 1 and 3.

Mundibiopharma stated that the context of pillar 2 was to transparently provide a reference link to a pdf of the full peer-reviewed paper published by Perkovic *et al*. The content of this paper provided full published information to support the content of pillar 1 (certified as MBL/INVK-19078a) to which it was immediately adjacent. Slide 33 within pillar 1 was from figure 1b of this paper and was the subject of an allegation by the complainant. Furthermore, by providing the reference source independent peer-reviewed paper a health professional could make their own decision whether the summary data and interpretations presented within the slides of pillar 1 were accurate, fair, balanced and capable of substantiation. Having certified pillar 1, Mundibiopharma did not separately certify this reference. Mundibiopharma submitted that as part of the preparation of the content of the microsite the signatory read Perkovic *et al* to ensure that it complied with the Code and was not inconsistent with the SPC.

Mundibiopharma submitted that the context of pillar 4 was to transparently provide a link to Neal *et al*. The content of the paper provided full published information to support the content of pillar 3 (certified as MBL/INVK-19078a), to which it was immediately adjacent.

Many of the slides of pillar 3 were derived from the data within Neal *et al* and Mundibiopharma's response to some of the complainant's allegations were answered by reference to this paper. Furthermore, by providing the reference source independent peer-reviewed paper a health professional could make their own decision that the summary data and interpretations presented within the slides of pillar 3 were accurate, fair, balanced and capable of substantiation. Having certified pillar 3, Mundibiopharma did not separately certify this reference. As the CANVAS trial data was a key paper to support Invokana, the signatory had read Neal *et al* to ensure that it was compliant with the Code and not inconsistent with the SmPC.

PANEL RULING

The Panel noted that the subject line of the email in question stated 'ISN-WCN Invokana (R) (canagliflozin) virtual booth: Get the latest data on SGLT2'. The body of the email also referred to Invokana and its mechanism of action as an SGLT2 inhibitor and invited the reader to, *inter alia*, review key cardiovascular and renal outcome data by accessing a link. Beneath this was another link titled 'Summary of Product Characteristics'. In the Panel's view, the email in question promoted Invokana.

The Panel noted the complainant's allegation that the email contained a link to the summary of product characteristics (SPC) rather than prescribing information.

The Panel noted that Clause 4.1 of the Code stated that prescribing information listed in Clause 4.2 must be provided in a clear and legible manner. Clause 4.2 listed the components of prescribing information. Failure to provide the required information listed in Clause 4.2 would be a breach of Clause 4.1. Clause 4.4 stated that in the case of digital material such as emails and suchlike, the prescribing information as required by Clause 4.1 may be provided either by inclusion in the digital material itself or by way of a clear and prominent direct single click link.

Clause 4.2 stated that the provision of prescribing information could be met by providing the SPC with the legal classification of the product and cost (excluding VAT). It further stated that cost was not required in advertisements in journals printed in the UK which had more than 15 per cent of their circulation outside the UK and audio-visual advertisements.

The Panel noted Mundibiopharma's submission that the cost of Invokana was not provided because the email in question which promoted the virtual booth was distributed across 16 European countries, including the UK, therefore there would be several different product costs. The Panel disagreed with Mundibiopharma's submission that cost was not required if more than 15 per cent of email circulation was outside the UK. In the Panel's view, the exemption for cost in the limited scenarios described in Clause 4.2 of the Code did not apply to the email in question.

The Panel considered that the link to the Invokana SPC in the email did not fulfil all the requirements of Clause 4.2 and the Panel therefore ruled a breach of Clause 4.1.

The Panel noted the complainant's allegation that the virtual booth referred to Vokanamet but the non-proprietary name (canagliflozin/metformin) was not stated and there was no prescribing information for this medicine.

The Panel noted the layout of the virtual booth. The main panel appeared to be a video about Invokana. To the right of this panel were four 'pillars' as described by Mundibiopharma. The header of the virtual booth featured the Invokana logo and the footer referred to additional resources titled 'Summary of Product Characteristics' and 'Invokana Patient Information'. The first mention of Vokanamet was in the title of pillar 4 which stated 'Key cardiovascular outcome trials for Invokana and Vokanamet'.

Clause 4.3 of the Code stated, *inter alia*, that for electronic advertisements the non-proprietary name of the medicine or the list of the active ingredients must appear immediately adjacent to the brand name at its first appearance in a size such that the information was readily readable. The Panel noted Mundibiopharma's submission that the non-proprietary name for Vokanamet was unintendedly omitted. The Panel noted that the complainant had not cited Clause 4.3 and that the case preparation manger had only asked Mundibiopharma to consider the clauses cited by the complainant. The Panel therefore made no ruling in relation to Clause 4.3 but, noting that Mundibiopharma had responded to the matter, considered it in relation to Clause 9.1. The Panel considered that the omission of the non-proprietary name for Vokanamet immediately adjacent to the brand name at its first appearance meant that Mundibiopharma had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted Mundibiopharma's submission that slide 2 of the decks downloadable from pillar 1 and pillar 3 contained the statement 'prescribing information for Invokana and Vokanamet can be found at the end of the document' and that Vokanamet prescribing information was included at the end of these two documents. The titles of pillar 1 and pillar 3 were 'Find out about the latest renal data for SGLT2is' and 'Find out about the latest cardiovascular data for SGLT2is'. In the Panel's view, it would not be sufficiently clear to a user of the virtual booth that he/she would have to click on pillar 1 or pillar 3, to download a slide-deck in order to view the Vokanamet prescribing information. However, the Panel noted the complainant's allegation that there was no prescribing information for Vokanamet on the microsite and that was not so. Based on the very narrow allegation, the Panel ruled no breach of Clause 4.1 in this regard.

The Panel noted the complainant's allegation that slide 33 of a deck titled 'Time to protect the diabetic kidney: renal outcomes in the CANVAS program', which could be downloaded from pillar 1, had 'made the outcomes look good by suppressing the y axis'.

Clause 7.8 stated, *inter alia*, that graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal. The supplementary information to this clause stated, *inter alia*, that particular care should be taken with graphs and tables to ensure that they did not mislead, for example by their incompleteness or by the use of suppressed zeros or unusual scales.

The Panel noted that the slide in question was headed 'Canagliflozin reduced the decline in eGFR compared with placebo' below which was the graph in question. The y-axis of the graph, adjusted mean eGFR, had a suppressed zero and went from 68 to 80 mL/min/1.73m^2. The x-axis, time since randomisation, went from 0 to 7 years. To the right of the graph was a prominent red box which stated that the canagliflozin vs placebo eGFR slope difference was 1.2 mL/min/1.73m^2 per year 95% CI [confidence interval] 1.0-1.4. The Panel noted Mundibiopharma's submission that the graph was a faithful copy from Perkovic *et al* 2018 and that Mundibiopharma had highlighted the suppressed zero on the y-axis which was not done in the publication. The Panel noted that irrespective of whether the graph was a faithful copy of

Perkovic *et al,* its use in promotional material had to comply with the Code. The Panel noted that the graph in Perkovic *et al* had a y-axis which went from 68 to 80 mL/min/1.73m^2 and that all plotted data in the two treatment arms were within this range. The Panel considered that the scale used in Perkovic *et al* and in the slide in question might aid the reader to analyse each data point on the graph. The Panel noted its comments above, including that the slope difference for canagliflozin vs placebo was prominently stated next to the graph within the slide in question and that the y-axis was clearly labelled, and considered that the complainant had not established that health professionals would be misled with regard to the difference between the treatment arms by virtue of a suppressed zero. No breach of Clause 7.8 was ruled.

With regard to the allegation that the prescribing information in this slide-deck was extremely difficult to read, the Panel noted that the supplementary information to Clause 4.1 of the 2016 Code listed recommendations to help achieve clarity. The Panel noted that the prescribing information at issue was on a downloadable PDF document and therefore the recommendations in the Code including legibility needed to be considered in the context of digital material. The Panel noted Mundibiopharma's submission about its legibility and that it was intended to be viewed via a computer screen within an internet browser. The Panel noted that the complainant had not explained why he/she found the prescribing information extremely difficult to read. The Panel considered that the prescribing information for Invokana and Vokanamet on the slide-deck in question was legible and no breach of Clause 4.1 was ruled.

The Panel noted the complainant's allegation that the y-axis 'was not correctly numbered, exaggerating the effect' in slides 14, 15 and 16 of a deck titled 'CANVAS program', which could be downloaded from pillar 3, and considered that the allegation was not clear. The Panel noted the complainant's subsequent statement 'Slide 30 the y axis is also suppressed' and that the complainant had alleged a breach of Clause 7.8 in each case. In the Panel's view, the subject of the allegation was that a suppressed zero in the y-axis of the graphs on slides 14, 15, 16 and 30 exaggerated the results.

The Panel noted that slides 14 to 16 featured 6 graphs which showed differences between canagliflozin and placebo in HbA1c, body weight, systolic blood pressure, diastolic blood pressure, LDL cholesterol and HDL cholesterol. Slide 30 featured a graph which showed differences between canagliflozin and placebo in change in urine albumin-to-creatinine ratio (UACR). The Panel noted Mundibiopharma's submission that the graphs on slides 14 to 16 were exact copies from the published article (Neal *et al* 2017) and that the graph in slide 30 was an exact copy from a presentation at the American Diabetes Association conference in 2017. The Panel noted that irrespective of whether the graphs were exact copies, their use in promotional material had to comply with the Code. The Panel further noted that the use of a suppressed zero was not limited to those graphs where the difference in treatment favoured canagliflozin; for example, the LDL cholesterol graph on slide 16 favoured placebo and the y-axis was from 82 to 100 mg/dl. The Panel considered that the use of a suppressed zero was not necessarily unacceptable. In each of the 7 graphs in question, the y-axis was clearly labelled, all data points were within the y-axis range and the mean difference between treatment arms and the 95% confidence interval was stated clearly within each slide. In the Panel's view, the scales used in the slides in question might aid the reader to analyse each data point on the graph. The Panel did not consider that the complainant had established, on the balance of probabilities, that the use of a suppressed zero in the graphs in question would mislead a health professional with regard to the difference between the treatment groups. The Panel therefore ruled no breach of Clause 7.8.

The Panel noted the complainant's allegation that the claim on slide 22 of the CANVAS program slide-deck 'Canagliflozin reduced risk of CV [cardiovascular] death' was in breach of Clauses 7.2 and 7.3 because the 95% confidence interval crossed 1 and the information beneath the graph 'basically states that this is a non-statistical potentially random outcome'. The complainant further stated that slide 23 which stated that canagliflozin reduced risk of mortality was similarly in breach of the Code. The complainant noted that the information on slides 22 and 23 was presented in the same way as information on another slide where the confidence intervals did not cross 1.

The Panel noted that the primary outcome measure in the CANVAS program was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Secondary outcomes planned for sequential conditional hypothesis testing included death from any cause and death from cardiovascular causes. If sequential testing was not significant for all the outcomes specified, the remaining outcomes were scheduled for assessment as exploratory variables in the integrated data set. The Panel noted that the study authors stated that significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (the composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke): HR 0.86; 95% CI, 0.75 to 0.97; $p<0.001$ for non-inferiority, $p=0.02$ for superiority. The study authors stated that superiority was not shown for the first secondary outcome in the testing sequence (death from any cause; $p=0.24$) and hypothesis testing was discontinued. Therefore, estimates for the fatal secondary outcomes, including death from any cause (HR 0.87, 95% CI, 0.74 to 1.01) and death from cardiovascular causes (HR 0.87, 95% CI, 0.72 to 1.06) were not considered to be significant.

The Panel noted Mundibiopharma's submission that slide 8 of the deck in question indicated that the CANVAS program followed a pre-specified statistical testing hierarchy, beginning with the primary composite endpoint, and slide 9 explained that because superiority for all-cause mortality was not met, that formal hypothesis testing of secondary endpoints below all-cause mortality in the testing hierarchy was discontinued from that point on. Thus, p-values were not recorded for the individual components of the primary composite endpoint.

The Panel noted the headline claim on slide 22 stated 'Canagliflozin reduced risk of CV death'. The hazard ratio (0.87) and confidence interval (0.72 to 1.06) were stated in a red box to the right of the graph. The footnote to the graph, in small font, stated, 'Intention-to-treat analysis, exploratory outcome, no p-value is reported due to hierarchical testing strategy, only nominal effect estimate is given'. The Panel noted Mundibiopharma's submission that this slide indicated that there was a non-significant reduction in cardiovascular death as the confidence interval was shown crossing unity. The Panel further noted that in the discussion section of the paper, the authors stated, 'All three components of the primary outcome – death from cardiovascular causes, nonfatal myocardial infarction, and non-fatal stroke – showed point estimates of effect that suggested benefit, although the individual effects did not reach significance'.

The Panel noted the hazard ratio and Mundibiopharma's submission that the point estimate was to the left of 1, favouring canagliflozin as illustrated in figure 2 of the Invokana SPC. The Panel considered that presenting data which did not reach statistical significance was not necessarily unacceptable, however, the presentation of such data, including claims, must not be misleading in this regard. The Panel noted that the supplementary information to Clause 7.8 under 'Artwork, Illustrations, Graphs and Tables' stated, 'Differences which do not reach statistical significance must not be presented in such a way as to mislead'.

The Panel considered the immediate and overall impression of the slide to a health professional. In the Panel's view, the headline claim 'Canagliflozin reduced risk of CV death', which was in prominent bold red font above the graph, implied that the difference between canagliflozin and placebo reached statistical significance which was not so. The 95% confidence interval stated within the slide and the footnote in small font below the graph did not negate the immediate misleading impression given by the headline claim. The Panel noted its comments above and considered that the claim 'Canagliflozin reduced risk of CV death' on slide 22 was misleading and was a misleading comparison of canagliflozin compared with placebo in this regard. The Panel ruled a breach of Clauses 7.2 and 7.3.

With regard to slide 23, the Panel noted that the headline claim, in prominent bold red font, stated, 'Canagliflozin reduced risk of mortality in both the intention-to-treat and left-truncated analyses'. The claim appeared above a table which gave the hazard ratio's and confidence intervals for all-cause mortality and cardiovascular death in the intention-to-treat and left-truncated dataset. The Panel noted its comments above about the pre-specified statistical testing hierarchy and that the results for all-cause mortality and cardiovascular death in the intention-to-treat and left-truncated analyses were not considered statistically significant. As noted above, presenting data which did not reach statistical significance was not necessarily unacceptable, however, the presentation of such data, including claims, must not be misleading in this regard. In the Panel's view, the headline claim 'Canagliflozin reduced risk of mortality in both the intention-to-treat and left-truncated analyses' implied that the difference between canagliflozin and placebo reached statistical significance which was not so, and the 95% confidence intervals and p-value in the table in the slide in question did not negate the immediate misleading impression given by the headline claim. The Panel therefore considered that the claim 'Canagliflozin reduced risk of mortality in both the intention-to-treat and left-truncated analyses' on slide 23 was misleading and was a misleading comparison of canagliflozin compared with placebo in this regard. The Panel ruled a breach of Clauses 7.2 and 7.3.

With regard to the allegation that the prescribing information in this slide deck was 'extremely difficult to read', the Panel noted that the prescribing information at issue was on a downloadable PDF document and therefore the recommendations in the Code needed to be considered in the context of digital material. The Panel noted that the complainant had not explained why he/she found the prescribing information difficult to read. The Panel considered that the prescribing information for Invokana and Vokanamet on the slide-deck in question was legible and no breach of Clause 4.1 was ruled.

With regard to the allegation that there were two links to items that did not appear to be part of the microsite and that both items required prescribing information and certification, the Panel noted Mundibiopharma's submission that the links in question were accessed by clicking once on pillars 2 and 4 within the microsite which provided a copy of Perkovic *et al* and Neal *et al,* respectively. The Panel noted Mundibiopharma's submission that pillars 1 and 2 were linked, as were pillars 3 and 4, and that the articles accessed from pillars 2 and 4 were references to support the content within pillars 1 and 3, respectively. The Panel further noted that pillars 1 and 3 were certified and that the signatory had read Perkovic *et al* and Neal *et al* to check that the articles complied with the Code and were not inconsistent with the SPC.

The Panel disagreed with Mundibiopharma's submission that certification of the articles was not required as 'each possible combination does not need to be certified' in the context of digital material as per the supplementary information to Clause 14.1. The Panel noted that the

supplementary information to Clause 14.1 of the 2019 Code stated, *inter alia*, that as the final form of digital material might not be static, consideration needs to be given to the context in which it appears, but each possible combination does not need to be certified. In the Panel's view, all promotional material required certification and the supplementary information to Clause 14.1 cited by Mundibiopharma pertained to navigation within digital material; it did not preclude any of the content from being certified. Pillars 2 and 4 were sections of the virtual booth designed to provide health professionals with access to Perkovic *et al* and Neal *et al*, respectively, and therefore the material should have been certified for such use. In the Panel's view, this was no different to a physical exhibition stand providing a reprint. The Panel ruled a breach of Clause 14.1.

With regard to prescribing information, the Panel noted its comments above including the requirements of Clauses 4.1, 4.2 and 4.4. The Panel noted Mundibiopharma's submission that there was a clear, prominent, direct single click link to the Invokana SPC on the microsite. In the Panel's view, the exemption for cost in the limited scenarios described in Clause 4.2 of the Code did not apply to the microsite in question. The Panel considered that the link to the Invokana SPC on the microsite did not fulfil all the requirements of Clause 4.2 and the Panel therefore ruled a breach of Clause 4.1.

The Panel noted its rulings of breaches of the Code and considered that Mundibiopharma had failed to maintain high standards and ruled a breach of Clause 9.1.

Clause 2 was a sign of particular censure and reserved for such use. In the particular circumstances of this case and noting that there was a link to the Invokana SPC on the microsite and that Invokana and Vokanamet prescribing information was available within two slide-decks on the microsite, the Panel ruled no breach of Clause 2.

Complaint received **26 April 2019**

Case completed **27 November 2019**