NO BREACH OF THE CODE

CASE AUTH/3427/11/20

LILLY v NOVO NORDISK

Promotional slide decks about cardiovascular outcome trials in type 2 diabetes

Eli Lilly and Company Limited complained about two slide decks produced by Novo Nordisk Ltd which provided insights from cardiovascular outcome trials in type 2 diabetes (refs UK19OZM00368 Nov 2019 and UK20DI00110 April 2020).

Novo Nordisk marketed Victoza (liraglutide) and Ozempic (semaglutide) both of which were indicated in the treatment of type 2 diabetes in certain patients.

Lilly marketed Trulicity (dulaglutide) which was similarly indicated in diabetes in adults. Liraglutide, semaglutide and dulaglutide were all glucagon-like peptide-1 receptor agonists (GLP-1RAs) an all three medicines summaries of product characteristics referred to study results with respect to effects on glycaemic control and cardiovascular events.

Lilly alleged that Novo Nordisk's presentation of a promotional slide deck to health professionals about the cardiovascular outcome trials (CVOTs) for liraglutide, semaglutide and dulaglutide represented and compared data in a way that was misleading; Novo Nordisk had chosen to ignore the generalisability of the data (or lack of) to certain patient populations.

Lilly stated that in the slide deck, the primary outcomes were presented for GLP-1 RAs' CVOTs. For the studies related to Victoza (LEADER) and Ozempic (SUSTAIN-6), the positive primary outcomes were presented without making it clear that cardiovascular benefit in those studies was confined to the sub-group of patients with established cardiovascular disease (secondary prevention).

Lilly stated that LEADER and SUSTAIN-6 had been assessed by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), and the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus report authors, who were unanimous in their views that both studies demonstrated evidence of cardiovascular benefit in patients with established cardiovascular disease (secondary prevention), but not in patients with cardiovascular risk factors (primary prevention).

Lilly further submitted that the slide deck did not encourage the rational use of Victoza and Ozempic by presenting them objectively and without exaggerating their properties.

Lilly noted that for the REWIND (Trulicity) study, the positive primary outcome was presented without making it clear that the cardiovascular benefit in REWIND extended beyond patients with established cardiovascular disease.

Lilly stated that in contrast to LEADER and SUSTAIN-6, REWIND demonstrated evidence of cardiovascular benefit in both patients with established cardiovascular disease (secondary prevention) and those with cardiovascular risk factors (primary prevention).

Lilly reiterated that the 2019 update to the joint ADA/EASD consensus report stated, 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who had not yet developed clinically manifest, or established, cardiovascular disease] was strongest for dulaglutide but lacking for other GLP-1 receptor agonists' (emphasis added).

Lilly stated that these conclusions drew a clear distinction between the cardiovascular benefit seen with Trulicity in REWIND and that of other GLP-1RAs, including Victoza and Ozempic, in a way that had been misrepresented in the slide deck. Lilly alleged that this was misleading, did not clearly reflect an up-to-date evaluation of all the evidence, and was not sufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicine.

Lilly further alleged that presenting only the primary outcomes for LEADER, SUSTAIN-6 and REWIND, particularly doing so on the same slide, inviting comparisons of the primary outcomes without making it clear that the study outcomes differed greatly in generalisability from a cardiovascular risk perspective, was incomplete, misleading and in breach of the Code.

Finally, Lilly alleged that given that the ADA/EASD consensus report, which was clear on all the points raised, was specifically referred to in the slide deck, the content of the slide deck represented a deliberate choice to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies and thus misled the audience. This represented a failure to maintain high standards in breach of the Code.

The detailed response from Novo Nordisk is given below.

The Panel noted that whilst Lilly had referred to two side decks (refs UK19OZM00368 Nov 2019 and UK20DI00110 April 2020) in the heading of its complaint, the complaint focused specifically on the slide deck titled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (ref UK19OZM00368). No specific allegations were raised in relation to the second slide deck (UK20DI00110). Novo Nordisk's response similarly focused on the first slide deck (ref UK19OZM00368). This approach was consistent with the inter-company dialogue. The Panel therefore made its rulings on slide deck titled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (ref UK19OZM00368).

The Panel noted that slide 24 of the deck in question was headed 'GLP-1RA CVOTs' above 'Primary outcomes' beneath which it stated in smaller font that direct comparisons between trials should not be made due to differences in trial design followed by 4 graphs each showing time to CV death, non-fatal MI or non-fatal stroke for Victoza (LEADER), Ozempic (SUSTAIN-6), Trulicity (REWIND), and albiglutide (HARMONY). A pop up box

which appeared on a later slide, slide 29, headed 'Beyond glycaemic control Potential mode of action for GLP-1RAs to impact cardiovascular disease' further stated 'There were significant differences in trial conduct, primary endpoints and duration of each of the CVOTs Further investigation is still required to fully explain the results from the GLP-1RA CVOTs seen to date'.

The Panel noted the details of REWIND, SUSTAIN-6 and LEADER trials including the inclusion criteria, the primary endpoint results and the various sub-group analyses.

The Panel noted Novo Nordisk's submission that none of the CVOTs (including REWIND) were designed or powered to demonstrate either safety or benefit within the specific sub-group of patients with established or high-risk cardiovascular disease and the SPCs for Victoza and Ozempic did not include data specific to those sub-populations; all data included pertained to the entire trial population. The Panel noted that Section 5.1 of the Trulicity SPC included a forest plot of analyses of individual cardiovascular event types, all cause death and consistency of effect across subgroups including prior CVD and no prior CVD for the primary endpoint. The results favoured Trulicity and were identical (hazard ratios) in both subgroups. No such differentiation between the subgroups was made in the Victoza and Ozempic SPCs.

The Panel noted Novo Nordisk's submission that Lilly had quoted an isolated statement from the 2019 American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report which had been taken out of context (page 3, third bullet point) 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who had not yet developed clinically manifest, or established, cardiovascular disease] was <u>strongest for dulaglutide but lacking for other GLP-1 receptor agonists'</u> (emphasis added). Novo Nordisk noted that this was not included in the summary table or the emboldened text or any of the figure algorithms of the publication. The algorithms referred to GLP-1RAs with proven cardiovascular disease benefit only, meaning one which had an indication for reducing cardiovascular disease events.

The Panel further noted Novo Nordisk's submission that the slide deck did not include any secondary endpoint analyses including secondary endpoints which could be seen to be more favourable within Novo Nordisk related data such as significant improvements in cardiovascular or all cause death demonstrated by Victoza in the LEADER trial but not by Trulicity in the REWIND trial. The Panel further noted Novo Nordisk's submission that those trials all recruited a population within a continuum of cardiovascular risk and the definition of primary and secondary prevention and the populations defined by the WHO as referred to by Lilly had not been applied consistently within the trials' protocols, defined sub-groups or subsequent exploratory analyses. In addition, the definition of high risk and established cardiovascular disease differed between each of the cardiovascular outcome trials.

The Panel noted that Buse *et al* detailed the 2019 Update to the Management of Hyperglycemia in Type 2 Diabetes, 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). The Panel noted that Buse *et al* stated that the REWIND trial of GLP-1RA Trulicity included a greater proportion of individuals with type 2 diabetes with high cardiovascular risk but without prior established cardiovascular disease (CVD) (68.5%) and with longer follow-up

(median 5.4 years) than prior CVOTs. The primary major adverse cardiovascular event (MACE) outcome occurred in 2.7 per 100 patient-years with a hazard ratio (HR) of 0.88 (95% CI0.79, 0.99) in favour of dulaglutide. Buse *et al* stated that there was no difference in the MACE effect in the sub populations with and without a history of CVD, although the treatment effect of Trulicity did not reach statistical significance when the groups were considered separately. Most other CVOTs with GLP-1RAs included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups. It further stated that whether the differences in outcomes in trial subgroups without established CVD were related to study details or to the assigned therapy was uncertain. It stated 'We previously recommended that established CVD was a compelling indication for treatment with a GLP-1RA or sodium–glucose co-transporter 2 (SGLT2) inhibitor. We now also suggest that to reduce risk of MACE,GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid, or lower extremity artery stenosis>50%,left ventricular hypertrophy, an estimated glomerular filtration rate (eGFR)<60 mLmin–1[1.73 m]–2, or albuminuria. To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention is strongest for Trulicity but lacking for other GLP-1 receptor agonists. Based on the studies published thus far, we believe that for patients with type 2 diabetes and established atherosclerotic CVD where MACE is the gravest threat, that the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists'

The Panel noted, that Victoza, Ozempic and Trulicity were similarly indicated and noted its comments above about the differences and similarities between the SPCs for all three medicines with respect to effects on glycaemic control and cardiovascular events.

The Panel considered that the layout of slide 24 inevitably invited comparison between the four CVOTs depicted irrespective of the subheading that direct comparisons between trials should not be made due to differences in trial design. The Panel noted, however, that the primary endpoint was shown for all the CVOT trials and that no secondary endpoints were shown for any of the trials, including data that might be described as favourable to Novo Nordisk. The Panel further noted that an overview of all the relevant national and international guidelines/consensus statement algorithms were included and no selected detailed guidance pertaining to specific use of one medicine over another was drawn out from any of these guidance documents.

Noting its comments above and the complainant's narrow allegations the Panel, on balance, did not consider that Lilly had established on the balance of probabilities that the presentation of the primary outcomes of the CVOTs for Trulicity, Ozempic and Victoza within the presentation in question was misleading, was not sufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicine or did not encourage the rational use of a medicine as alleged. No breaches of the Code were ruled. On appeal by Lilly the Appeal Board upheld the Panel's rulings of no breaches of the Code. The appeal on these points was unsuccessful.

The Panel noted Lilly's allegation that given that the ADA/EASD consensus report was specifically referred to in the slide deck, the content of the slide deck represented a deliberate choice to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies and thus misled the audience in relation to Clause 9.1. The Panel considered that its comments above applied here and, noting its no

breach rulings above, the Panel consequently ruled no breach of the Code. On appeal by Lilly the Appeal Board upheld the Panel's rulings of no breach of the Code. The appeal on this point was unsuccessful.

Eli Lilly and Company Limited complained about two slide decks produced by Novo Nordisk Ltd which provided insights from cardiovascular outcome trials in type 2 diabetes (refs UK19OZM00368 Nov 2019 and UK20DI00110 April 2020).

Novo Nordisk marketed Victoza (liraglutide) and Ozempic (semaglutide) both of which were indicated in the treatment of type 2 diabetes in certain patients. The summaries of product characteristics (SPCs) for both medicines referred to study results with respect to effects on glycaemic control and cardiovascular events.

Lilly marketed Trulicity (dulaglutide) which was similarly indicated in diabetes in adults and which also referred to study results with respect to its effects on glycaemic control and cardiovascular events in its SPC. Liraglutide, semaglutide and dulaglutide were all glucagon-like peptide-1 receptor agonists (GLP-1RAs).

COMPLAINT

Lilly alleged that Novo Nordisk's presentation of a promotional slide deck to health professionals about the cardiovascular outcome trials (CVOTs) for liraglutide, semaglutide and dulaglutide was in breach of the Code. The slide deck represented and compared data in a way that any objective interpretation of the foremost global sources of authority in diabetes would say was misleading to clinicians. Those sources of authority placed great emphasis on the generalisability of the data (or lack of) to certain patient populations, an emphasis that Novo Nordisk had chosen selectively to ignore. There was a significant risk that this had led to suboptimal and irrational treatment for a large number of diabetes patients.

Lilly alleged breaches of Clauses 7.2, 7.3, 7.10 and 9.1.

By way of background Lilly submitted that cardiovascular disease was a major cause of morbidity and mortality in type 2 diabetes but that in recent years, several glucose-lowering therapies for type 2 diabetes had shown reduction in risk of cardiovascular events (such as myocardial infarction or stroke) in cardiovascular outcome trials (CVOTs). It was important in evaluating reduction of risk of CV events to determine whether a therapy had evidence of primary prevention, secondary prevention, or both.

Lilly explained that with regard to the cardiovascular therapy area, the World Health Organization (WHO) defined primary prevention as reduction in the incidence of cardiovascular events (such as myocardial infarction or stroke) in 'people with risk factors who had not yet developed clinically manifest cardiovascular disease'. Secondary prevention was defined as a reduction in the incidence of cardiovascular events in 'people with established coronary heart disease, cerebrovascular disease or peripheral vascular disease (collectively termed [established] cardiovascular disease)'.

Lilly submitted that clarity on whether a therapy had demonstrated evidence of primary prevention and/or secondary prevention was critical for prescribers as those populations were different and the prescribing decision for individual patients would be informed by the data from the respective products' CVOTs.

Several studies had demonstrated that the proportion of a typical type 2 diabetes population that had established cardiovascular disease (secondary prevention) was about a third or less. Amongst the CVOTs for GLP-1RAs, only the Trulicity CVOT (REWIND) had demonstrated evidence of primary prevention in addition to evidence of secondary prevention.

Lilly stated that in the slide deck, the primary outcomes were presented for GLP-1RAs CVOTs. For the studies related to Victoza (LEADER) and Ozempic (SUSTAIN-6), the positive primary outcomes were presented without making it clear that cardiovascular benefit in those studies was confined to the sub-group of patients with established cardiovascular disease.

LEADER and SUSTAIN-6 had been assessed by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), and the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus report authors, who were unanimous in their views that both studies demonstrated evidence of cardiovascular benefit in patients with established cardiovascular disease (secondary prevention), but not in patients with cardiovascular risk factors (primary prevention):

- The EMA assessment report for LEADER stated, 'These data indicate that liraglutide could reduce 3-point MACE [major adverse cardiovascular events], and especially CV-death in type 2 diabetes patients with established cardiovascular disease' and noted that 'For subjects >60 years with risk factors only, no positive effect on MACE could be detected.' The EMA assessment report for Ozempic stated, 'In CVOT (sic) a number of subjects were included with risk factors 'only'. In these subjects, no effect on MACE was seen, but the numbers were too small to draw firm conclusions (10 events with semaglutide and 9 events with placebo).'

- The same conclusions were drawn by the FDA; the indications relating to reduction of cardiovascular risk in the Victoza and Ozempic US labels stated that each was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease' (emphasis added).

The study findings had also been reported in arguably the highest source of authority in diabetes care, the joint ADA and EASD consensus report, which was updated in 2019. In the updated report, it was stated, 'Most other CVOTs with GLP-1 receptor agonists [other than the dulaglutide CVOT, REWIND] had included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups.' It was concluded that, 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who had not yet developed clinically manifest, or established, CV disease] was strongest for dulaglutide but lacking for other GLP-1 receptor agonists' (emphasis added).

Lilly stated that it was clear therefore that the cardiovascular benefit demonstrated in LEADER and SUSTAIN-6 could be generalised to type 2 diabetes patients with established cardiovascular disease (secondary prevention) for whom benefit was demonstrated, but not to patients with cardiovascular risk factors (primary prevention) for whom benefit was not demonstrated.

Lilly noted that in Case AUTH/3245/9/19, related to the promotion of Ozempic, the Panel considered 'the immediate and overall impression to a health professional' of the data as

presented for the CVOT SUSTAIN-6, ruling breaches of the Code based on the material not being 'sufficiently clear', nor sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of Ozempic in terms of the claims for CV benefits'.

Lilly stated that it believed that the slide deck failed in a similar way. Lilly considered that depicting the primary outcomes from LEADER and SUSTAIN-6 without making it clear that the benefit could only be generalised to a population with established cardiovascular disease (secondary prevention), did not clearly reflect an up-to-date evaluation of all the evidence and was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicines. Lilly alleged a breach of Clause 7.2.

Lilly further submitted that the slide deck did not encourage the rational use of Victoza and Ozempic by presenting them objectively and without exaggerating their properties. A breach of Clause 7.10 was alleged.

Lilly noted that the slide deck presented the primary outcomes for GLP-1RAs' CVOTs. For the REWIND (Trulicity) study, the positive primary outcome was presented without making it clear that the cardiovascular benefit in REWIND extended beyond patients with established cardiovascular disease.

In contrast to LEADER and SUSTAIN-6, REWIND demonstrated evidence of cardiovascular benefit in both patients with established cardiovascular disease and those with cardiovascular risk factors. REWIND had also been assessed by the key regulatory and clinical sources of authority mentioned earlier, which were unanimous in their views that cardiovascular benefit in REWIND, uniquely amongst the GLP-1RAs, was demonstrated in both patients with established cardiovascular disease (secondary prevention) and those with cardiovascular risk factors (primary prevention):

The EMA included a table in the REWIND section of the Trulicity SPC showing, amongst others, the sub-group analysis conducted to determine whether there was consistent cardiovascular benefit in patients with established cardiovascular disease ('prior CVD') and those with cardiovascular risk factors ('no prior CVD'), showing 'consistency of effect across subgroups for the primary endpoint'.

The FDA drew the same conclusion; the indication relating to reduction of cardiovascular risk in the Trulicity US label stated that it was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who had <u>established cardiovascular disease or multiple cardiovascular risk factors</u> (emphasis added).'

- Lilly reiterated that the 2019 update to the joint ADA/EASD consensus report stated, 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who had not yet developed clinically manifest, or established, cardiovascular disease] was <u>strongest for dulaglutide but lacking for other GLP-1 receptor agonists'</u> (emphasis added).

Lilly stated that these conclusions drew a clear distinction between the cardiovascular benefit seen with Trulicity in REWIND and that of other GLP-1RAs, including Victoza and Ozempic, in a way that had been misrepresented in the slide deck. Lilly alleged that this was misleading, did not clearly reflect an up-to-date evaluation of all the evidence, and was not sufficiently complete

to enable recipients to form their own opinions of the therapeutic value of the medicine. Lilly alleged a breach of Clause 7.2.

Lilly further alleged that presenting only the primary outcomes for LEADER, SUSTAIN-6 and REWIND, particularly doing so on the same slide, inviting comparisons of the primary outcomes without making it clear that the study outcomes differed greatly in generalisability from a cardiovascular risk perspective, was incomplete, misleading and in breach of Clause 7.3.

Finally, Lilly alleged that given that the ADA/EASD consensus report, which was clear on all the points raised, was specifically referred to in the slide deck, the content of the slide deck represented a deliberate choice to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies and thus misled the audience. This represented a failure to maintain high standards in breach of Clause 9.1.

When writing to Novo Nordisk, the Authority asked it to consider the requirements of Clauses 7.2, 7.3, 7.10 and 9.1 of the Code.

RESPONSE

Novo Nordisk stated that the intent and purpose of the two slide decks was to provide health professionals with an introduction and overview of the primary CVOTs across a range of class of medicines for the treatment of type 2 diabetes (dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors and GLP-1RAs). The slide decks had been created to enable presentation during shorter meetings aimed at health professionals working in the treatment of type 2 diabetes. For example, a one-hour meeting at which forty minutes was spent presenting the information and twenty minutes was available for questions and discussions. The purpose of the decks was not to promote one medicine within a class over another but rather to educate the audience on the recent developments with respect to these cardiovascular outcomes.

In the slide deck UK19OZM00368, data from those trials had been placed alongside each other to decrease repetitiveness and the number of slides. However, it was clearly stated on any slides which showed data from the trials, that direct comparisons between trials should not be made due to differences in trial designs. The primary endpoint was consistently shown for all the trials and no secondary endpoints were shown. An overview of all the relevant national and international guidelines/consensus statement algorithms were included and no selected detailed guidance pertaining to specific use of one medicine over another was drawn out from any of these guidance documents. The information within the slide decks and the licensed indications for the respective Novo Nordisk medicines was in accordance with the EMA licences. Novo Nordisk submitted that it would not be appropriate to include the FDA assessments and/or therapeutic indications in the material.

Novo Nordisk maintained that the slide decks provided a fair and balanced overview of the CVOT data included. Novo Nordisk strongly disagreed with the allegation that the slide decks misrepresented the cardiovascular outcome data. Both decks complied with the Code. Novo Nordisk denied breaches of Clauses 7.2, 7.3, 7.10 and 9.1. Novo Nordisk noted that Lilly had focused on the slide deck ‘Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?’ (ref UK19OZM00368) therefore Novo Nordisk’s response was focused on that deck.

Novo Nordisk stated that none of the CVOTs (including REWIND) were designed or powered to demonstrate either safety or benefit within the specific sub-group of patients with established or high-risk cardiovascular disease. Lilly referred to the EMA assessment reports for Victoza and Ozempic, specifically statements regarding MACE endpoints in LEADER and SUSTAIN-6. None of those trials (including REWIND) had demonstrated a significant benefit in the primary Major Adverse Cardiovascular Events (MACE) outcomes. That was true in both sub-group populations (established or high-risk cardiovascular disease). Victoza, Ozempic and Trulicity had the same indication. Furthermore, the SPCs for Victoza and Ozempic did not include data specific to those sub-populations and all data included pertained to the entire trial population. The only graph pertaining to the CVOTs included within the SPCs for Victoza and Ozempic was for the primary endpoint for the full trial cohort. Therefore, the information presented in the slide deck was consistent with the SPC for both products. Novo Nordisk strongly disagreed with the assertion that not including data from exploratory analyses of the primary outcome within a selected sub-group of patients exaggerated what was presented or made the slide deck unfair, unbalanced or an inaccurate reflection of the evidence. Novo Nordisk denied breaches of Clauses 7.2. and 7.10.

Novo Nordisk also refuted the allegation that the slide deck was misleading in its presentation of the REWIND data and in breach of Clauses 7.2 or 7.3, for reasons stated above. The slide deck did not include any secondary endpoint analyses. That included secondary endpoints which could be seen to be more favourable within Novo Nordisk related data such as significant improvements in cardiovascular or all cause death demonstrated by Victoza in the LEADER trial but not by Trulicity in REWIND.

Novo Nordisk stated that furthermore, those trials all recruited a population within a continuum of cardiovascular risk. The definition of primary and secondary prevention and the populations defined by the WHO as referred to by Lilly had not been applied consistently within the trials' protocols, defined sub-groups or subsequent exploratory analyses. In addition, the definition of high risk and established cardiovascular disease differed between each of the cardiovascular outcome trials. This was why such indirect comparisons and conclusions should not be made between exploratory analyses.

Novo Nordisk noted that Lilly had quoted an isolated statement from the 2019 American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report. This had been taken out of context (page 3, third bullet point). It was not included in the summary table or the emboldened text or any of the figure algorithms of the publication. The algorithms referred to GLP-1RAs with proven cardiovascular disease benefit only, meaning one which had an indication for reducing cardiovascular disease events. This was included as part of the licensed indications for Trulicity, Victoza and Ozempic.

Novo Nordisk noted that the ADA/EASD consensus report highlighted that REWIND did not achieve statistical significance within the sub-groups and stated 'Whether the differences in outcomes in trial subgroups without established CVD were related to study details or to the assigned therapy is uncertain'. Whilst the recently updated American Diabetes Association (ADA) Standards of Medical Care in Diabetes included many of the same recommendations as the ADA/EASD consensus report, it did not include the statement or recommendation regarding the REWIND data. The slide deck focused on the summary algorithms and figures from the respective national and international guidelines. None of those guidelines included such a statement or recommendation regarding the REWIND data.

Novo Nordisk stated that it was clear that the slide deck was fair and balanced and provided clinicians with an introductory overview of cardiovascular outcome trials in patients with type 2 diabetes. For the reasons stated above the company strongly refuted that it had breached Clauses 7.2, 7.3, 7.10 of the Code. Novo Nordisk had maintained high standards and was therefore not in breach of Clause 9.1.

Novo Nordisk did not consider any elements of its response or enclosures to be confidential with the exception of the job bag certificates for each of the slide decks as these include the names of the signatories.

PANEL RULING

The Panel noted that whilst Lilly had referred to two side decks (refs UK19OZM00368 Nov 2019 and UK20DI00110 April 2020) in the heading of its complaint, the complaint focused specifically on the slide deck titled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (ref UK19OZM00368). No specific allegations were raised in relation to the second slide deck (UK20DI00110). Novo Nordisk's response similarly focused on the first slide deck (ref UK19OZM00368). This approach was consistent with the inter-company dialogue. The Panel therefore made its rulings on slide deck titled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (ref UK19OZM00368).

The Panel noted Lilly's concern that the slide deck presented the primary outcomes for GLP-1RAs' CVOTs and did not make it clear that in contrast to LEADER (Victoza study) and SUSTAIN-6 (Ozempic study) in which the benefit could only be generalised to a population with established cardiovascular disease (secondary prevention), REWIND (Trulicity study) demonstrated evidence of cardiovascular benefit in both patients with established cardiovascular disease (secondary prevention) and those with cardiovascular risk factors (primary prevention).

The Panel noted Novo Nordisk's submission that the intent and purpose of the slide deck in question was to provide health professionals with an introduction and overview of the primary CVOTs across a range of classes of medicines for the treatment of type 2 diabetes including GLP-1RAs. Its purpose was not to promote one medicine within a class over another but rather to educate the audience on the recent developments with respect to the cardiovascular outcomes.

The Panel noted that the slide deck at issue (ref UK19OZM00368) began by introducing Victoza and Ozempic and their indications. Subsequent slides sat within 5 agenda items: the link between CVD and T2D; the background and rationale for CVOTs with glucose lowering drugs; CVOT landscape and summary of key results; current scientific hypotheses for outcomes seen in these CVOTs; and impact on guidelines and further considerations.

The Panel noted that slide 24 of the deck in question was headed 'GLP-1RA CVOTs' above 'Primary outcomes' beneath which it stated in smaller font that direct comparisons between trials should not be made due to differences in trial design followed by 4 graphs each showing time to CV death, non-fatal MI or non-fatal stroke for Victoza (LEADER), Ozempic (SUSTAIN-6), Trulicity (REWIND), and albiglutide (HARMONY). A pop up box which appeared on a later slide, slide 29, headed 'Beyond glycaemic control Potential mode of action for GLP-1RAs to impact cardiovascular disease' further stated 'There were significant differences in trial conduct,

primary endpoints and duration of each of the CVOTs Further investigation is still required to fully explain the results from the GLP-1RA CVOTs seen to date'.

The Panel further noted that slide 34, headed 'Recommendations for adults with T2D', detailed that the ACC/AHA guideline 2019 recommended, *inter alia*, that 'For adults with T2D and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a SGLT-2i or a GLP-1RA to improve glycaemic control and reduce CVD risk'. The Panel noted that no specific GLP-1RA was recommended; the recommendation was classed as weak (IIb) and the level of evidence was of moderate quality (Level B-R). The Panel queried whether the meaning of class IIb evidence should have been made more prominent on the slide.

The Panel noted that in Marso *et al* (LEADER trial) patients with type 2 diabetes who were at high risk for cardiovascular disease were randomly assigned, in a 1:1 ratio, to receive liraglutide or placebo. The major inclusion criteria were an age of 50 years or more with at least one cardiovascular coexisting condition or an age of 60 years or more with at least one cardiovascular risk factor, as determined by the investigator. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke. Pre-specified analyses of subgroups included the risk of CVD in two subgroups:

- Patients ≥ 50 years with established CVD (n=7598), hazard ratio 0.83 (95% CI: 0.74-0.93) favouring liraglutide
- Patients ≥ 60 Years and risk factors for CVD (n=1742), hazard ratio 1.20 (95% CI: 0.86-1.67) favouring placebo.

The results section referred to the benefit of those with cardiovascular disease at baseline. Overall, Marso *et al* concluded that among patients with type 2 diabetes, who were at high risk for cardiovascular events while they were taking standard therapy, those in the liraglutide group had lower rates of cardiovascular events and death from any cause than did those in the placebo group.

The Panel noted that the EMA assessment report for LEADER stated that pre-specified exploratory analyses were performed to evaluate the consistency of the treatment effect between liraglutide and placebo in time to first MACE across multiple subgroups. It stated that interpretation of these should be made with caution as the study was not powered to detect small or moderate differences in treatment effect between subgroups and because adjustments for multiplicity were not made. It further stated that a potential difference in treatment effect between cardiovascular risk subgroups was indicated (p=0.04), albeit the risk for false significance (type 1 error) as a result of multiple testing should be kept in mind and that the potential differential effect between cardiovascular risk subgroups could not be explained by differences in other subject characteristics, concomitant medication or exposure to trial drug between the two subgroups. In addition, post hoc 'on-treatment' sensitivity analyses in subjects ≥60 years with only risk factors for cardiovascular disease did not show an increased hazard ratio compared to the primary subgroup analysis, as would be expected if treatment with liraglutide was associated with cardiovascular harm in this subgroup. Further, there was no evidence that the treatment effect of liraglutide for changes in HbA1c, body weight and SBP differed between the cardiovascular risk subgroups. Moreover, the difference in hazard ratios observed for first MACE between the cardiovascular risk subgroups could not be explained by a potential heterogeneous treatment effect across the covariates included in a post hoc sensitivity

analysis using a backward elimination technique. Exploratory post hoc analyses by medical history of MACE (specified as non-fatal MI or non-fatal stroke) were performed to investigate whether the observed difference between the cardiovascular risk subgroups was driven by differences related to previous occurrence of MACE. These analyses resulted in hazard ratios favouring liraglutide, both for subjects with a history of MACE (0.84 [0.72; 0.97]95% CI) and for subjects without a previous MACE (0.89 [0.76; 1.05]95% CI), thus supporting benefits of liraglutide in both primary and secondary prevention of cardiovascular disease. Consequently, the most plausible explanation for the observed difference is believed to be related to uncertainties associated with the estimate, as the subgroup of subjects aged ≥60 years with only risk factors for cardiovascular disease accounted for a relatively small proportion of the total trial population (~20%) and MACEs (~10%) observed in the trial.

The Panel noted that in Marso *et al* (SUSTAIN-6 trial), 3297 patients with type 2 diabetes who were on a standard-care regimen were randomly assigned to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. Key inclusion criteria were an age of 50 years or more with established cardiovascular disease or an age of 60 years or more with at least one cardiovascular risk factor. At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both and 17% of patients had cardiovascular risk factors and were 60 years or older. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome was evaluated in sub-groups according to demographic and disease measures at baseline. The trial was not powered to show superiority. Marso *et al* concluded that in patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the non-inferiority of semaglutide.

The Panel noted that in Gerstein *et al* (REWIND trial) men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1.5mg) or placebo. The trial was powered to test superiority and its primary endpoint was the first occurrence of any component of the composite outcome, which comprised non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown cause. It appeared that patients aged 50 years or older had to have vascular disease (ie a previous myocardial infarction, ischaemic stroke, revascularisation, hospital admission for unstable angina, or imaging evidence of myocardial ischaemia); those aged 55 years or older had to have myocardial ischaemia, coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73m², or albuminuria; and those aged 60 years or older had to have at least two of tobacco use, dyslipidaemia, hypertension, or abdominal obesity. When assessed within predefined subgroups the hazard ratio of the intervention on the primary outcome was similar in participants with (31.5%) and without previous cardiovascular disease. Gerstein *et al* stated that most of the participants in REWIND did not have previous cardiovascular disease or a previous cardiovascular event and the broad inclusion criteria, high proportion of women, and the representativeness of the recruited participants in REWIND suggested that dulaglutide **might** be effective for both primary and secondary cardiovascular prevention in a high proportion of people with type 2 diabetes.

The Panel noted Novo Nordisk's submission that none of the CVOTs (including REWIND) were designed or powered to demonstrate either safety or benefit within the specific sub-group of

patients with established or high-risk cardiovascular disease and the SPCs for Victoza and Ozempic did not include data specific to those sub-populations; all data included pertained to the entire trial population. The Panel noted that Section 5.1 of the Trulicity SPC included a forest plot of analyses of individual cardiovascular event types, all cause death and consistency of effect across subgroups including prior CVD and no prior CVD for the primary endpoint. The results favoured Trulicity and were identical (hazard ratios) in both subgroups. No such differentiation between the subgroups was made in the Victoza and Ozempic SPCs.

The Panel noted Novo Nordisk's submission that Lilly had quoted an isolated statement from the 2019 American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report which had been taken out of context (page 3, third bullet point) 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who had not yet developed clinically manifest, or established, cardiovascular disease] was strongest for dulaglutide but lacking for other GLP-1 receptor agonists' (emphasis added). Novo Nordisk noted that this was not included in the summary table or the emboldened text or any of the figure algorithms of the publication. The algorithms referred to GLP-1RAs with proven cardiovascular disease benefit only, meaning one which had an indication for reducing cardiovascular disease events.

The Panel further noted Novo Nordisk's submission that the slide deck did not include any secondary endpoint analyses including secondary endpoints which could be seen to be more favourable within Novo Nordisk related data such as significant improvements in cardiovascular or all cause death demonstrated by Victoza in the LEADER trial but not by Trulicity in the REWIND trial. The Panel further noted Novo Nordisk's submission that those trials all recruited a population within a continuum of cardiovascular risk and the definition of primary and secondary prevention and the populations defined by the WHO as referred to by Lilly had not been applied consistently within the trials' protocols, defined sub-groups or subsequent exploratory analyses. In addition, the definition of high risk and established cardiovascular disease differed between each of the cardiovascular outcome trials.

The Panel noted that Buse *et al* detailed the 2019 Update to the Management of Hyperglycemia in Type 2 Diabetes, 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). The Panel noted that Buse *et al* stated that the REWIND trial of the GLP-1RA Trulicity included a greater proportion of individuals with type 2 diabetes with high cardiovascular risk but without prior established cardiovascular disease (CVD) (68.5%) and with longer follow-up (median 5.4 years) than prior CVOTs. The primary major adverse cardiovascular event (MACE) outcome occurred in 2.7 per 100 patient-years with a hazard ratio (HR) of 0.88 (95% CI0.79, 0.99) in favour of dulaglutide. Buse *et al* stated that there was no difference in the MACE effect in the sub populations with and without a history of CVD, although the treatment effect of Trulicity did not reach statistical significance when the groups were considered separately. Most other CVOTs with GLP-1RAs included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups. It further stated that whether the differences in outcomes in trial subgroups without established CVD were related to study details or to the assigned therapy was uncertain. It stated 'We previously recommended that established CVD was a compelling indication for treatment with a GLP-1 receptor agonist or sodium–glucose co-transporter 2 (SGLT2) inhibitor. We now also suggest that to reduce risk of MACE,GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid, or lower extremity artery stenosis>50%,left ventricular hypertrophy, an estimated

glomerular filtration rate (eGFR)<60 mLmin–1[1.73 m]–2, or albuminuria'. 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention is strongest for Trulicity but lacking for other GLP-1 receptor agonists'. Based on the studies published thus far, we believe that for patients with type 2 diabetes and established atherosclerotic CVD where MACE is the gravest threat, that the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.

The Panel noted, that Victoza, Ozempic and Trulicity were similarly indicated and noted its comments above about the differences and similarities between the summaries of product characteristics (SPCs) for all three medicines with respect to effects on glycaemic control and cardiovascular events.

The Panel considered that the layout of slide 24 inevitably invited comparison between the four CVOTs depicted irrespective of the subheading that direct comparisons between trials should not be made due to differences in trial design. The Panel queried whether that subheading ought to have been more prominent to balance the immediate visual impression of comparability and similarity between the primary outcomes in the trials depicted. The Panel did not know how the slide would be described when presented and noted Novo Nordisk's submission that there would normally be 20 minutes discussion at the end of the presentation. The Panel noted, however, that the primary endpoint was shown for all the CVOT trials and that no secondary endpoints were shown for any of the trials, including data that might be described as favourable to Novo Nordisk. The Panel further noted that an overview of all the relevant national and international guidelines/consensus statement algorithms were included and no selected detailed guidance pertaining to specific use of one medicine over another was drawn out from any of these guidance documents.

Noting its comments above and the complainant's narrow allegations the Panel, on balance, did not consider that Lilly had established on the balance of probabilities that the presentation of the primary outcomes of the CVOTs for Trulicity, Ozempic and Victoza within the presentation in question was misleading, was not sufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicine or did not encourage the rational use of a medicine as alleged. No breach of Clauses 7.2, 7.3 and 7.10 was ruled.

The Panel noted Lilly's allegation that given that the ADA/EASD consensus report was specifically referred to in the slide deck, the content of the slide deck represented a deliberate choice to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies and thus misled the audience in relation to Clause 9.1. The Panel considered that its comments above applied here and, noting its no breach rulings above, the Panel consequently ruled no breach of Clause 9.1.

Appeal Board of 18 January 2022

APPEAL FROM LILLY

Lilly appealed all of the Panel's rulings, maintaining that the combined Novo Nordisk slide deck was misleading, insufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicines presented and did not encourage the rational use of the medicines, in breach of Clauses 7.2, 7.3, and 7.10. of the Code. Lilly further maintained that deliberate omission of key statements from the updated ADA/EASD consensus report represented a failure to maintain high standards, in breach of Clause 9.1. of the Code.

Summary

Lilly stated that Novo Nordisk had presented slide decks UK19OZM00368 Nov 2019 and UK20DI00110 April 2020 as a combined deck and it was the combined deck that was the subject of its complaint. The combined deck was clearly a promotional deck that was intended to highlight the cardiovascular (CV) benefit data seen with GLP-1RAs in CV outcome trials (CVOTs), and their resulting favourable positioning in guidelines, in particular the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus report.

What was misleading in the deck was that:

- CVOTs differed in terms of study design and populations, so it was not appropriate to directly compare study outcomes (such as glucose lowering, weight loss, CV hazard ratios) between studies. The primary outcome data for GLP-1 RAs was presented side-by-side in the deck on slides 24 and 25 of UK19OZM00368 Nov 2019, creating an immediate and overall, but misleading, impression to health care professionals regarding the different therapies' potency in reducing CV risk. Slide 25, which was not from a published meta-analysis but rather created by Novo Nordisk, depicted the Novo Nordisk product semaglutide as having a hazard ratio far to the left (favouring treatment over placebo) of the other therapies (albiglutide was no longer commercially available), encouraging the audience to draw inaccurate conclusions in favour of semaglutide. Lilly alleged that a subheading 'Direct comparisons between trials should not be made due to differences in trial design' was insufficient to reverse the misleading impression created.

- Lilly submitted that it was appropriate, and of great clinical importance, to analyse CV risk sub-analyses from individual CVOTs to determine whether they showed evidence of primary CV prevention, secondary CV prevention, or both. LEADER (liraglutide), SUSTAIN 6 (semaglutide) and REWIND (dulaglutide) had been assessed by the European Medicines Agency (EMA), the Food and Drug Administration (FDA), and the ADA/EASD consensus report authors, who were unanimous in their views that REWIND, but not LEADER or SUSTAIN 6, demonstrated evidence of CV benefit not only in patients with established CV disease (secondary prevention), but also in patients with CV risk factors (primary prevention). This was a critical point of distinction in favour of dulaglutide, and the slide deck was silent on that distinction, despite using the ADA/EASD consensus report as the key source of authority in the combined slide deck. The need to be clear that unlike dulaglutide, neither liraglutide nor semaglutide had demonstrated CV primary prevention benefit was an important point of principle that applied to materials beyond just the slide deck in question.

Lilly stated that Novo Nordisk's response had created confusion regarding the nature of the slide deck and in particular, interpretation of CVOTs. The company's interpretation of the CVOTs in question was scientifically unsound and was clearly in conflict with that of the EMA, FDA and ADA/EASD consensus report.

Lilly maintained that, for all the reasons cited above, the slide deck was incomplete and deliberately misleading and in breach of Clauses 7.2, 7.3, 7.10, and 9.1. of the Code.

Key Panel decisions with which Lilly disagreed

Lilly stated that it was not clear from the Panel rulings whether 'noting' of submissions made by Novo Nordisk signalled the Panel's agreement but given that the Panel had not stated disagreement with any of the submissions noted and had ruled in favour of Novo Nordisk on all counts, assumed that the Panel had accepted Novo Nordisk's submissions.

1. The Panel wrongfully excluded the UK20DI00110 April 2020 component of the slide deck from their deliberations despite its clear relevance to the complaint

Lilly submitted that Novo Nordisk had sponsored at least one presentation that combined slide decks UK19OZM00368 Nov 2019 and UK20DI00110 April 2020, entitled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' It was the combined slide deck with that title that had been the subject of Lilly's complaint. The company stated that all its correspondence on the matter having been headed 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' slide deck (UK19OZM00368 Nov 2019 and UK20DI00110 April 2020)'.

A presentation that used the combined deck and which Lilly attended was delivered on 25 April 2020 (copy provided). Lilly did not mention this specific presentation in the original correspondence as Lilly expected that Novo Nordisk would be clear that the challenge was to the combined deck (given that they had used the combined deck in presentations, and the headings in the company's correspondence used 'slide deck' in the singular and included both the UK19OZM00368 Nov 2019 and UK20DI00110 April 2020 components) and did not anticipate that Novo Nordisk, and hence the Panel, would choose to focus their response exclusively on the UK19OZM00368 Nov 2019 component.

As outlined in its correspondence, Lilly stated that the basis for its allegation that the combined slide deck represented a failure to maintain high standards in breach of Clause 9.1 of the Code was, '**given that the ADA/EASD consensus report, which is clear on all the points raised, is specifically referred to in the slide deck, the content of the slide deck represents a deliberate choice to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies and thus mislead the audience."**

The component comprising slide deck UK20DI00110 April 2020 consisted of over 20 slides that focussed on the 2018 ADA/EASD consensus report and its 2019 update. The 2019 update was clear on the generalisability of the REWIND benefit data, but not the LEADER and SUSTAIN 6 data, to include a primary prevention CV population. Failing to mention this critical point of differentiation anywhere in a combined slide deck that included over 20 slides on the consensus report represented a deliberate choice by Novo Nordisk to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies.

Considering the above, Lilly had expected that the Panel would see the relevance to its complaint of the UK20DI00110 April 2020 component of the slide deck but recognised that in light of Novo Nordisk, and hence the Panel, choosing to focus their response exclusively on the UK19OZM00368 Nov 2019 component, additional context as to why the UK20DI00110 April 2020 component was relevant would be helpful. The 2018 ADA/EASD consensus report included all the LEADER and SUSTAIN 6 data, and restricted recommendations for GLP-1RA use after metformin to patients with established CV disease (secondary prevention). As slide 7 of UK20DI00110 April 2020 made clear, REWIND was the only new GLP-1RA CVOT contributing to the 2019 update (the others mentioned were SGLT2 inhibitor studies). As slide 18 of UK20DI00110 April 2020 made clear, the 2019 update extended the recommendations for

GLP-1RA use after metformin beyond established CV disease to include patients with specific indicators of high CV risk (primary prevention). This extension was based on REWIND, with the age criterion and specific indicators of high CV risk depicted on slides 19 and 20 of UK20DI00110 April 2020 having been taken directly from the REWIND protocol.[1] (Gerstein HC *et al*, Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394 (10193):121-130).

Novo Nordisk sought to derive benefit for its products by mentioning the extension to the recommendations for GLP-1RAs in the ADA/EASD consensus report, whilst deliberately choosing to not mention that the extension was based entirely on REWIND data, despite both the context and content of the 2019 update making that distinction clear.

2. The Panel wrongfully assessed the combined slide deck as educational rather than promotional

Lilly alleged that the slide deck was clearly promotional in nature. The first slide indicated that prescribing information was available at the meeting and the indications for liraglutide and semaglutide were included on slides 3 and 4 of UK19OZM00368 Nov 2019. Including educational content was a sine qua non of presentations conducted in line with the Code and did not thereby make the presentation intrinsically non-promotional.

Lilly alleged that it was inconceivable that Novo Nordisk would be presenting a talk on CVOTs in type 2 diabetes if its own therapies had not shown evidence of CV benefit. At its core, the combined slide deck was drawing attention, in a promotional context, to the CV benefits of GLP-1RAs, including liraglutide and semaglutide, and the resulting favourable positioning of GLP-1RAs in guidelines. Lilly maintained that Novo Nordisk had done so in a way that misled by not being clear on the generalisability of the REWIND benefit data, but not the LEADER and SUSTAIN 6 data, to include a primary prevention CV population.

3. The Panel interpreted the CV risk sub-analyses from the CVOTs incorrectly

Lilly stated that it specifically avoided an in-depth analysis of how CVOTs were interpreted, as the EMA, FDA and ADA/EASD consensus report had independently analysed the CVOTs in question to determine whether they showed evidence of primary CV prevention, secondary CV prevention, or both, concluding that REWIND, but not LEADER or SUSTAIN 6, demonstrated evidence of CV benefit not only in patients with established CV disease (secondary prevention), but also in patients with CV risk factors (primary prevention). Lilly had expected that citing these three key sources of authority would be sufficient to make its case, but as the Panel appeared to have conducted its own analysis, guided by Novo Nordisk's scientifically unsound interpretation of the CVOTs in question, Eli Lilly recognised that a detailed exposition of how the CVOTs were interpreted by the EMA, FDA and ADA/EASD consensus report would be helpful.

Whilst it was not appropriate to compare study outcomes (such as glucose lowering, weight loss, CV hazard ratios) between CVOTs, what was appropriate, and of great clinical importance, was to analyse CV risk sub-analyses from individual CVOTs to determine whether they showed evidence of primary CV prevention, secondary CV prevention, or both.

Novo Nordisk appeared to believe that to conclude that REWIND demonstrated evidence of benefit in patients with established CV disease, or those with CV risk factors, statistical

significance would need to have been demonstrated within those specific CV risk sub-groups. This was a fundamental misunderstanding of how CVOTs and the CV risk subgroup analyses were interpreted. In the analysis of intervention studies, it was often important to investigate whether treatment effects vary among subgroups of patients defined by individual characteristics. This was generally best done by using tests for interaction. If the subgroups were sufficiently large to allow a valid interaction analysis to be performed and if the test for interaction was not statistically significant, it signified that there was a consistent effect seen among the subgroups being analysed. As an example, in REWIND, the p value for the sex subgroup interaction analysis was 0.60,[1] (Gerstein HC et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394 (10193):121-130.) signifying that there was consistent benefit seen between males and females. Statistical significance was not achieved within each subgroup of males or females, but that was irrelevant as the study was powered for the total population rather than for men or women individually. Given that the overall study was positive, that there were sufficient numbers of both men and women to support a valid interaction analysis, and that there was consistent benefit seen between men and women, one would conclude that <u>both groups benefited</u> ie dulaglutide demonstrated CV benefit in both men and women in REWIND. If one were to interpret these data as Novo Nordisk was suggesting, one would have to conclude that neither men nor women derived benefit in a study that demonstrated benefit in the overall population, raising the intriguing question of who exactly did benefit. **The purpose of the forest plots in the REWIND section of the dulaglutide SPC (Section 5.1, Figure 2) showing 'consistency of effect across subgroups for the primary endpoint' was to make the point, *inter alia*, that there was consistent CV benefit in patients with established CV disease ('prior CVD') and those with CV risk factors ('no prior CVD'), ie both groups benefited** (Trulicity (dulaglutide) SPC).

In contrast, as concluded by the ADA/EASD consensus report, 'Most other CVOTs with GLP-1 receptor agonists [other than the dulaglutide CVOT, REWIND] had included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups (emphasis added)' (Buse JB, *et al* 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2019; https://doi.org/10.2337/dci19-0066.) What the ADA/EASD consensus report was concluding, like the EMA assessment reports and the FDA, was that neither liraglutide nor semaglutide demonstrated evidence of CV benefit in patients with CV risk factors (the primary prevention population) in LEADER and SUSTAIN 6. As the consensus report pointed out, the numbers of patients in the primary prevention subgroups in LEADER and SUSTAIN 6 were small, so the findings represent 'absence of evidence' of primary prevention benefit, rather than 'evidence of absence' of effect. In other words, it was unknown what the effects of those therapies would be in a primary prevention population. In contrasting the primary CV prevention benefit seen in REWIND, but not LEADER or SUSTAIN 6, the ADA/EASD consensus report stated, 'Whether the differences in outcomes in trial subgroups without established CVD were related to study details or to the assigned therapy was uncertain' (Buse *et al*) 2019. In other words, the differences seen in primary prevention benefit between the studies, which was the crux of this matter, could be due **either** to differences in the study populations **or** differences between the pharmacological effects of the therapies. The ADA/EASD consensus report concluded, 'To date, the level of evidence to support the use of GLP-1 receptor agonists for primary prevention [ie people with risk factors who have not yet developed clinically manifest, or established, CV disease] <u>is strongest for dulaglutide but lacking for other GLP-1 receptor agonists</u>' (emphasis added).

4. The Panel wrongfully assessed the algorithm in the ADA/EASD Consensus Report as assuming equivalence between those GLP-1 RAs with an indication for reducing CV events

Lilly submitted that Novo Nordisk pointed out that Figure 1 in the ADA/EASD consensus report recommended that any GLP-1RA with a label indication of reducing CVD events should be considered but neglected to mention what the product labels specifically said in that regard.

All the CV benefits of glucose lowering therapies, including the GLP-1RAs, were implicit in the EU labels (as opposed to the US labels, where agents with evidence of CV benefit were explicitly indicated for reduction of CV risk). In the EU labels, all of liraglutide, semaglutide and dulaglutide were indicated for 'the treatment of adults with insufficiently controlled type 2 diabetes mellitus' (intended to encompass both glucose lowering and CV benefits), with all their SPCs stating, in section 4.1, 'For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.' Differences in generalisability of the CV benefit data of the three therapies were also implicit in the EU labels, with the differences captured in sections 5.1. Section 5.1 of the Trulicity (dulaglutide) SPC but not the Victoza (liraglutide) SPC) or (Ozempic (semaglutide) SPC) contained a series of forest plots (Figure 2) showing 'consistency of effect across subgroups [including the primary and secondary prevention CV risk subgroups] for the primary endpoint'. The absence of these sub-analysis data from the liraglutide and semaglutide SPCs reflected the fact that neither of those therapies, as made explicit by the EMA assessment reports, FDA and ADA/EASD consensus report, had demonstrated CV benefit in a primary CV prevention population. The fact that the CV benefits of glucose lowering therapies were implicit in the EU labels, making them much less clear than the US labels, did not change the EMA's interpretation of the respective CVOTs, or their intent with respect to how the differences between the therapies were captured in the product labels.

The FDA labels were explicit, with the liraglutide and semaglutide US labels stating that each was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (emphasis added)', whilst the indication relating to reduction of CV risk in the dulaglutide US label stated that it was, 'indicated … to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who had established cardiovascular disease or multiple cardiovascular risk factors (emphasis added).

In conclusion, Lilly maintained its position that the combined Novo Nordisk slide deck was misleading, was insufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicines presented and did not encourage the rational use of the medicines, in breaches of Clauses 7.2, 7.3, and 7.10. of the Code. Lilly further maintained that deliberate omission of key statements from the ADA/EASD consensus report represented a failure to maintain high standards, in breach of Clause 9.1 of the Code.

RESPONSE FROM NOVO NORDISK

Novo Nordisk submitted that as previously stated, it was fully committed to finding resolution through intercompany dialogue (ICD). Novo Nordisk updated deck UK19OZM00368 and committed to other changes when presenting the data. It was disappointing that a satisfactory resolution could not be reached.

Novo Nordisk's response throughout intercompany dialogue and to the letter of complaint via the PMCPA had focussed on both slide decks (UK19OZM00368 and UK20DI00110). Novo Nordisk submitted that its response to the Panel was transparent throughout, as was Novo Nordisk's response to Lilly throughout the several rounds of intercompany dialogue. Novo Nordisk disagreed with the comment that 'the decks are intended to highlight the cardiovascular (CV) benefit data seen with GLP-1 receptor agonists (RAs) in CV outcome trials (CVOTs), and their resulting favourable positioning in guidelines'. The content of the slide decks covered the evidence of recent cardiovascular data for different classes of medicines and similarly the ADA/EASD consensus paper covered the recommendation for all classes of medicines based on holistic review of patient needs (cardiovascular/ hypoglycaemia, weight, and cost) (Gerstein HC *et al* 2019.). Additionally, Novo Nordisk agreed that promotional presentations should equally remain educational and balanced. Novo Nordisk submitted that both slide decks fulfilled these requirements.

As previously stated in the intercompany dialogue with Lilly and Novo Nordisk's letter to the PMCPA on 7 December 2020, the purpose of the slide deck UK19OZM00368 was to provide clinicians with an overview summary of the CVOTs, focusing on primary endpoints of the trials only, and how the CVOTs had impacted international guidelines. The primary endpoint was consistently shown for all the trials and no secondary or exploratory endpoints were presented. The intent and purpose of this slide deck was not to promote the use of one GLP-1RA over another, but rather to be used by expert health professionals to educate the audience on the recent developments with respect to cardiovascular outcomes in a peer-to-peer manner. In addition, it was clearly stated on the slides that direct comparisons between trials should not be made due to differences in trial designs. Novo Nordisk also agreed to amend the deck and include the baseline characteristics for participants in these trials to point out the differences between trials. A pop-up box which appeared on slide 29 headed 'Beyond glycaemic control Potential mode of action for GLP-1RAs to impact cardiovascular disease' states; 'There were significant differences in trial conduct, primary endpoints and duration of each of the CVOTs. Further investigation was still required to fully explain the results from the GLP-1RA CVOTs seen to date'.

Novo Nordisk maintained the view that all cardiovascular outcome trials (including REWIND) were designed or powered to demonstrate the safety and efficacy for the primary end point of time to the first occurrence of composite MACE in the full study cohort and not powered to make conclusions on individual patient sub-groups. More importantly the SPCs were consistent across these medications without any distinct specification of primary or secondary cardiovascular prevention. Lilly referred to the FDA labels for liraglutide, subcutaneous semaglutide and dulaglutide. This was irrelevant, the FDA did not have jurisdiction as a UK regulator. The information provided in the slide deck was consistent with the SPCs for both products, liraglutide and subcutaneous semaglutide.

The ADA/EASD consensus guideline 2018/2019, which was the focus of slide deck UK20DI00110, did not specify any particular GLP1-RA to be recommended (Gerstein HC *et al* 2019). Lilly had requested Novo Nordisk to single out an isolated statement from the publication, which was not included in the summary table or the bolded text or any of the figure algorithms of the publication. In fact, the ADA/EASD consensus report highlighted that the REWIND trial did not achieve statistical significance within the sub-groups and stated; 'Whether the differences in outcomes in trial subgroups without established CVD are related to study

details or to the assigned therapy is uncertain.' Therefore, Novo Nordisk did not understand why it was being asked to include a statement of this kind.

In conclusion, Novo Nordisk supported the Panel's decision of no breach of Clauses 7.2, 7.3, 7.10 and 9.1 of the 2019 Code. Novo Nordisk was categorically clear that both decks provided a fair and balanced overview of the cardiovascular outcome trial data included. Novo Nordisk strongly disagreed with the continued allegation that Novo Nordisk was misrepresenting the cardiovascular outcome data and that its slide decks were insufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicines presented.

FINAL COMMENTS FROM LILLY

Lilly submitted that Novo Nordisk's response continued to offer no satisfactory response to its concerns. Lilly therefore maintained its position on all points.

APPEAL BOARD RULING - 18 January 2022

The Appeal Board made rulings in relation to Lilly's appeal.

Following the Appeal Board meeting of 18 January it was determined, after the parties were asked for submissions on a procedural point identified by the PMCPA, that the Appeal Board had made a procedural error in relation to its consideration of the appeal of the Panel's rulings of no breach of Clauses 7.2, 7.3 and 9.1. The Appeal Board had ruled on a matter that was not the subject of intercompany dialogue or one ruled upon by the Panel in its consideration of the alleged breaches of Clauses 7.2, 7.3 and 9.1. An independent referee upheld that decision. It followed that the Appeal Board's decision on 18 January 2022 in relation to Clauses 7.2, 7.3 and 9.1 was set aside and had no effect.

The Appeal Board's decision on 18 January 2022 in relation to Lilly's appeal of the Panel ruling of no breach of Clause 7.10 was not covered by the procedural error and remained. That decision is set out below.

The Appeal Board noted that the Panel made its rulings in relation to the slide deck titled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (ref UK19OZM00368) because in the Panel's view, whilst Lilly had referred to two slide decks in the heading of its complaint, the complaint focused specifically on the first slide deck (ref UK19OZM00368) and no specific allegations were raised in relation to the second slide deck (ref UK20DI00110). The Appeal Board noted in its original response to the Panel Novo Nordisk submitted that Lilly had focused on the slide deck 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (UK19OZM00368) and therefore its response was focused on that deck.

Both Lilly and Novo Nordisk contrary to its submission to the Panel submitted at appeal that the case concerned both slide decks and thus the Appeal Board considered the appeal on that basis. The Appeal Board noted that at appeal, Lilly had provided further particulars in this regard including that Novo Nordisk had sponsored at least one presentation entitled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' that combined slide decks UK19OZM00368 Nov 2019 and UK20DI00110 April 2020, and it was the combined slide deck with that same title that had been the subject of Lilly's original complaint. No combined slide deck was provided either to the Panel or to the Appeal Board. The Appeal Board further

noted that at appeal, Lilly had also provided details with regard to the relevance of the second slide deck (ref UK20DI00110 April 2020) to its complaint including that it consisted of over 20 slides that focussed on the 2018 ADA/EASD consensus report and its 2019 update; the deliberate omission of key statements from the updated ADA/EASD consensus report was the basis of Lilly's allegation that the combined slide deck represented a failure to maintain high standards.

Novo Nordisk's position at appeal was clearly that both slide decks were promotional and their content was educational. The Appeal Board agreed that the slides were promotional. The Panel had not specifically commented on this point and appeared to consider the slide decks to be promotional, there was no comment or implication that the Panel considered that the slide decks were not promotional.

Novo Nordisk had agreed during intercompany dialogue to withdraw the 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' slide deck and include a slide which represented the difference in trial participants' baseline CV risk characteristics whenever LEADER, SUSTAIN-6 and REWIND trials were presented alongside each other in any future relevant materials.

The Appeal Board noted that the slide deck (ref UK19OZM00368) began by introducing Victoza and Ozempic and their indications. Subsequent slides sat within 5 agenda items: the link between CVD and T2D; the background and rationale for CVOTs with glucose lowering drugs; CVOT landscape and summary of key results; current scientific hypotheses for outcomes seen in these CVOTs; and impact on guidelines and further considerations.

The Appeal Board noted that the slide (slide 19) immediately before the section of the agenda 'CVOT landscape and summary of key results' which included the cardiovascular outcome trial comparisons at issue was titled 'CVOTs in patients with type 2 diabetes' and set out the trial name, n number and duration of the various cardiovascular outcome trials involving insulin, GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium–glucose cotransporter-2 inhibitors (SGLT-2is) set against a timeline of when each was conducted. The Appeal Board further noted that a pop-up box which appeared on a later slide, slide 29, headed 'Beyond glycaemic control Potential mode of action for GLP-1RAs to impact cardiovascular disease' further stated 'There were significant differences in trial conduct, primary endpoints and duration of each of the CVOTs. Further investigation is still required to fully explain the results from the GLP-1RA CVOTs seen to date'.

The Appeal Board noted Lilly's submission that as CVOTs differed in terms of study design and populations it was not appropriate to directly compare study outcomes. The Appeal Board noted that slide 24 of the slide deck (ref UK19OZM00368), which appeared to form the basis of the Panel's ruling, was headed 'GLP-1RA CVOTs' above 'Primary outcomes' beneath which it stated in smaller font that direct comparisons between trials should not be made due to differences in trial design. That was followed by 4 graphs each showing time to CV death, non-fatal MI or non-fatal stroke for Victoza (LEADER), Ozempic (SUSTAIN-6), Trulicity (REWIND), and albiglutide (HARMONY). The Appeal Board considered that the layout of slide 24 inevitably invited comparison between the four cardiovascular outcome trials depicted. The immediate visual impression was of comparability and similarity between the primary outcomes in the trials depicted.

The Appeal Board noted the details of the LEADER, SUSTAIN-6 and REWIND trials, as set out in the Panel's ruling, including the inclusion criteria, the primary endpoint results and the various sub-group analyses.

The Appeal Board carefully considered Novo Nordisk's submission that none of the CVOTs (including REWIND) were designed or powered to demonstrate either safety or benefit within the specific sub-group of patients with established or high-risk cardiovascular disease and that in the REWIND (Trulicity) trial, statistical significance was not met within each of the individual sub-groups including that which included patients that had risk of cardiovascular disease (primary prevention). The Appeal Board noted that Buse *et al* which detailed the 2019 Update to the Management of Hyperglycemia in Type 2 Diabetes, 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) stated that the REWIND trial of the GLP-1RA Trulicity included a greater proportion of individuals with type 2 diabetes with high cardiovascular risk but without prior established cardiovascular disease (CVD) (68.5%) and with longer follow-up (median 5.4 years) than prior CVOTs. The primary major adverse cardiovascular event (MACE) outcome occurred in 2.7 per 100 patient-years with a hazard ratio (HR) of 0.88 (95% CI0.79, 0.99) in favour of dulaglutide. Buse *et al* stated that there was no difference in the MACE effect in the sub populations with and without a history of CVD, although the treatment effect of Trulicity did not reach statistical significance when the groups were considered separately. Most other CVOTs with GLP-1RAs had different patient populations; they included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups. The Appeal Board put particular weight on the ADA/EASD consensus report's (Buse *et al)* comment that it was uncertain whether the differences in outcomes in trial subgroups without established CVD were related to study details or to the assigned therapy.

The Appeal Board agreed with Novo Nordisk's submission that the slide deck did not include any secondary endpoint analyses, including secondary endpoints. It noted Novo Nordisk's submission that the secondary endpoint analyses data could have portrayed its data as more favourable, such as the significant improvements in cardiovascular or all cause death demonstrated by Victoza in the LEADER trial but not by Trulicity in the REWIND trial. The Appeal Board saw merit in Novo Nordisk's submission that those trials all recruited a population within a continuum of cardiovascular risk and the WHO definition of primary and secondary prevention and the populations defined by WHO as referred to by Lilly, had not been applied consistently within the trials' protocols, defined sub-groups or subsequent exploratory analyses. In addition, the definition of high risk and established cardiovascular disease differed between each of the cardiovascular outcome trials.

The Appeal Board noted that Victoza, Ozempic and Trulicity were similarly indicated and bore in mind the differences and similarities between the SPCs for all three medicines with respect to effects on glycaemic control and cardiovascular events. The Appeal Board did not consider that the FDA licence indications of Trulicity, Ozempic and Victoza referred to by Lilly were relevant to this case.

The Appeal Board, in the light of its comments above, did not consider that Lilly had established, on the balance of probabilities, that the presentation of the trial outcomes for Victoza (LEADER), Ozempic (SUSTAIN-6) and Trulicity (REWIND) without reference to primary and secondary prevention, did not encourage the rational use of a medicine as alleged. The Appeal Board therefore upheld the Panel's ruling of no breach of Clause 7.10. The appeal on this point was unsuccessful.

Post 18 January 2022 meeting

The Chair decided that whilst Lilly was not obliged to do so it might if it so wished submit further comment within the ambit of the appeal, and if any comments were provided, they would be provided to Novo Nordisk for comment. Any comments from Novo Nordisk would be provided to Lilly for information only.

FURTHER APPEAL SUBMISSION FROM LILLY

Lilly's further submission in relation to its appeal of the Panel's rulings of no breach of Clauses 7.2, 7.3. and 9.1 of the Code included identical content to its original appeal submission as well as additional comment. To avoid repetition, only the additional information that was not previously submitted is included below.

Lilly stated that clarity on whether a therapy had demonstrated evidence of primary prevention and/or secondary prevention was critical for prescribing health professionals, as these populations were different and the prescribing decision for individual patients would be informed by the data from the respective products' CVOTs.

Lilly alleged that in the slide deck, the primary outcomes were presented for GLP-1RA CVOTs. For the studies related to the products being promoted, namely liraglutide (LEADER) and semaglutide (SUSTAIN-6), the positive primary outcomes were presented without making it clear that CV benefit in those studies was confined to the sub-group of patients with established CV disease (secondary prevention). For the study related to dulaglutide (REWIND), the positive primary outcome was presented without making it clear that CV benefit in REWIND extended beyond patients with established CV disease (secondary prevention) to include patients with risk factors only (primary prevention).

Lilly alleged that presenting the primary outcomes for *any* of the three CVOTs without making clear whether they showed evidence of primary CV prevention, secondary CV prevention or both was misleading, did not clearly reflect an up-to-date evaluation of all the evidence, and was not sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicines. Accordingly, the combined slide deck was in breach of Clause 7.2.

Lilly stated that comparisons were only allowed in promotional material if they were not misleading. Lilly alleged that placing the primary outcomes from the CVOTs on the same slides, inviting comparisons of the studies, without making it clear that the study outcomes differed greatly in generalisability from a CV risk perspective, favouring REWIND (dulaglutide), was incomplete, misleading and in breach of Clause 7.3.

Lilly further alleged that given that the ADA/EASD consensus report, which was clear on all the points raised, was specifically and extensively referred to in the slide deck, the content of the slide deck represented a deliberate choice to avoid disclosing the differing generalisability from a CV risk perspective of the respective studies and thus mislead the audience. This represented a failure to maintain high standards in breach of Clause 9.1.

Key Panel rulings with which Lilly disagreed included that the Panel interpreted the CV risk sub-analyses from the CVOTs incorrectly. This was in addition to those previously raised by Lilly. Lilly stated that the analysis of CVOTs was complex and it did not expect the Panel to attempt to

conduct its own analysis. The CVOTs in question had all been independently analysed by three key sources of authority, the EMA, FDA and the ADA/EASD consensus report authors, to determine whether they showed evidence of primary CV prevention, secondary CV prevention, or both. The conclusions were unequivocal that REWIND, but not LEADER or SUSTAIN 6, demonstrated evidence of CV benefit not only in patients with established CV disease (secondary prevention), but also in patients with CV risk factors (primary prevention).

RESPONSE FROM NOVO NORDISK

Novo Nordisk had no further comments.

APPEAL BOARD RULING - 16 June 2022

The Appeal Board was asked to consider the appeal in relation to Clauses 7.2, 7.3 and 9.1 afresh, confining its decision to the allegations made in the complaint as raised by Lilly and considered by the Panel.

The Appeal Board noted that the Panel made its rulings in relation to the slide deck titled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (ref UK19OZM00368) because in the Panel's view, whilst Lilly had referred to two slide decks in the heading of its complaint, the complaint focused specifically on the first slide deck (ref UK19OZM00368) and no specific allegations were raised in relation to the second slide deck (ref UK20DI00110). The Appeal Board noted in its original response to the Panel, Novo Nordisk submitted that Lilly had focused on the slide deck 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' (UK19OZM00368) and therefore its response was focused on that deck.

Both Lilly and Novo Nordisk contrary to its submission to the Panel submitted at appeal that the case concerned both slide decks and thus the Appeal Board considered the appeal on that basis. The Appeal Board noted that at appeal, Lilly had provided further particulars in this regard including that Novo Nordisk had sponsored at least one presentation entitled 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' that combined slide decks UK19OZM00368 Nov 2019 and UK20DI00110 April 2020, and it was the combined slide deck with that same title that had been the subject of Lilly's original complaint. No combined slide deck was provided either to the Panel or to the Appeal Board. The Appeal Board further noted that at appeal, Lilly had also provided details with regard to the relevance of the second slide deck (ref UK20DI00110 April 2020) to its complaint including that it consisted of over 20 slides that focussed on the 2018 ADA/EASD consensus report and its 2019 update; the deliberate omission of key statements from the updated ADA/EASD consensus report was the basis of Lilly's allegation that the combined slide deck represented a failure to maintain high standards.

Novo Nordisk's position at appeal was clearly that both slide decks were promotional and their content was educational. The Appeal Board agreed that the slides were promotional. The Panel had not specifically commented on this point and appeared to consider the slide decks to be promotional, there was no comment or implication that the Panel considered that the slide decks were not promotional.

Novo Nordisk had agreed during intercompany dialogue to withdraw the 'Insights from cardiovascular outcome trials in type 2 diabetes; what have we learnt?' slide deck and include a

slide which represented the difference in trial participants' baseline CV risk characteristics whenever LEADER, SUSTAIN-6 and REWIND trials were presented alongside each other in any future relevant materials.

The Appeal Board noted that the slide deck (ref UK19OZM00368) began by introducing Victoza and Ozempic and their indications. Subsequent slides sat within 5 agenda items: the link between CVD and T2D; the background and rationale for CVOTs with glucose lowering drugs; CVOT landscape and summary of key results; current scientific hypotheses for outcomes seen in these CVOTs; and impact on guidelines and further considerations.

The Appeal Board noted that the slide (slide 19), immediately before the section of the agenda 'CVOT landscape and summary of key results' which included the cardiovascular outcome trial comparisons at issue, was titled 'CVOTs in patients with type 2 diabetes' and set out the trial name, n number and duration of the various cardiovascular outcome trials involving insulin, GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium–glucose cotransporter-2 inhibitors (SGLT-2is) set against a timeline of when each was conducted. The Appeal Board further noted that a pop-up box which appeared on a later slide, slide 29, headed 'Beyond glycaemic control Potential mode of action for GLP-1RAs to impact cardiovascular disease' further stated 'There were significant differences in trial conduct, primary endpoints and duration of each of the CVOTs. Further investigation is still required to fully explain the results from the GLP-1RA CVOTs seen to date'.

The Appeal Board considered that the layout of slide 24 inevitably invited comparison between the four CVOTs depicted but the subheading stated that comparisons between trials should not be made due to differences in trial design.

The Appeal Board noted the details of the LEADER, SUSTAIN-6 and REWIND trials, as set out in the Panel's ruling, including the inclusion criteria, the primary endpoint results and the various sub-group analyses. The Appeal Board further noted that LEADER, SUSTAIN-6 and REWIND were cardiovascular safety trials and carefully considered Novo Nordisk's submission that none of the CVOTs (including REWIND) were designed or powered to demonstrate either safety or benefit within the specific sub-group of patients with established or high-risk cardiovascular disease and that in the REWIND (Trulicity) trial, statistical significance was not met within each of the individual sub-groups including that which included patients that had risk of cardiovascular disease (primary prevention). The Appeal Board noted that Buse *et al,* which detailed the 2019 Update to the Management of Hyperglycemia in Type 2 Diabetes, the 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) stated that the REWIND trial of the GLP-1RA Trulicity included a greater proportion of individuals with type 2 diabetes with high cardiovascular risk but without prior established cardiovascular disease (CVD) (68.5%) and with longer follow-up (median 5.4 years) than prior CVOTs. The primary major adverse cardiovascular event (MACE) outcome occurred in 2.7 per 100 patient-years with a hazard ratio (HR) of 0.88 (95% CI0.79, 0.99) in favour of dulaglutide. Buse *et al* stated that there was no difference in the MACE effect in the sub populations with and without a history of CVD, although the treatment effect of Trulicity did not reach statistical significance when the groups were considered separately. The Appeal Board noted that this was accepted by the Lilly representatives at the appeal who referred to interaction analyses and the consistency of effect in the sub populations (with and without a history of CVD). Most other CVOTs with GLP-1RAs had different patient populations; they included a minority of patients with risk factors only but without evidence of benefit on MACE outcomes in the lower-risk subgroups. The Appeal Board put particular weight on the

ADA/EASD consensus report's (Buse *et al*) comment that it was uncertain whether the differences in outcomes in trial subgroups without established CVD were related to study details or to the assigned therapy. The Appeal Board agreed with Novo Nordisk's submission that the slide deck did not include any secondary endpoint analyses, including secondary endpoints. It noted Novo Nordisk's submission that presenting the secondary endpoint analyses data could have portrayed its data as more favourable, such as the significant improvements in cardiovascular or all cause death demonstrated by Victoza in the LEADER trial but not by Trulicity in the REWIND trial. The Appeal Board saw merit in Novo Nordisk's submission that those trials all recruited a population within a continuum of cardiovascular risk and the WHO definition of primary and secondary prevention and the populations defined by WHO as referred to by Lilly, had not been applied consistently within the trials' protocols, defined sub-groups or subsequent exploratory analyses. In addition, the definition of high risk and established cardiovascular disease differed between each of the cardiovascular outcome trials. The Appeal Board noted that Victoza, Ozempic and Trulicity were similarly indicated and bore in mind the differences and similarities between the SPCs for all three medicines with respect to effects on glycaemic control and cardiovascular events. The Appeal Board did not consider that the FDA licence indications of Trulicity, Ozempic and Victoza referred to by Lilly were relevant to this case. The Appeal Board, in the light of its comments above, did not consider that Lilly had established, on the balance of probabilities, that the presentation of the trial outcomes for Victoza (LEADER), Ozempic (SUSTAIN-6) and Trulicity (REWIND) without reference to primary and secondary prevention was misleading or was not sufficiently complete to enable recipients to form their own opinions of the therapeutic value of the medicine as alleged. The Appeal Board upheld the Panel's rulings of no breaches of Clauses 7.2 and 7.3. The appeal on these points was unsuccessful.

The Appeal Board further noted that an overview of all the relevant national and international guidelines/consensus statement algorithms were included and no selected detailed guidance pertaining to specific use of one medicine over another was drawn out from any of these guidance documents. The Appeal Board considered that the ADA/EASD consensus report recommendation of GLP-1RAs did not recommend one GLP-1RAs over another.

The Appeal Board noted that the ADA/EASD guideline overall did not recommend one GLP-1RA over another and any differences noted were not statistically significant. The Appeal Board did not consider that Lilly had established that in not disclosing the differing generalisability from a CV risk perspective of the respective studies within the combined slide deck, which referred to the ADA/EASD consensus report, Novo Nordisk had made a deliberate choice to mislead the audience as alleged. The Appeal Board noted its comments above and did not consider that there was evidence to show that Novo Nordisk had failed to maintain high standards in this regard and it upheld the Panel's ruling of no breach of Clause 9.1. The appeal on this point was unsuccessful.

Complaint received **18 November 2020**

Case completed **16 June 2022**