CASE AUTH/2653/11/13

NOVO NORDISK v SANOFI

Provision of insufficient data from head-to-head study

Novo Nordisk complained about a Lyxumia (lixisenatide) presentation issued by Sanofi. Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as add-on therapy to achieve glycaemic control in adult type 2 diabetics otherwise inadequately controlled with oral glucose-lowering medicines and/or basal insulin together with diet and exercise. Novo Nordisk marketed Victoza (liraglutide) which was also a GLP-1 receptor agonist for use in type 2 diabetes.

Novo Nordisk referred to two slides. Slide 4 was headed 'New Lyxumia provides significantly greater reductions in PPG [post-prandial glucose] excursion and exposure compared with liraglutide'. This was followed by a graph headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily (p<0.0001)' referenced to Kapitza *et al* (2013). The graph showed mean change from pre-meal plasma glucose. The test meal was given 30 minutes after the medicine and the graph showed the data for every 30 minutes for 4.5 hours.

Slide 23 was headed 'Comparative effects on glucagon suppression' and featured a graph headed 'Lyxumia 20mcg once-daily provides a greater decrease in post-meal glucagon secretion than liraglutide 1.8mg once-daily' referenced to Kapitza *et al* and data on file. The graph compared mean plasma glucagon against theoretical time (0-4 hours 30 minutes). The final statement 'Glucagon AUC [area under curve] 0.30-4.30h (h-pg/mL) mean change from baseline. Estimated treatment difference – 21.2 p = 0.032' was referenced to data on file.

Novo Nordisk noted that the efficacy sections of both products' summaries of product characteristics (SPCs) presented the data for glycaemic control first (HbA_{1c} reductions, change in body weight and proportion of patients reaching the target of <7% HbA_{1c}). Novo Nordisk submitted that these were the three most recognised measures of diabetes/ glycaemic control used in clinical practice and by bodies such as the National Institute for Health and Care Excellence (NICE). Examples were given regarding the effect of hyperglycaemia as measured by updated mean HbA_{1c} and correcting post-meal hyperglycaemia.

The SPC efficacy sections for both products also showed results for changes in fasting plasma glucose (FPG), postprandial glucose (PPG) and body weight. In addition effects on beta cell function, cardiovascular evaluation and paediatric population were discussed.

Novo Nordisk submitted that the correct way to present and compare efficacy looking at PPG excursions of once-daily GLP-1 receptor agonists was to present the 24 hour PPG profile. Kapitza *et al* had published these data but Sanofi had not presented these results. The title of slide 4, 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide', suggested that Lyxumia provided a greater reduction in PPG excursion than Victoza after every meal. Slide 4 failed to clarify that the claim was only true in respect of the test meal post-injection.

Kapitza *et al* showed that Victoza was superior (60% better) in the most clinically relevant measure of glucose control ie HbA_{1c} lowering efficacy. Sanofi did not provide these results in the presentation although at slide 8 HbA_{1c} efficacy data was used to show non-inferiority between Lyxumia and exenatide. This result was even more important considering Kapitza *et al* was the only head-to-head comparison of Victoza and Lyxumia. Novo Nordisk submitted that these results should thus not be ignored.

Another clinically relevant efficacy measure available from Kapitza *et al* was weight reduction. The study had shown that Victoza was superior to Lyxumia (50% better). Nevertheless, Sanofi did not present these results. Sanofi also did not refer to the fasting plasma glucose (FPG) data in the comparison of Lyxumia and Victoza when Victoza provided significantly greater reductions in FPG than Lyxumia.

Novo Nordisk alleged that Sanofi had used data from Kapitza *et al* very selectively to present Lyxumia more favourably. Clinically relevant results showing advantages for Victoza (24 hour glucose control, HbA_{1c} reductions and weight reductions) had been ignored while only results of less clinically relevant outcome measures with advantages for Lyxumia (PPG reductions after the test meal only and glucagon suppression) had been presented. Novo Nordisk alleged that this was misleading.

The response from Sanofi is detailed below.

The Panel noted that the presentation was entitled 'When it is time to add to basal insulin' followed by a reference to Lyxumia and 'A positive addition can make all the difference'. The next two slides were headed 'Choices to control PPG can be complex for patients on basal insulin' and 'Prandial GLP-1 receptor agonists have a greater effect on PPG than non-prandial agents'. The Panel noted that the presentation had been withdrawn following Case AUTH/2604/5/13. Sanofi stated that slides 4 and 23 remained unchanged and were still in use.

The presentation was designed, at least in part, to compare the clinical use of the available GLP-1 receptor agonists and the treatment choices

available in that regard for type 2 diabetics uncontrolled on existing treatment regimens. However, as Victoza was only licensed to be given in combination with oral antidiabetic medicines and not insulin, the Panel queried whether a comparison of Lyxumia with Victoza should have been included at all in a presentation entitled 'When it's time to add to basal insulin'. The comparative information about Lyxumia and Victoza was limited to PPG excursion (slide 4) and post-meal glucagon secretion (slide 23) data from Kapitza *et al* which was a pharmacodynamic comparison, and according to Novo Nordisk, the only direct comparison, of the two medicines.

The Panel noted Sanofi's submission that Kapitza *et al* was not a comparison of the efficacy of the two medicines as defined by overall glycaemic control. Sanofi had further submitted that the duration of the study (28 days) and the fact that mean HbA_{1c} was a secondary outcome in a study which was designed to measure short-term pharmacodynamic differences between Lyxumia and Victoza, meant that any differences noted between the two in terms of glycaemic control might not reflect clinical use. The authors stated that 'With respect to clinical reality, a limitation of this study is the relatively short observation time of 28 days. Indeed direct conclusions with regard to long-term metabolic control should not be made'. The Panel noted Novo Nordisk's submission that although Sanofi had not shown the HbA_{1c} efficacy data for Lyxumia vs Victoza (based on Kapitza *et al*), the company had included such data for Lyxumia vs exenatide. The Panel noted, however, that the Lyxumia/exenatide data was from a 24 week study to compare the safety and efficacy of the two medicines.

Slide 4, 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide' featured a graph headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily (p<0.0001)'. In text less obvious than the headings, the x axis denoted the timing of the test medicine and of the test meal. Slide 28 was headed 'Comparative effects on glucagon supression' and the featured graph was headed 'Lyxumia 20mcg once-daily provides greater decrease in postmeal glucagon secretion than liraglutide 1.8mg once-daily'. There was no reference on slide 28 to a test meal. The Panel considered that it was not sufficiently clear that the data shown in both slides had been taken from a 28 day pharmacodynamic study and related only to the results from one standardised test meal and not to every meal of the day. The Panel noted the limitations of the study when considering long-term metabolic control. In the Panel's view, given the context in which they appeared ie a presentation designed to detail Lyxumia vs competitor medicines, the slides, although not required to include all of the data from Kapitza *et al*, did not give enough information about the study to enable readers to form their own opinion of the long-term therapeutic value of Lyxumia vs Victoza. In that regard the slides were misleading and a breach was ruled.

Novo Nordisk Limited complained about a Lyxumia (lixisenatide) presentation (ref GBIE.LYX.13.02.15) issued by Sanofi. Lyxumia was a glucagon-like peptide-1 (GLP-1) receptor agonist indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicines and/or basal insulin when these, together with diet and exercise did not provide adequate glycaemic control. Novo Nordisk marketed Victoza (liraglutide which was also a GLP-1 receptor agonist for use in type 2 diabetes. Both medicines were administered once-daily.

Novo Nordisk referred to slides 4 and 23. Slide 4 was headed 'New Lyxumia provides significantly greater reductions in PPG [post-prandial glucose] excursion and exposure compared with liraglutide'. This was followed by a graph headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily (p<0.0001)' referenced to Kapitza *et al* (2013). The graph showed mean change from pre-meal plasma glucose. The test meal was given 30 minutes after the medicine and the graph showed the data for every 30 minutes for 4.5 hours.

Slide 23 was headed 'Comparative effects on glucagon suppression'. This was followed by a graph headed 'Lyxumia 20mcg once-daily provides a greater decrease in postmeal glucagon secretion than liraglutide 1.8mg once-daily' referenced to Kapitza *et al* and data on file. The graph compared mean plasma glucagon against theoretical time (0-4 hours 30 minutes). The final statement 'Glucagon AUC [area under curve] 0.30-4.30h (h-pg/mL) mean change from baseline. Estimated treatment difference – 21.2 p = 0.032' was referenced to data on file.

Kapitza *et al* assessed the pharmacodynamics of Lyxumia vs Victoza in type 2 diabetics insufficiently controlled on metformin.

COMPLAINT

Novo Nordisk alleged that the presentation was promotional and was aimed at health professionals who treated patients with type 2 diabetes. The presentation compared Lyxumia with other GLP-1 receptor agonists, Novo Nordisk's product Victoza and AstraZeneca and Bristol-Myers Squibb's product Bydureon (exenatide).

The efficacy sections (5.1) within the summaries of product characteristics (SPCs) for both products presented the data for glycaemic control first. The data, presented in tabular form, focussed on HbA_{1c} reductions, change in body weight and proportion of patients reaching the target of <7% HbA_{1c}. Novo Nordisk submitted that these three measures were the most recognised measures of diabetes/glycaemic control and were used extensively in clinical practice and well recognised and used by regulatory bodies. For example, The National Institute for Health and Care Excellence (NICE) in its clinical guideline for the management of type 2 diabetes in primary and secondary care stated that 'The risk of each of the microvascular and macrovascular complications of Type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean HbA_{1c}'. The International Diabetes

Federation (IDF) recognised that 'There is currently a lack of direct randomised clinical trial evidence that correcting postmeal hyperglycaemia improves clinical outcomes [Level 1-]'. This was reflected and summarised in the most recent NICE clinical guideline 87 for the management of type 2 diabetes where criteria for the use and continuation of GLP-1 receptor agonists were linked to HbA_{1c} and weight lowering efficacy.

The SPC efficacy sections for both Lyxumia and Victoza also showed results for changes in fasting plasma glucose (FPG), postprandial glucose (PPG) and body weight. In addition effects on beta cell function, cardiovascular evaluation and paediatric population were discussed.

With regard to the comparison of Lyxumia and Victoza (slides 4 and 23), Novo Nordisk noted that Kapitza *et al* was a Sanofi sponsored study.

The data comparing Lyxumia and Victoza only presented reductions of PPG excursions after the test meal post-injection (slide 4) and the comparative effect on glucagon suppression (slide 23). Novo Nordisk alleged that presenting this primary endpoint in isolation to compare the two medicines was a biased, selective and unbalanced representation of Kapitza *et al*.

Novo Nordisk submitted that the correct way to present and compare efficacy looking at PPG excursions of once-daily GLP-1 receptor agonists was to present the 24 hour PPG profile. These data were published in Kapitza *et al* (figure 1B), however Sanofi had not presented these results. Slide 4 was entitled 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide' which suggested that Lyxumia provided a greater reduction in PPG excursion than Victoza after every meal. Slide 4 failed to clarify that the claim was only true in respect of the test meal post-injection.

Kapitza *et al* had clearly shown that Victoza was superior (60% better) in the most clinically relevant measure of glucose control ie HbA_{1c} lowering efficacy. Sanofi did not provide these results in the presentation. This was surprising as Sanofi used HbA_{1c} efficacy data in slide 8 to show non-inferiority between Lyxumia and exenatide. This result was even more important considering Kapitza *et al* was the only head-to-head study which compared Victoza and Lyxumia. Novo Nordisk submitted that these results should thus not be ignored.

Another clinically relevant efficacy measure available from Kapitza *et al* was weight reduction. The study had shown that Victoza was superior to Lyxumia (50% better). Nevertheless, Sanofi did not present these results.

Sanofi also did not refer to the fasting plasma glucose (FPG) data in the comparison of Lyxumia and Victoza when Victoza provided significantly greater reductions in FPG than Lyxumia.

In summary, Novo Nordisk alleged that Sanofi had used data from Kapitza *et al* very selectively to present Lyxumia more favourably. Clinically relevant results showing advantages for Victoza (24 hour glucose control, HbA_{1c} reductions and weight reductions) had been ignored while only results of less clinically relevant outcome measures with advantages for Lyxumia (PPG reductions after the test meal only and glucagon suppression) had been presented. Novo Nordisk alleged that this was misleading in breach of Clause 7.2.

Novo Nordisk noted that Sanofi had stated in inter-company dialogue that it was not obliged to present any results representing efficacy, if such result related to secondary outcome measures. In Kapitza *et al* these were, *inter alia*, 24 hour glucose profile, HbA_{1c} reductions and weight lowering efficacy. In Novo Nordisk's view, Sanofi's argument was flawed as results of any study should be looked at in entirety; otherwise conclusions made on selective data were subject to bias. In addition, as discussed above, the results not shown by Sanofi were of upmost clinical relevance to the patient, physician and regulatory bodies.

In addition, FDA guidance stated 'the link between a modifying effect on postprandial glucose excursions to clinical outcomes is not sufficiently strong to consider the use of this pharmacodynamic endpoint as a surrogate for efficacy'. The same guidance stated 'For purposes of drug approval and labelling, final demonstration of efficacy should be based on reduction in HbA_{1c}, which will support an indication of glycaemic control', thereby emphasising the importance of HbA_{1c} reductions as an outcome measure.

To add to this, the European Medicines Agency (EMA) guideline on clinical investigation of medicines in the treatment or prevention of diabetes stated (when discussing insulin efficacy) that 'Reduction in the amplitude between postprandial hyperglycaemic peaks and fasting blood glucose values is desirable, but will not be accepted as a claim of superiority of a new insulin compared to an established insulin, unless accompanied by a relevant improvement in blood glucose control (measured by HbA_{1c}), hypoglycaemia or other clinically meaningful outcomes'. The EMA also noted that 'Weight gain is frequent in diabetic patients trying to implement intensive glucose control. The evolution of body weight will also be taken into account in the global evaluation of the efficacy and safety, particularly in type 2 diabetic patients'.

Based on the above, Novo Nordisk disagreed with Sanofi's view that HbA_{1c}/weight measurements and 24 hour glucose profiles were irrelevant and should not be presented based on the notion that they were secondary outcome measures in Kapitza *et al*.

Sanofi had also stated in inter-company dialogue that it was inappropriate to use 24 hour glucose profile data from Kapitza *et al* to substantiate any claims about efficacy of Victoza and Lyxumia beyond the test meal. Sanofi stated: 'It is clearly inappropriate therefore to make any claim about the postprandial effects outside of the test conditions - the scientific basis is clearly too weak to substantiate

this'. Novo Nordisk noted that the authors did not refer to this as being a scientific weakness of the study.

Kapitza *et al* stated 'At day 28, plasma glucose levels were much lower with [Lyxumia] than with [Victoza] during the post breakfast period (i.e., from ~45 minutes to ~4h after drug administration), whereas from 4.5h onwards (and before breakfast), plasma glucose levels were lower for [Victoza] than for [Lyxumia] at all-time points'. Furthermore the authors concluded, 'Specific patterns of coverage appeared to reflect the distinct pharmacokinetic profiles of [Lyxumia] and [Victoza], with [Lyxumia] providing particularly good coverage of breakfast-associated glycaemia, as clearly showed in the standardized breakfast meal test, and [Victoza] providing better fasting control and PPG coverage beyond the morning meal'. Therefore Sanofi's justification for not presenting these important findings was misplaced.

Sanofi had also used a similar argument to justify the absence of the HbA_{1c} efficacy results from Kapitza *et al* in the presentation. Kapitza *et al* demonstrated the mean HbA_{1c} decreased in both treatment groups from 7.2% to 6.9% (–0.32%) with Lyxumia vs. 7.4% to 6.9% (–0.51%) with Victoza, $p<0.01$. Sanofi stated that using the HbA_{1c} efficacy to compare Victoza and Lyxumia (as measured after 28 days) was scientifically weak and inappropriate. However, the only caution the authors expressed when discussing HbA_{1c} efficacy of both medicines, as correctly noted by Sanofi, was that 'direct conclusions with regard to long-term metabolic control should not be made'. This appeared to be a logical conclusion considering that full efficacy of any medicine in HbA_{1c} control would be shown after ~90 days due to the (patho) physiology of HbA_{1c}. Novo Nordisk noted that this comment did not preclude conclusions that could be made about comparative efficacy of both products after 28 days of exposure.

Nevertheless, it was well recognised that HbA_{1c} levels represent weighted average of glucose control over 90 days before measurement. Figure 2B in Tahara *et al*, (1995) showed the period of 30 days (similar to Kapitza *et al*) preceding the HbA_{1c} measurement consistently contributed to ~50% of final HbA_{1c} efficacy. This had been recognised by the National Glycohemoglobin Standardization Program (NGSP), 1996 responsible for harmonising HbA_{1c} testing. More recently this had been confirmed in the 'real world' setting and presented at 2013 European Association for the Study of Diabetes (EASD) conference. Hirst *et al*, (2013) showed that after just 4 weeks (as in Kapitza *et al*), HbA_{1c} reductions were ~60% of final HbA_{1c} reductions. The authors also suggested 'that many patients would benefit from returning to their GP earlier than 12 weeks following a change in their medication to have their HbA_{1c} checked'.

Therefore it was obvious that HbA_{1c} reductions after 4 weeks provided a good and consistent measure of glycaemic control showing ~50%-60% of final HbA_{1c} reductions, as shown by Hirst *et al* and Tahara *et al*. This was even more obvious when results of Kapitza *et al* were extrapolated using conclusions from Hirst *et al* and Tahara *et al*. Comparative HbA_{1c} reductions from Kapitza *et al* for Lyxumia and Victoza showed ~60% better lowering profile for Victoza. That was in line with the comparative placebo adjusted HbA_{1c} reductions detailed in the SPCs for both medicines (0.5% to 0.75% for Lyxumia and 0.90% to 1.1% for Victoza).

RESPONSE

Sanofi stated that the presentation at issue was delivered to health professionals by Lyxumia-trained representatives within a remote (internet based) sales call. The presentation was withdrawn from use on 25 June 2013 in keeping with the undertaking given in Case AUTH/2604/5/13. A new presentation was subsequently re-issued with amendments made to the elements relevant to that case, but slides 4 and 23 remained unchanged as they related to different information.

The complaint related to the use of data from Kapitza *et al*, a 28-day pharmacodynamic study which compared the effects of Lyxumia and Victoza on postprandial glucose excursion. The study demonstrated that there was a greater reduction in postprandial glucose excursion with Lyxumia than Victoza, as would be expected from the different pharmacokinetic profiles of each medicine (short- and long-acting agents respectively).

The study involved administration of study medicine to fasted subjects in the morning, followed by a standardised test meal (breakfast) 30 minutes later. The postprandial glucose excursion was assessed by eight blood glucose measurements in the four-hour period after the test meal, during which no further food intake occurred. After this tightly controlled period there was no standardisation of meals or meal times. Assessments were made at baseline (the day before the first administration of study medicine) and repeated on day 28 of treatment.

The primary outcome measure was the glucose excursion in the four-hour period after the standardised test meal, the primary endpoint was the change in post prandial glucose excursion from baseline to day 28. Secondary endpoints included the change in 24 hour glucose profile over the 24 hour study period (as measured by six blood glucose measurements between hours 6:30 and 24), and the change in HbA_{1c} from baseline to day 28.

Sanofi noted that Novo Nordisk had alleged that through presenting the primary endpoint of the study (the change in postprandial blood glucose concentration in the period 30 minutes to 4 hours 30 minutes after injection), but not every secondary endpoint studied (specifically change in HbA_{1c} from baseline, and the 24 blood glucose profile as opposed to the change 00:30 - 04:30hrs), Sanofi had misled the reader in breach of Clause 7.2.

Novo Nordisk had alleged that to fail to show the data beyond the four hour time period misled because Sanofi had not provided the reader with

information that suggested that Lyxumia was not effective for a full 24 hour period, and that this was required to demonstrate efficacy in the reduction of postprandial glucose excursion.

Sanofi disagreed with this position on the basis that the study design was focussed on the tightly controlled time period up until the 04:30 hour time point, and that to try to make any claims based on the data beyond this would in itself be misleading as the uncontrolled trial conditions did not allow conclusions to be drawn with the same level of rigour. As the primary endpoint was clearly presented without any attempt to mislead, Sanofi did not consider it appropriate to demonstrate those secondary endpoints where the design of the study had not permitted a robust confirmation of effect.

Sanofi noted that in Novo Nordisk's view, the correct way to demonstrate postprandial glucose excursion control was to show a 24 hour glucose profile, different to the 0:30 – 4:30 hour profile examined by the primary endpoint of this study.

Sanofi stated that, as a supportive trial rather than a pivotal study the endpoint demonstrated was not defined by regulatory requirements. Kapitza *et al* was designed to examine any difference in this specific pharmacodynamic effect between Lyxumia and Victoza, and thus understand the differences in mechanism of action, not to compare the efficacy of the two as defined by overall glycaemic control. The four hour window was selected because the post-meal glucose excursion would usually be completed in this period (as demonstrated in the results), hence to answer the scientific question 'What is the effect on postprandial glucose excursion?', a study of four hours was appropriate.

Although Sanofi understood Novo Nordisk's desire to see that conclusions were made on the data gathered beyond the primary outcome, it was clear that the study was designed with the strongest scientific focus on the four hour period in which the primary endpoint was assessed (ie the 0:30 – 4:30 hours time period). Beyond this time point the absence of controlled meals and meal times and the low frequency of blood testing did not allow such conclusions to be made with any certainty, and Sanofi submitted that this justified not using these secondary outcome measures in promotion.

With regard to the biological sampling, Sanofi explained that the blood testing schedule in the four hours related to the measure of the primary endpoint required the collection of eight samples at intervals of between 15 and 30 minutes. After this point there were only a further six samples taken, at intervals of between 2 and 9.5 hours. It was clear that this would weaken the ability to accurately measure the postprandial response after the initial control period and no meaningful conclusions could be made on the efficacy of either medicine in the period 4:30 – 24 hours.

Furthermore, the lack of standardisation of food intake and timing after 4:30 hours meant that there was no obvious time point that could be used to specifically compare the postprandial effects after mid-day and evening meals. This was clearly reflected in the results where the rise in blood glucose after the standardised breakfast meal was not repeated to the same magnitude at any point in the rest of the day at the baseline assessment – similarly sized excursions would normally be expected after mid-day and evening meals, and it was clear that these did not occur at baseline. Two graphs were provided to demonstrate what would be expected in response to normal mealtimes and what was observed by Kapitza *et al*. In the absence of a baseline post-prandial excursion, the scientific question of demonstrating a reduction could not be answered - it was inappropriate to draw any conclusion on the effects between Lyxumia and Victoza at these time points as the baseline observations did not document an increase in blood glucose that would be expected had a meal been taken.

Sanofi stated that one of the graphs from Polonsky *et al* (1998) demonstrated the postprandial excursions in patients with type 2 diabetes (upper line), showing a readily identifiable and similar magnitude excursion in relation to breakfast, mid-day and evening meals. In contrast, the second graph from Kapitza *et al* showed that the lack of controlled meals after the initial test meal resulted in no significant baseline postprandial excursion in response to any mid-day meal, and only a diminished excursion in response to an evening meal.

Sanofi therefore submitted that even if it were considered necessary to demonstrate postprandial effects over the course of a full day rather than in response to an individual test meal, it was not appropriate to use this study as the design did not allow conclusions to be drawn with certainty after the controlled period ended at 4 hours and 30 minutes. Sanofi noted that although Novo Nordisk proposed that Lyxumia did not have a postprandial effect for all three meals in the day when given once in the morning, this had been demonstrated conclusively by Lorenz *et al* (2013), and Sanofi used this study to illustrate this point in promotional material.

Lorenz *et al* demonstrated a reduction in post-prandial glucose excursion with Lyxumia after each of three meals in the day; each reduction was significant compared with the placebo-treated comparator group.

In conclusion, Sanofi strongly considered that to present data that was clearly not supported by the study design would be contrary to the Code – it would be unacceptable to make a claim about the effects of Lyxumia and Victoza from interpretation of the data outside of the controlled period of the study (ie beyond 4 hours and 30 minutes). Novo Nordisk's proposal to do this failed to recognise the letter and spirit nature of the Code.

Sanofi denied a breach of Clause 7.2.

Sanofi noted Novo Nordisk's allegation that it was misleading for Sanofi to fail to present the reduction in HbA_{1c} demonstrated as a secondary endpoint in Kapitza *et al*, as a relevant diabetes endpoint had

been missed out. In support of its position Novo Nordisk provided FDA and EMA guidelines, albeit those which defined the requirements for marketing authorization and not the promotion of medicines, that indicated that change in HbA_{1c} was the principle outcome that was required to demonstrate efficacy. Novo Nordisk argued that the fact that HbA_{1c} was an important endpoint was sufficient to require it to be presented in this material, even though it was a secondary, not primary, endpoint.

Sanofi contested that Kapitza *et al* was a short term pharmacodynamic study with the primary objective of examining the glycaemic response to Lyxumia and Victoza after a standard test breakfast. The data Sanofi presented was the primary endpoint and primary outcome of the study, and this could never be inappropriate.

Furthermore, Sanofi maintained that the presentation of secondary endpoints needed to be judged according to the scientific aims and objectives of the study. It was clear that the findings of a short-term pharmacodynamic study were not appropriate to support any conclusion on long-term glycaemic control, as stated by the authors. HbA_{1c} reflected the weighted average of blood glucose over the lifetime (90 - 120 days) of red-blood cells. HbA_{1c} was therefore recognised as only being able to provide an assessment of glucose control over the preceding 2-3 months, and was too coarse a measure to quantify effect in a 28 day study. Although Novo Nordisk quoted examples where HbA_{1c} might be measured in the short-term to indicate the direction of benefit (ie whether control was improving) rather than to quantify the degree of benefit in itself, Sanofi noted that the 0.3% - 0.5% reductions in HbA_{1c} demonstrated by Kapitza *et al* were significantly lower than the reductions quoted in the Lyxumia and Victoza SPCs, which fell broadly in the range of 0.75% - 2.0%; this further suggested that these results should not be used to compare metabolic control.

Regardless, the FDA and EMA notes for guidance concerned the requirements for demonstration of efficacy in appropriately designed confirmatory trials of a minimum 6-12 months – whereas Kapitza *et al* lasted just 28 days and was mechanistic pharmacodynamic study, not a confirmatory efficacy study. With regard to studies of 8 weeks duration or less, the guidance notes also stated that plasma glucose was the appropriate outcome measure, as reported by Kapitza *et al* (EMA Guidance section 4.1.3.2). The use of these guidelines to suggest that HbA_{1c} was the most important measure of glycaemic control was therefore entirely inappropriate, and should certainly not be used to suggest how the results of Kapitza *et al* should be presented in promotional material.

In summary, Sanofi reiterated that Kapitza *et al* was a 4 week study and it was therefore entirely inappropriate to draw any conclusions on long-term glycaemic control. To make any claim regarding superiority of change in HbA_{1c} would similarly be completely at odds with the intent of the authors who stated, 'With respect to clinical reality, a limitation of this study is the relatively short observation time of 28 days. Indeed, direct conclusions with regard to long-term metabolic control should not be made.'

Sanofi therefore submitted that omission of this information rather than its inclusion was the appropriate course of action, required by the Code to avoid misleading the reader through presentation of an inappropriate comparison.

With regard to Novo Nordisk's view that changes in weight should be presented, Sanofi submitted that the same reasoning applied – Kapitza *et al* was of too short a duration to draw any conclusion on weight loss. The authors' recognition that a 28 day duration was of too short a time to make any conclusion on metabolic outcomes applied as equally to weight as it did to HbA_{1c}, and to show this would have exactly the same level of disrespect for the requirements of the Code as it would to show the change in HbA_{1c}.

In summary, Sanofi submitted that it was inappropriate to draw conclusions on the outcomes of metabolic parameters such as HbA_{1c} and weight due to the short-term nature of Kapitza *et al*, and that to present this information would be akin to making claims incapable of substantiation, itself breaches Clauses 7.2 and 7.3.

With regard to fasting plasma glucose, Sanofi noted that Novo Nordisk had not previously raised this issue within inter-company dialogue, and it was therefore surprised to see it raised within this complaint.

In response Sanofi questioned the relevance of a reduction in fasting glucose levels in a study that examined the postprandial response. Although a statistically different result had been demonstrated, it was in a secondary endpoint that was not directly relevant to the primary objective of the study. The fact that the result existed in itself was not sufficient reason to see it included in promotional material, and given that the outcome was disconnected to the primary objective of the study there was little logical rationale to include it in material, and nor was it a requirement of the Code. No breach had previously been suggested through its omission, nor did Sanofi consider that one had occurred through its omission.

In conclusion, Sanofi submitted that the allegations were inappropriate – Kapitza *et al* clearly indicated that the study was of too short a duration to draw conclusions on metabolic control, and the guidelines for development quoted by Novo Nordisk similarly supported this position. To be alleged to be in breach through omitting to follow both these directions was therefore poorly considered, and Sanofi was confident that high standards had been maintained and that no breach of the Code had occurred.

In response to a request for further information, Sanofi provided a copy of an additional reference and a copy of the updated presentation (ref GBIE. LYX.13.06.11(3)).

PANEL RULING

The Panel noted that the presentation referred to by Novo Nordisk was entitled 'When it is time to add to basal insulin' followed by a reference to Lyxumia and 'A positive addition can make all the difference'. The next two slides were headed 'Choices to control PPG can be complex for patients on basal insulin' and 'Prandial GLP-1 receptor agonists have a greater effect on PPG than non-prandial agents'. The Panel noted that the presentation had been withdrawn following Case AUTH/2604/5/13. Sanofi stated that slides 4 and 23 remained unchanged and were still in use. The Panel noted that in the updated presentation entitled 'A positive addition when it's time to add to basal insulin', slide 23 had been amended such that the x axis recorded data from 1 hour after study drug administration (slide 23 had originally shown data points for 0 hours and 30 minutes and the x axis was labelled 'Theoretical time').

The Panel noted that the presentation referred to by Novo Nordisk (ref GBIE.LYX.13.02.15) was used by representatives in a remote (internet-based) sales call with health professionals. In the Panel's view, the presentation was designed, at least in part, to compare the clinical use of the available GLP-1 receptor agonists and the treatment choices available in that regard for type 2 diabetics uncontrolled on existing treatment regimens. However, as Victoza was only licensed to be given in combination with oral antidiabetic medicines and not insulin, the Panel queried whether a comparison of Lyxumia with Victoza should have been included at all in a presentation entitled 'When it's time to add to basal insulin'. The comparative information about Lyxumia and Victoza was limited to PPG excursion (slide 4) and post-meal glucagon secretion (slide 23) data from Kapitza *et al* which was a pharmacodynamic comparison, and according to Novo Nordisk, the only direct comparison, of the two medicines.

The Panel noted Sanofi's submission that Kapitza *et al* was not a comparison of the efficacy of the two medicines as defined by overall glycaemic control. The primary efficacy endpoint was the change in baseline to day 28 in the area under the plasma-glucose concentration time curve in the 4 hour period after the start of a standardised breakfast test meal. Secondary efficacy measures included mean HbA_{1c} and 24 hour glucose control. The Panel noted Sanofi's submission that the duration of the study (28 days) and the fact that mean HbA_{1c} was a secondary outcome in a study which was designed to measure short-term pharmacodynamic differences between Lyxumia and Victoza, meant that any differences noted between the two in terms of glycaemic control might not reflect clinical use. The authors themselves had stated in the discussion section of the paper that 'With respect to clinical reality, a limitation of this study is the relatively short observation time of 28 days. Indeed direct conclusions with regard to long-term metabolic control should not be made'. The Panel noted Novo Nordisk's submission that although Sanofi had not shown the HbA_{1c} efficacy data for Lyxumia vs Victoza (based on Kapitza *et al*), the company had included such data for Lyxumia vs exenatide. The Panel noted, however, that the Lyxumia/exenatide data was longer term data taken from Rosenstock *et al* (2013), a 24 week study to compare the safety and efficacy of the two medicines.

The Panel noted that slide 4 was headed 'New Lyxumia provides significantly greater reductions in PPG excursion and exposure compared with liraglutide'. The featured graph was headed 'Lyxumia 20mcg once-daily significantly reduced PPG excursion vs liraglutide 1.8mg once daily ($p<0.0001$)'. In text less obvious than the headings, the x axis denoted the timing of the test medicine and of the test meal. Slide 28 was headed 'Comparative effects on glucagon supression' and the featured graph was headed 'Lyxumia 20mcg once-daily provides greater decrease in postmeal glucagon secretion than liraglutide 1.8mg once-daily'. There was no reference on slide 28 to a test meal. The Panel considered that it was not sufficiently clear that the data shown in both slides had been taken from a 28 day pharmacodynamic study and related only to the results from one standardised test meal and not to every meal of the day. The Panel noted the authors' comments cited above with regard to the limitations of the study when considering long-term metabolic control. In the Panel's view, given the context in which they appeared ie a presentation designed to detail Lyxumia vs competitor medicines, the slides, although not required to include all of the data from Kapitza *et al*, did not give enough information about the study to enable readers to form their own opinion of the long-term therapeutic value of Lyxumia vs Victoza. In that regard the slides were misleading and a breach of Clause 7.2 was ruled.

Complaint received **14 November 2013**

Case completed **30 January 2014**