

Cohen D. Has pancreatic damage from glucagon suppressing diabetes drugs been underplayed? *BMJ* 2013;346:f3680

Webappendix 4: Correspondence between the BMJ and the manufacturers or marketers of liraglutide, a GLP-1 based drug

Liraglutide

DIALOGUE STARTS

BMJ questions 31/05/13

The BMJ has been looking at the track record of GLP-1 and DPP-4 drugs in the treatment of Type 2 diabetes and will examine the evidence available about the efficacy and safety of the drugs, in particular the risks of pancreatitis, thyroid and pancreatic cancer.

I'm emailing you so I can reflect your position. I would be most grateful if you could answer the following questions by the morning of the 3rd June.

1. In the course of the investigation, the BMJ look at the literature around the effects of glucagon suppression – one of the claimed benefits incretin mimetics. It is notable that studies have studied the effects of the pathophysiology of both complete and partial glucagon suppression in animals by a range of methods. Over time, each method has led to alpha-cell hyperplasia. This is not a wanted effect, as it may increase the risk of neuroendocrine tumour formation. The latest study by Butler et al in *Diabetes* has highlighted this, but – as they point out – this could have been anticipated.

In your submissions to the regulatory authorities in both Europe and the US, there is no discussion about the potential adverse effects of glucagon suppression. Could you please explain why?

2. Professor Dan Drucker has stated in publications and conferences that the therapeutic window of alpha-cell suppression is unclear. In light of the findings published by Butler et al in *Diabetes* this year, what are you actively doing to establish the pathophysiology of liraglutide? Please provide evidence

3. In 2012, Niels Nyborg and Novo Nordisk published a study in *Diabetes* that suggested that there were no structural changes in animals treated with liraglutide. However, in regulatory document the regulators noted the following changes:

“An increased pancreatic weight was observed in young healthy cynomolgus monkeys following four weeks (males only) and 52 weeks treatment...Further investigations of the pancreatic tissues collected in the 52-week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group”

The BMJ also has received the pathology reports under FOI and notes that the pancreas mass increases with dose in this particular study.

Furthermore, an FDA reviewer noted that there were statistically significant changes in the weight of both sexes of in 52 weeks and in males at 28 weeks. He believed these changes to be treatment related.

- Why did Novo Nordisk miss out data and discussion of those findings from the final publication?

- this omission keeping within the spirit of transparency in science?

4. In the 87 week monkey study conducted by Novo Nordisk, there were only 5 monkeys in each group. In each of the groups, the mean pancreas weight of the treated animals in both sexes was higher than the control. Do you agree that this finding – given the small numbers and the small increases in mean - does not override the significance of the changes seen at 52 weeks?

5. The protocol of this study also states that only the thyroid was processed for histology. However, in response to questions posed by the CHMP at EMA, you have stated that “no signs of treatment related inflammatory changes or pancreatitis were observed”. How do you explain this? Did you ever provide a detailed pancreas histology report to EMA or the FDA?

6. Novo Nordisk relied on this study to suggest that there was no increase in pancreas weight in the 87 week study. However, the mean in the study reports does not match that in the graph supplied in response to CHMP questions – nor do the individual weights match up. The means on the graph supplied to the CHMP are lower than those in the report. How do you explain this?

7. In 2008, Novo Nordisk started routinely collecting pancreatic enzyme data. Other than in one study this does not seem to be published. Could you explain why not?

8. In Vrang et al (2012), studies on ZDF rats those treated with liraglutide, histology showed that there was increased ductal proliferation and acinar to ductal metaplasia and one of those treated with exenatide had a “hemorrhagic pancreas” at necropsy with “moderate apoptosis-like necrosis, minimal inflammatory infiltration and slight hemorrhage/edema”. In the same report pancreas amylase was increased in the incretin treated rats.

However, the title suggested that there was no evidence of pancreatitis in liraglutide. Do you think this title gives a misleading impression since there was pancreatic pathology and elevated enzymes?

9. Currently, there is a lack of cardiovascular outcome trial data. When is your first study going to report results?

10. In data submitted to the FDA about thyroid tumours, Novo Nordisk did not present

calcitonin data as individual arithmetic data, but chose to present log transformation of data to produce geometric means. Isn't there a risk this method would conceal important elevated results?

11. Again, in data presented to the FDA looking at alpha-cell mass in animal studies, average results were presented. This showed a small, non-statistically significant increase in alpha cell mass in rats treated for 1 week and 6 weeks.

-Since animals respond differently to GLP-1 challenge, does Novo Nordisk agree that individual reports would be more informative?

-Does Novo Nordisk agree that this does not rule out that GLP-1 treatment may lead to alpha-cell hyperplasia?

9 .Novo Nordisk has had a glucagon antagonist drug in development. Could you please say why this has not made it onto the market?

Novo Nordisk reply 03/06/13

1. In the course of the investigation, the BMJ look at the literature around the effects of glucagon suppression – one of the claimed benefits incretin mimetics. It is notable that studies have studied the effects of the pathophysiology of both complete and partial glucagon suppression in animals by a range of methods. Over time, each method has led to alpha-cell hyperplasia. This is not a wanted effect, as it may increase the risk of neuroendocrine tumour formation. The latest study by Butler et al in Diabetes has highlighted this, but – as they point out – this could have been anticipated.

In your submissions to the regulatory authorities in both Europe and the US, there is no discussion about the potential adverse effects of glucagon suppression. Could you please explain why?

This is incorrect. A number of animal studies with GLP-1, exendin-4, liraglutide, different DPP-4 inhibitors do not find alpha-cell hyperplasia and studies in the same animal models have shown that the GLP-1 receptor is not involved in mediating the alpha-cell hyperplasia (1;2). Complete removal or blocking of the glucagon receptor, or important signalling components, have caused alpha-cell hyperplasia. This is separate from the relatively modest lowering of glucagon secretion induced by GLP-1.

2. Professor Dan Drucker has stated in publications and conferences that the therapeutic window of alpha-cell suppression is unclear. In light of the findings published by Butler et al in Diabetes this year, what are you actively doing to establish the pathophysiology of liraglutide? Please provide evidence.

Independent studies with liraglutide focusing on the pancreas in different rodent models have been published and no alpha cell abnormalities were found (3-8). These studies have all applied the most accurate methodology. Novo Nordisk continues to collaborate with academic groups and has provided liraglutide for mechanistic studies of the pancreas, and no abnormalities have been described in these studies (9-12). A recent reevaluation of our data from different animal models has reconfirmed the lack of adverse effects on alpha-cells.

3. In 2012, Niels Nyborg and Novo Nordisk published a study in Diabetes that suggested that there were no structural changes in animals treated with liraglutide. However, in regulatory document the regulators noted the following changes:

“An increased pancreatic weight was observed in young healthy cynomolgus monkeys following four weeks (males only) and 52 weeks treatment...Further investigations of the pancreatic tissues collected in the 52-week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group”

The BMJ also has received the pathology reports under FOI and notes that the pancreas mass increases with dose in this particular study.

Furthermore, an FDA reviewer noted that there were statistically significant changes in the weight of both sexes of in 52 weeks and in males at 28 weeks. He believed these changes to be treatment related.

- Why did Novo Nordisk miss out data and discussion of those findings from the final publication?

- Is this omission keeping within the spirit of transparency in science?

We can confirm that the majority of results from our non-clinical pancreas safety studies have been published in the peer-reviewed journal Diabetes by Nyborg et al (13) and in a separate paper by Vrang et al (14). When publishing nonclinical data in a scientific journal, limitations on the article length do not allow for the inclusion of all study results. That particular paper was written with a focus on inflammation of the pancreas (pancreatitis), and Novo Nordisk focused on the primary results from pivotal studies (i.e., those of highest exposure: the 87-week monkey study and the long-term rodent studies). Most importantly, no macroscopic or microscopic changes were noted in any cell type in any of the monkey studies in the pancreas Job number: UK/CC/0513/0062a Date of Prep: May 2013

with a relation to treatment with liraglutide. Liraglutide did not induce pancreatitis in mice, rats, or monkeys when dosed for up to 2 years and at exposure levels up to 60 times higher than in humans. This statement, as noted, also is accurate for the 52 week study.

Novo Nordisk believes that the results of the regulatory non-clinical studies are well-represented in the manuscript by Nyborg et al (13). In relation to international guidelines on disclosure of results from clinical trials, Novo Nordisk is in full compliance, as described at <http://www.novonordisk-trials.com/website/content/our-way-of-disclosure.aspx>. As a company, we strive to publish our research in international, peer-reviewed journals, including both efficacy and safety data. Adverse events in our clinical trials are described in the core manuscripts from the individual trials. All data is represented in a fair and balanced manner, fully adhering to Good Publication Practice (15).

4. In the 87 week monkey study conducted by Novo Nordisk, there were only 5 monkeys in each group. In each of the groups, the mean pancreas weight of the treated animals in both sexes was higher than the control. Do you agree that this finding – given the small numbers and the small increases in mean - does not override the significance of the changes seen at 52 weeks?

The number of monkeys in studies is always low. This is for ethical reasons. Novo Nordisk, ethical committees, and the public are concerned with the use of monkeys in research and we strive to keep the numbers as low as possible. Importantly, there was no increase in pancreas size in the 87 week study and what is most important is that there were no adverse cellular changes in the 4, 13, 52 or the 87 weeks study.

5. The protocol of this study also states that only the thyroid was processed for histology. However, in response to questions posed by the CHMP at EMA, you have stated that “no signs of treatment related inflammatory changes or pancreatitis were observed”. How do you explain this? Did you ever provide a detailed pancreas histology report to EMA or the FDA?

The 87 week study was originally designed to look into thyroid histology and amended to additionally evaluate the pancreas. As stated above and published in Nyborg et al (16), there were no adverse findings induced with liraglutide, no pancreatitis, no pancreas cancer, and no early pancreas cancer related changes of special interest (PanINs).

Regarding the histology report, it formed the basis of the Nyborg et al, pancreas safety monkey tables.

6. Novo Nordisk relied on this study to suggest that there was no increase in pancreas weight in the 87 week study. However, the mean in the study reports does not match that in the graph supplied in response to CHMP questions – nor do the individual weights match up. The means on the graph supplied to the CHMP are lower than those in the report. How do you explain this?

The calculations should be done exactly as stated in the report and should then match across documents.

7. In 2008, Novo Nordisk started routinely collecting pancreatic enzyme data. Other than in one study this does not seem to be published. Could you explain why not?

Novo Nordisk has published pancreatic enzyme data from two studies, one in patients with type 2 diabetes and one in patients with obesity/overweight. The results were shared with the scientific community at Digestive Disease Week 2012 (17;18). In relation to international guidelines on disclosure of results from clinical trials, Novo Nordisk is in full compliance, as described at <http://www.novonordisk-trials.com/website/content/our-way-of-disclosure.aspx>.

As a company, we strive to publish our research in international, peer-reviewed journals, including both efficacy and safety data.”

8. In Vrang et al (2012), studies on ZDF rats those treated with liraglutide, histology showed that there was increased ductal proliferation and acinar to ductal metaplasia and one of those treated with exenatide had a “hemorrhagic pancreas” at necropsy with “moderate apoptosis-like necrosis, minimal inflammatory infiltration and slight hemorrhage/edema”. In the same report pancreas amylase was increased in the incretin treated rats.

However, the title suggested that there was no evidence of pancreatitis in liraglutide. Do you think this title gives a misleading impression since there was pancreatic pathology and elevated enzymes?

The title is not misleading. Importantly, the study did not find any abnormalities in the pancreas associated with liraglutide treatment. Various pancreas pathological lesions were described in a small number of animals, but to an equal extent or even higher frequencies in the various control groups compared to the liraglutide groups. ZDF rats are fragile and severely sick animals, and even in these, there are no adverse findings induced by liraglutide. Additionally, there were no increases in pancreatitis, no changes in duct structures, no proliferation, no hyperplasia seen with relation to liraglutide treatment. The study also found no regional differences in the pancreas. There was a small increase in amylase, but no adverse findings in the tissues. This is thoroughly discussed in the paper.

9. Currently, there is a lack of cardiovascular outcome trial data. When is your first study going to report results?

The LEADER® cardiovascular outcome study (NCT01179048) will prospectively evaluate the overall safety of liraglutide. The trial has enrolled 9340 patients with type 2 diabetes and a high cardiovascular risk profile; patients are randomised 1:1 in a double blind study design to liraglutide or placebo and will be followed for a minimum of 42 months for the primary endpoint of adjudicated macrovascular events including non-fatal myocardial infarction, stroke, or cardiovascular death. Adjudication of all adverse reactions related to pancreatitis and any neoplasm is an integral part of the protocol throughout the duration of the LEADER® study. The LEADER® study will report in 2016. The MACE analysis performed for the FDA in 2009 has been published in Marso et al (19).

10. In data submitted to the FDA about thyroid tumours, Novo Nordisk did not present calcitonin data as individual arithmetic data, but chose to present log transformation of data to produce geometric means. Isn't there a risk this method would conceal important elevated results?

The calculations were done as agreed with FDA and EMA. Individual patient data has also been evaluated, as clearly described in the publication of the data (20).

11. Again, in data presented to the FDA looking at alpha-cell mass in animal studies, average results were presented. This showed a small, non-statistically significant increase in alpha cell mass in rats treated for 1 week and 6 weeks.

- Since animals respond differently to GLP-1 challenge, does Novo Nordisk agree that individual reports would be more informative?

- Does Novo Nordisk agree that this does not rule out that GLP-1 treatment may lead to alpha-cell hyperplasia?

Assuming we are talking about this study, published (6) in 2003, your statement is incorrect. There is an increase in beta-cell mass after one week, which is gone after 6 weeks, but there

are no increases in alpha-cell mass. The exact numbers are 0.72 ± 0.08 (control), 0.76 ± 0.04
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(liraglutide) after one week, and 0.99 ± 0.04 (control) and 1.00 ± 0.09 (liraglutide) after 6 weeks. The difference between liraglutide and controls is non-significant.

9. Novo Nordisk has had a glucagon antagonist drug in development. Could you please say why this has not made it onto the market?

Our glucagon antagonist did not make it to market because we never succeeded making a compound that could be absorbed from the stomach. This was a tablet focused program.

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BMJ questions 03/06/13

I would like to come back to you about a point that I'm finding confusing. You have stated that there was "no increase in pancreas size" in the 87 week study.

But from the tables on pages 187 and 189 of the pathology reports, the pancreases are bigger in the higher doses. I cannot see how this can be used to suggest the increases in the 52 week study are, therefore, not relevant.

Novo Nordisk response 04/06/13

Thank you for your follow up question.

Overall, there is no increase in pancreas size in monkeys with liraglutide. As you have previously noted, in the 52-week study there was, in the females, a dose-dependent and statistically significant increase in pancreas size. There was no such increase in males. In the 87-week study, we saw no increases in pancreas size. This doesn't mean that you will not be able to find numbers that go either up or down; however, in all scientific studies, a number needs to go significantly up in order to be considered an increase. So you will see some of the average numbers go up, and some go down, but the conclusion is that there are not any significant increases. Also, please remember that the point of the studies is to identify pathology, ie adverse cellular or tissue findings, and the studies all showed, both the 52-week or 87-week studies, that liraglutide did not induce any adverse findings related to cells and tissues.

BMJ questions 05/06/13

One last question. I have a copy of the histology from the 52 week study that analyses the beta and non-beta cell mass in pancreatic islets. However, studies have shown that the alpha-cell hyperplasia that occurred in the 2002 Novo Nordisk PNAS study, the study by Yu et al, and Butler et al in Diabetes the alpha-cells occur in the ducts too.

It doesn't appear from that study that this was tested for. Could you confirm why?

Novo Nordisk response 06/06/13

Can you clarify if you mean Novo Nordisk PNAS 2003 – not 2002, and it has to be Gu et al, not Yu et al. Otherwise it doesn't make sense to us? Also it would be helpful to have the complete references, so that we are sure we talk about the same data

BMJ questions 06/06/13

I mean Novo Nordisk, PNAS 2002 (it may have been published in 2003). I also mean Yu, R et al. PLoS One 2011

Novo Nordisk response 06/06/13

Meanwhile I want to make you aware of an important misunderstanding re question 6 in your original list of questions:

Novo Nordisk relied on this study to suggest that there was no increase in pancreas weight in the 87 week study. However, the mean in the study reports does not match that in the graph supplied in response to CHMP questions – nor do the individual weights match up. The means on the graph supplied to the CHMP are lower than those in the report. How do you explain this?

In the initial response we did not quite understand this question, but later realised the problem in the mismatching documents. A human error occurred in the process of writing up the CHMP document which led to the body weight of the animals being submitted in graph instead of pancreas weight. While this is unfortunate it does not change the overall or individual conclusions. EMA has the actual study report. [Note: Accurate graphs provided by Novo Nordisk]

Novo Nordisk response 06/06/13

Assuming that the Novo Nordisk 2002 study is in fact the one from 2003 (1), then this is a paper which shows that complete removal of the glucagon receptor causes alpha-cell hyperplasia. A later study - the one we gave you also in the first response - showed that this alpha-cell hyperplasia is not mediated by the GLP-1 receptor (2).

Other papers also show that complete removal of glucagon receptor signalling causes alpha-cell hyperplasia, like Yu et al (3), but again it has been clearly shown not to be mediated by GLP-1R (2). Also other more different studies find alpha-cell hyperplasia, and also there has been shown not to be related to GLP-1 (4).

This is in sharp contrast to the small lowering of glucagon levels that takes place with GLP-1 analogues that has never been shown to lead to alpha-cell hyperplasia. The Butler study does not show that it is 7 patients on sitagliptin, and one on exenatide and a very poorly matched control group. A very large number of papers are available in the literature that does not show alpha-cell hyperplasia after GLP-1 treatment. To just mention a few with liraglutide, these papers are published in highly respected scientific journals (5-7), as we also mentioned them in the previous answer 2.

Lastly, the 52 week monkey study was focused on finding out why there was an increase in pancreas size. Alpha-cells constitute such a small part of the pancreas that would be impossible to lead to an increase in pancreas size. Nevertheless, alpha-cells are included as they are the majority on the non-beta-cells in that study, and again there were no changes around alpha-cells.

References

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BMJ questions 06/06/13

Thanks for the clarification, Katrine. Whilst you say that the difference was not statistically significant that wasn't that because it was underpowered to detect anything other than an increase of about 50%? One of the groups had an increase of 32%, but the sample size was small. Plus the protocol stated that it was not set up to statistically analyse the organ weights.

Novo Nordisk response 07/06/13

To the first part of you question:

No, we would not be willing to say that. There is no difference when a number is not significant. We agree to the clear dose-dependent and statistically significant increase in female monkeys only, in the 52 week study, but importantly the 87 week study did not confirm this in females, and it did confirm no increase in males, and both the FDA and EMA agreed to that. Apart from the statistical evidence, a biological finding also has to be reproducible, and again that is not the case here, no dose-dependent significant increases in any study but the 52 week, and only in the females. The number of monkeys are as previously explained low for ethical reason, it is not a question of under-powering. The studies were focused on the histopathological analysis and are not at all underpowered and as you know those studies did not show any pathology, cellular damages in any way caused by liraglutide.

You also state: I'm more interested to know if you looked for alpha-cells outside the islets. It's not clear that you did. If you could point me to the relevant part of the 52 week report I would be most grateful.

As to alpha-cells outside the islets: Yes, those would be included, as we stain for glucagon across the entire pancreas, so if there were more of those that would be detected. As we also mention above, reproducibility of biological data is very important in science. That also goes for those other studies you mention. We have a lot of studies documenting that liraglutide does not induce any pathology. This specific point about alpha-cells outside the islet comes from one study by Peter Butler, that has a very poorly matched control group, and where 7 out of 8 patients are on sitagliptin and the last one on exenatide. There is not a single study available that confirms these findings, despite the fact that GLP-1's effects on the pancreas has been studied in detail in hundreds of publications since the early 90'ies.

There is no specific page in the report we can point you to. These are complicated studies – you need to read the method section to understand that sections across the entire pancreas was used, and then you need to look for the results part that show absolute mg non-beta. The results are: 77.5 ± 10.5 for vehicle and 70.4 ± 10.4 for liraglutide. This number is in fact numerically lower for liraglutide, but since it is not significant it is naturally only counted as no effect.

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DIALOGUE STARTS

Novo Nordisk question to BMJ 21/05/13

I just learned from EMA that BMJ has requested access to Novo Nordisk's liraglutide data, and was wondering if you know who from BMJ has made the request. Based on your previous interest in the debate around incretins and safety, I thought you would probably know. We just want to ensure that you have a complete set of data.

BMJ response 22/05/13

Thanks for your mail and your concern. As you correctly anticipated I have sent the request to EMA. I am currently preparing some questions for you in this connection which I will send to you soon. But as it so happens, I am missing the report on the 87 week monkey studies that was part of your application. EMA doesn't seem to have it. It would be of great help if you could send it to me asap

Novo Nordisk reply 22/05/13

Thanks, Deborah. I will send the 87 week monkey study asap.

Novo Nordisk email 23/05/13

As promised, I have attached the 87 week subcutaneous toxicity study in cynomolgus monkeys on liraglutide (Study ID 203262). In the document you will see it is labelled 'For internal use only'. This is how our documents are labelled for practical reasons, however it should of course not limit your use of it.

DIALOGUE ENDS

DIALOGUE STARTS

BMJ questions 17/04/13

I am writing a news story based on the Quarterwatch report that will be published later today. I would appreciate a reply to the following questions by Friday morning.

Do you have any comments about the Quarterwatch report that suggests that the injectable GLP-1 drugs are associated with an increased signal of pancreatitis, pancreatic cancer and thyroid cancer?

Have you performed any similar analyses? If so, have you published them?

Animal studies showed c-cell hyperplasia in rodents. Is it not the case that human thyroid C cells express the GLP-1 receptor, as do some papillary thyroid carcinomas?

What do you say to the point that the drugs might be cancer promoters and that would explain the increased signals?

What is your view about precancerous pancreatic lesions having GLP-1 receptors?

What do you say to the allegation that not enough is known about the long-term pathophysiological effects of these drugs on the pancreas and thyroid?

Don't you think there's a risk if a drug has a proliferative action and that the GLP-1 receptor is expressed in many different places that there's a risk of unwanted proliferation?

The Quarterwatch report also highlights a high-dose toxicology study of liraglutide in cynomolgus monkeys that revealed a 65% increase in exocrine pancreatic tissue. Could you provide more information about that?

Novo Nordisk statement 19/04/13

I believe we have responded to several of the topics discussed in the Quarterwatch report in previous conversations. At this point, I just want to reiterate that Novo Nordisk is committed to patient safety. We have reviewed the totality of safety information available to us, and remain confident in the safety profile of Victoza®. We continue to work closely with the FDA to provide an on-going assessment of Victoza®'s risk-benefit profile. For additional information about Victoza®, please refer to our FDA-approved product labeling.

DIALOGUE ENDS

DIALOGUE STARTS

BMJ questions 22/03/13

I am writing a news story about the paper published in Diabetes today. It analyses eight human pancreata from patients who have been on GLP-1 based therapy - sitagliptin and exenatide. I was wondering if I could have your:

- general response to paper
- is this a class effect?
- are you aware of what happens to alpha cells when glucagon is suppressed?
- have you ever studied the effects of glucagon suppression on the pancreas?
- have you ever noted this effect on the exocrine pancreas in the past?
- why do you think these effects were not picked up in animal models?

Novo Nordisk statement 24/03/13

As a world leader in diabetes care, Novo Nordisk is committed to patient safety. We have reviewed the totality of safety information available to us, and remain confident in the safety profile of Victoza[®]. We continue to work closely with the FDA to provide an on-going assessment of Victoza[®]'s risk-benefit profile. The study by Butler et al published in Diabetes does not include Liraglutide. The number of patients included in the study is small and the groups are seemingly not well-matched in relation to age at diagnosis, duration of diabetes, BMI and concomitant medication. Finally, it is unclear how long the patients were treated and when the treatment occurred in relation to the time of death.

DIALOGUE ENDS

DIALOGUE STARTS

BMJ questions 15/03/13

I'm emailing to ask you response to the FDA statement made about the GLP-1 drugs yesterday. I would also appreciate a response to the questions I asked about the JAMA Internal Medicine study, now you will have had a chance to look at it (see emails below).

- do you have any comments about the announcement made by the FDA?
- have you analysed tissue samples from pancreata from humans who have been on liraglutide or any of the incretins?

- what measures did you take to look for pancreatic damage in any of your clinical trials or post-marketing studies eg enzyme rises, scans etc?

Novo Nordisk statement 18/03/13

Hereby as promised our response to your questions:

- According to the statement issued by FDA last week, the Agency has not reached any new conclusions regarding the potential safety risks of any drugs in the incretin class, including Victoza®. Clinical studies have demonstrated the efficacy and safety profile of Victoza® for people with type 2 diabetes. Novo Nordisk is committed to patient safety and continuously monitors the safety profile of Victoza®.

- We have not analysed human tissue samples, but as you can see in the attached article (Nyborg et al) we did a pre-clinical study in Monkeys (as well as in mice and rats), concluding that liraglutide did not induce pancreatitis in mice, rats, or monkeys when dosed for up to 2 years and at exposure levels up to 60 times higher than in humans.

- Upon request from the regulatory agencies, Novo Nordisk monitors pancreatic enzymes in all our clinical trials involving GLP-1 analogues, and has been doing so for trials starting after 2008. Regular imaging of the pancreas has not been performed in the clinical trials but pancreatic safety continues to be major focus for Novo Nordisk, both in our clinical trials and in postmarketing safety surveillance.

DIALOGUE ENDS

DIALOGUE STARTS

BMJ questions 22/02/13

I am writing a news story based on a study and linked commentary that are to appear in the medical journal, JAMA Internal Medicine, on Monday.

The study assesses the risks of acute pancreatitis from taking GLP-1 and DPP-4 drugs. The researchers looked specifically at exenatide and sitigliptin and after they adjusted for confounding variables, they concluded that patients who take the drugs have double the risk of being hospitalised for pancreatitis.

Since you market liraglutide, I would be grateful if you could answer the following questions:

1. Do you agree that the risks of pancreatitis are a class effect?
2. Did or do you see any evidence of acute pancreatitis or low grade chronic pancreatitis in your clinical studies?

- Have these results been published?

- If so where?

3. Have you seen any changes in the pancreas in your animal studies, such as low grade pancreatitis or changes in pancreas size?

- Have these results been published?

- If so where?

4. What are the inclusion criteria that you require for a case of pancreatitis to be confirmed in your post marketing studies?

5. If a patient discontinues drug in a post marketing study and later has an event, how is this handled?

Novo Nordisk statement 25/02/13

I am sorry but we cannot offer comments to a story based on a study we have not had a chance to read since it has not yet been published. We would be happy to comment after the study has been published and we have had a chance to look into it.

DIALOGUE ENDS