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

Webappendix 2: Correspondence between the BMJ and the manufacturers or marketers of exenatide, a GLP-1 based drug

**Exenatide**

**BMJ questions 23/05/13**

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 29th May.

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.

   Moreover, in 1999 a rodent study in *Diabetes* suggested that alpha-cells increase in number with GLP-1/exendin-4 (exenatide) use.

   - 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. In light of the findings published by Butler et al in *Diabetes* this year, what are you actively doing to establish the pathophysiology of incretin mimetics in regard to glucagon suppression? Please provide evidence

3. Clive Taylor, a pathologist, who was asked to act as an expert witness in litigation, and has examined pancreas tissue from monkeys which were used for Amylin’s own animal studies of exenatide. He says that those animals treated with Byetta showed pancreatic abnormalities which the control group, not exposed to the drug, did not. He feels that Amylin should allow independent experts access to the material, because they require further analysis.

   - Do you agree?

   - If not, why not?
4. The BMJ has received the pathology reports for the monkey studies under FOI. In the monkeys treated with exenatide the pathologists noted hypercellularity in the islets of Langerhans—home to both alpha and beta cells. In the 93 day study, the pathologist noted that only two of the animals with hypercellularity had an increase in beta-cell number.

A report after 273 days of exenatide treatment suggested that “hypercellularity of the islets was thought to represent the expansion of one or more islet cell types in response to AC2993 administration”. Why did you not stain for other cell types notably alpha-cells?

5. In regulatory documents, the BMJ has found that enzyme levels were measure in a trial that you lead. In this trial those taking weekly exenatide (Bydureon) and had enzyme levels that increased in a higher a higher percentage after 26 weeks of treatment compared the other two drugs.

However, when the trial was published in the Lancet (Bergenstahl et al 2010), this data was not published. Nor is this the only case of unpublished data. Others such as Buse et al (Lancet 2013) did not contain enzyme data. Academics have told the BMJ that this data would be interesting. Why was this data not published?

6. In an internal presentation in 2008, why did Lilly change a statement from: “While it is difficult to prove causal association between exenatide and pancreatitis, a causal association is likely” to “an association is suspected”? And why does Lilly not say publicly that even this is suspected?

7. Thyroid neoplasms were noted in the premarket clinical trials. When EMA asked for further data, Lilly said that there were no calcitonin measurements or histopathology. Nor were these neoplasms published in the equivalent papers. Could you please explain why?

8. Currently, there is a lack of cardiovascular outcome trial data. When is your first study going to report results for either incretin drug?

AstraZeneca and Bristol-Myers Squibb statement 30/05/13:

Per your inquiry, I wanted to provide the following on behalf of AstraZeneca and Bristol-Myers Squibb:

AstraZeneca and Bristol-Myers Squibb continuously review available data for exenatide and saxagliptin. The weight of currently available evidence, including extensive preclinical, clinical and post-marketing data, does not confirm a causal relationship between saxagliptin or exenatide and pancreatitis and/or pancreatic cancer. AstraZeneca and Bristol-Myers Squibb are confident in the safety profiles of Byetta®, Bydureon®, Onglyza®, Kombiglyze™ XR and Komboglyze as demonstrated by extensive clinical trial and safety surveillance data, and believe that current product labeling appropriately describes the benefits and risks.
As part of the approval process for both drugs, there were pre-clinical and clinical studies assessing safety and efficacy. There also have been post-marketing studies evaluating the safety and efficacy of Byetta® and ongoing post-marketing studies of Bydureon®. The available data from these studies, including the 91-day and 273-day monkey studies, were shared with regulators, including the FDA and EMEA. Information regarding the potential risk of acute pancreatitis in patients being treated with exenatide or saxagliptin therapies is included in the warning and precaution sections of the Byetta, Bydureon, Onglyza, Kombiglyze XR and Komboglyze labels throughout the world, which advise patients and physicians to discontinue treatment with these therapies if pancreatitis is suspected.

Our companies have two ongoing long-term, prospective, randomized placebo-controlled cardiovascular outcomes clinical trials - SAVOR (saxagliptin) and EXSCEL (exenatide) - that will provide additional data on the risk of pancreatitis and pancreatic cancer as part of the overall evaluation of safety in these trials. The SAVOR trial, which began in May 2010, has enrolled approximately 16,500 patients and EXSCEL, which began in June 2010, is anticipated to enroll approximately 9,500 patients. Data from the SAVOR trial is expected in the second-half of 2013.

AstraZeneca and Bristol-Myers Squibb have an unwavering commitment to patient safety. We closely monitor the use of our medications through comprehensive surveillance programs and work with health authorities and scientific experts to ensure patients and physicians have a clear understanding of the risk:benefit profile of our medications. AstraZeneca and Bristol-Myers Squibb will take appropriate actions as warranted in the best interest of patients.

Lilly statement 30/05/13

Given that Bristol-Myers Squibb has acquired Amylin and all of the rights to Byetta/Bydureon, you are correct in reaching out to XXX as it relates to exenatide. (And I see that he just responded to you.) You can direct any future enquiries or follow-ups to BMS.

Since one of your questions pertains to Lilly’s actions specifically (question #6), we wanted to provide the following comment on your question:

In an internal presentation in 2008, why did Lilly change a statement from: “While it is difficult to prove causal association between exenatide and pancreatitis, a causal association is likely” to “an association is suspected”. And why does Lilly not say publicly that even this is suspected?

Lilly evaluated data on an ongoing basis to ensure it adequately communicated the risks of Byetta. Lilly concluded that the FDA-approved labeling for Byetta appropriately communicated the potential risk of acute pancreatitis to health care providers.

The FDA approved “Dear Health Care Provider” letter stated as early as October 2007, that “while causality cannot be firmly established, an association is suspected. To better
understand the relationship, if any, between the use of BYETTA and reports of acute pancreatitis, Amylin and Lilly will continue to carefully monitor such events through ongoing surveillance and analysis, in addition to ongoing epidemiologic investigation.”

Amylin and Lilly also provided information to health care practitioners concerning pancreatitis in updated labeling in 2007, and a “Dear Health Care Provider” letter and updated labeling in 2009.

BMJ questions 17/04/13

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?

Bristol-Myers Squibb and AstraZeneca .statement 18/04/13

I did get your email and appreciate the chance to provide comment on behalf of Bristol-Myers Squibb and AstraZeneca.

The analysis published on incretin mimetic agents for diabetes by ISMP in “QuarterWatch” provides an overview of specific adverse events reported in association with specific drug exposures in the FDA’s AERS database over a 12 month period ending June 30, 2012.

While these types of analyses may be used to generate hypotheses, they cannot demonstrate causality due to a variety of factors, including that the data in the AERS database are subject to reporting biases and are often limited by a lack of information concerning important variables such as confirmation of diagnosis, specific patient characteristics and co-morbidities, duration of a patient’s disease, prior drug exposures, and concomitant medication use.
The authors themselves caution that their analysis “should be interpreted in light of the known limitations of a reporting system that does not collect data systematically.” As stated in the publication, the “submission of an individual report does not in itself establish that the suspect drug caused the event described – only that an observer suspected a relationship.” Further, the authors acknowledge that their analysis does not establish a causal relationship between either pancreatitis or pancreatic cancer and GLP-1 therapy. According to the authors, the signals that they purported to observe “require further investigation to determine the frequency of occurrence and to establish a causal relationship to the suspect drug.”

Odds ratios assume similar reporting rates for specific events for all of the medications examined. However, spontaneous adverse event reporting may be affected by external events such as label updates, Dear Doctor Letters, or media coverage, any of which could cause an increased level of reporting for a specific medication. In addition, the authors acknowledge that “drugs that are a litigation target may have a higher reporting rate because of publicity and advertising for clients” and that the majority of exenatide reports came from consumers rather than health professionals. For all these reasons, direct comparison of event rates of different agents generated from this type of analysis should be interpreted with caution, as the authors themselves acknowledge. These data need to be put into context with data from clinical trials and epidemiology studies, which are better suited to assess risk.

Bristol-Myers Squibb and AstraZeneca are confident in the benefit-risk profile of Byetta, Bydureon, Onglyza and Kombiglyze XR as demonstrated by extensive clinical trial data and safety surveillance data. As part of standard safety surveillance, Bristol-Myers Squibb and AstraZeneca closely monitor and evaluate all adverse event reports and share that information with regulatory authorities. Patients should contact their healthcare providers if they have any questions about their medications. If patients suspect pancreatitis, they should stop taking Byetta, Bydureon, Onglyza or Kombiglyze XR and contact their healthcare provider right away. In the U.S., incidence of acute pancreatitis is two- to three-times higher in patients with diabetes compared to the general population. Recent U.S. estimates suggest an incidence of 0.7 cases of pancreatitis per 1,000 adults per year in the general population.

In the Onglyza clinical program (Phase 2b/3 trials), there was no safety signal related to cancer in the pancreas. In addition, there was no safety signal seen in carcinogenicity studies in the two animal species (mouse and rat) studied. Further, there was no saxagliptin-related evidence of ductal metaplasia in any of the nonclinical toxicology studies conducted in mouse, rat, dog, or monkey. In the exenatide clinical program (Phase 2b/3 trials), there was no safety signal related to cancer in the pancreas. In addition, there was no safety signal seen in carcinogenicity studies in the two animal species (mouse and rat) studied. Further, there was no exenatide-related evidence of ductal metaplasia in any of the nonclinical toxicology studies conducted in mouse, rat or monkey.

**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 studies 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?

**Lilly statement 26/03/13**

Thank you for your inquiry regarding the study by Butler, et al. published online in Diabetes.

We cannot comment specifically on this small study involving only one exenatide-treated patient. What we can tell you is that an extensive nonclinical safety program was conducted to support the marketing applications of exenatide twice daily (BID) and exenatide once weekly (QW). In those studies, exenatide administration was not associated with any observed drug-related pancreatic tissue damage or toxicity.

**BMJ questions 15/03/13**

I'm emailing to ask you response to the FDA statement made about the GLP-1 drugs yesterday.

- 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 exenatide 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?

**BMJ questions 25/02/13**

I am writing a news story based on a study and linked commentary that are being published in the medical journal, JAMA Internal Medicine, today.
The study assesses the risks of acute pancreatitis from taking GLP-1 and DPP-4 drugs. The researchers looked specifically at exenatide and sitagliptin 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 exenatide, 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?

**Lilly response 26/02/13**

Exenatide has a well-established safety profile based on preclinical, clinical, post-marketing and epidemiological studies. Nearly 2 million patients have used exenatide worldwide since it was introduced in 2005.

With regards to the findings published in the recent JAMA Internal Medicine article, these data are in contrast to most other studies, which did not find a significantly increased risk of acute pancreatitis in patients using exenatide in comparison with other glucose-lowering medications. It’s important to note that patients with type 2 diabetes have a greater incidence of pancreatitis than patients who do not have diabetes, independent of specific blood glucose-lowering therapy use.

With regard to evidence of pancreatitis in our preclinical and clinical studies:

- In preclinical studies using normal and diabetic rodent models, and obese diabetic rats, no adverse effects of exenatide have been noted on the pancreas, including pancreatic exocrine structure and functions. Exenatide did not worsen acute pancreatitis in diabetic ob/ob mice and was considered to be without adverse effect on the pancreatic exocrine structure and function at all dose concentrations in
type 2 diabetic obese ZDF rats.ii These findings are in contrast to the results of two studies conducted by an external group. This group reported an exendin-4 (exenatide)-induced subtle increase in pancreatic inflammation in normal rats suggestive of asymptomatic low-grade chronic pancreatitis and chronic pancreatitis-like changes in a genetically engineered mouse model (KrasG12D) of pancreatic neoplasia.iv

- In our clinical studies, the proportion of patients experiencing pancreatitis has been similar among exenatide, placebo and comparator-controlled exposed subjects.
- Five post-marketing retrospective cohort studies – including a study conducted independent of Lilly or Amylin – have used a longitudinal design and insurance claims data to evaluate the risk of acute pancreatitis in patients using exenatide. These studies have not demonstrated significantly increased risk of acute pancreatitis associated with exenatide compared to other antidiabetic therapies. v,vi,vii,viii,ix
- Prior to the publication of the paper by Singh et al., only one publication suggested an association between GLP-1-based therapies and acute pancreatitis, which was based on a cross-sectional analysis of spontaneously reported adverse events in the FDA Adverse Event Reporting System (AERS). This study, “Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies” by Michael Elashoff, et al., was published in the February 2011 e-publication of Gastroenterology. However, as the authors of this analysis acknowledge, limitations of AERS data do not allow any causal conclusions to be drawn.x

As far as we understand, your question relates to the criteria to establish diagnosis of acute pancreatitis which were used in post-marketing studies. These criteria vary and depend on the type of study and data available. For example, in a retrospective cohort study reported by Dore et al., the criteria required two of the following: 1) abdominal pain, 2) pancreatic enzyme elevation meeting predefined criteria, or 3) radiographic evidence of pancreatitis.vi In other studies, cases of acute pancreatitis were defined as hospitalizations with diagnosis code for acute pancreatitis.v Episodes of pancreatitis that are reported to us after exposure to exenatide are routinely assessed as being associated with exenatide.

Patient safety is of utmost concern for us, and we will continue to support drug safety programs that monitor for events of pancreatitis. Lilly remains confident in the positive risk-benefit profile of exenatide and its value as a treatment option for type 2 diabetes.

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### References


