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

Webappendix 3: Correspondence between the BMJ and the manufacturers or marketers of linagliptin, a GLP-1 based drug

Linagliptin

**DIALOGUE STARTS**

**BMJ questions 17/04/13**

I am writing a story based on the Quarterwatch report that will be published later today. I would appreciate it if you could answer the following questions by Friday morning UK time.

Do you have any comments about the Quarterwatch report that suggests that the DPP-4 drugs are associated with an increased signal of pancreatitis and pancreatic cancer?

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

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?

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?

**Boehringer Ingelheim statement 18/04/13**

Pancreatitis is a serious but uncommon condition which is known to occur more frequently in patients with type 2 diabetes. Pancreatitis has been reported in clinical trials and spontaneous post marketing sources. Guidelines for the use of linagliptin in patients with suspected pancreatitis are included in the prescribing information of the treatment. Patient safety is of the upmost importance to Boehringer Ingelheim and Eli Lilly and Company, and the use of all their licensed treatments, including Trajenta®, are closely monitored with information and educational materials provided to healthcare professionals remaining continuously updated.

Boehringer Ingelheim and Eli Lilly and Company remain in continuous communication with the regulatory authorities and ensure that all clinical trial data is published. In addition,
updated safety reports have been provided to both the U.S Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) which can be found documented on the authority’s websites.

**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.

- 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 linagliptin 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?

**Boehringer Ingelheim statement 18/03/13**

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**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 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 linagliptin, 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?

Boehringer Ingelheim statement 25/02/13

Do you agree that the risks of pancreatitis are a class effect?

Pancreatitis is a serious but uncommon condition which is known to occur more frequently in patients with type 2 diabetes. For various DPP-4 inhibitors and GLP-1 receptor agonists pancreatitis has been described in clinical studies or postmarketing reports. Pancreatitis is included in the side-effect profile of the approved linagliptin labels.

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?

The frequency of pancreatitis reports was low in linagliptin treated patients as well as in comparator treated patients (placebo or active comparator). The number of reports of
pancreatitis was higher in linagliptin treated patients compared to comparator treated patients. The data are reflected in the approved linagliptin labels and pancreatitis is included in the side-effect profile.

BI policy is to publish all clinical trials which will occur. Updated safety reports have been submitted to the regulatory authorities. Further details on the safety dataset at submission are documented on the EMA and FDA website.

**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?**

Linagliptin did not cause histological changes in the pancreas of animals indicative of pancreatitis or pancreatic injury, despite long-term exposure to very high doses of drug.

The data from the extensive animal safety studies conducted to support registration of linagliptin have been submitted to regulatory agencies worldwide. A summary of the assessment by the FDA, including around the data on animal studies can be found in the publically available documents under: [http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201280Orig1s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201280Orig1s000TOC.cfm)

No histological changes in the pancreas were found in an additional study using diabetic animals (Chen L, et al. Curr Mol Med 2012; (12) 8: 995-1004; Data on file)

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

For postmarketing studies (Phase IV studies), the same criteria for the assessment of safety as for any other clinical study, including Phase III studies apply: As for any adverse event, cases of pancreatitis need to be reported by the investigator. This has to occur independent of an assessment of causality by the investigator.

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

Any patients who prematurely discontinue treatment have a follow up visit where safety data is collected. The time period for this visit depend on the individual clinical trial, and is typically 28 days after the end of treatment visit. Any adverse events (i.e. pancreatitis) are captured under the treatment group and designated as a “post treatment” adverse event. These are reported accordingly in the clinical trial report, and as part of safety updates for the regulatory authorities.

**DIALOGUE ENDS**