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

Webappendix 5: Correspondence between the BMJ and the manufacturers or marketers of lixisenatide, a GLP-1 based drug

**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 lixisenatide 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?

**Sanofi response 18/03/13**

**Do you have any comments about the announcement made by the FDA?**

- We understand that the U.S. Food and Drug Administration (FDA) has not reached any new conclusions about safety risks with incretin-based drugs, which include GLP-1 receptor agonists and DPP4-inhibitors, and that this early communication is intended only to inform the public and health care professionals that the FDA intends to obtain further information in order to properly evaluate the new findings. We further understand that the FDA will communicate its final conclusions and recommendations when its review is complete or when the FDA has additional information to report. The safety and well-being of patients with diabetes are always of the utmost importance to Sanofi. We therefore await the results of the FDA’s evaluation of the unpublished new information.

**Have you analysed tissue samples from pancreata from humans who have been on lixisenatide or any of the incretins?**

- No imbalance in the cases of pancreatitis has been observed in the lixisenatide development program when comparing patients exposed to the drug versus the control group. Anato-mopathology studies such as those mentioned in the FDA communication (i.e., examination of pancreata of patients with type 2 diabetes who were exposed to incretin-based therapies and died for unknown reasons) were not performed as a part of the lixisenatide clinical program.

**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?**

- No imbalance in the cases of pancreatitis has been observed in the lixisenatide development program when comparing patients exposed to the drug versus the control group. In the lixisenatide development program, close monitoring of amylase and lipase was implemented, and special attention was paid to clinical signs and/or symptoms suggestive of pancreatitis. In the presence of suspected pancreatitis and/or
confirmed elevation of amylase and/or lipase, gastroenterological evaluation and imaging testing (ultrasound and/or CT or MRI) was performed in order to confirm or exclude the diagnosis of pancreatitis.

**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 lixisenatide, 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?

**Sanofi response 25/02/13**
1. Do you agree that the risks of pancreatitis are a class effect? Acute pancreatitis has been possibly associated with the use of incretin-based therapies, which include DPP-4 inhibitors and GLP-1 receptor agonists.

2. Did or do you see any evidence of acute pancreatitis or low grade chronic pancreatitis in your clinical studies? In the GetGoal programme, out of more than 5,000 patients, acute pancreatitis was reported in 2 (<0.1%) patients in the lixisenatide group and in 1 (<0.1%) in the comparator group (placebo).

   - Have these results been published? Please find GetGoal references and dates attached
   - If so where? Please find GetGoal references and dates attached

3. Have you seen any changes in the pancreas in your animal studies, such as low grade pancreatitis or changes in pancreas size? There is nothing reported on pancreas size or pancreas organ weight in lixisenatide non-clinical studies, and there are no reports of pancreatitis in any toxicology studies conducted with lixisenatide.

4. What are the inclusion criteria that you require for a case of pancreatitis to be confirmed in your post marketing studies? In post-marketing studies, the criteria for the diagnosis will likely depend on the study design (prospective vs. retrospective, observational vs. interventional, company sponsored vs. investigator sponsored), since this will determine the data that will be available for assessment.

5. If a patient discontinues drug in a post marketing study and later has an event, how is this handled? The handling of adverse events would depend on study design (prospective vs. retrospective, observational vs. interventional, company sponsored vs. investigator sponsored), which will determine the data available for assessment. In the lixisenatide development program, investigators were instructed to follow-up with patients who prematurely discontinue from studies, until the planned end of the study period for each of those patients. In addition, if any serious adverse events are brought to the attention of investigators after the end of the study period, and if these are considered by the investigators to be possibly related to the investigational product, the investigators are instructed to report these events to Sanofi Pharmacovigilance.

**DIALOGUE ENDS**