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

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

**Alogliptin**

**DIALOGUE STARTS**

**BMJ questions 15/03/13**

I'm emailing to ask your 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 alogliptin 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?

**Takeda response 15/03/13**

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

As indicated in the Drug Safety Communication issued yesterday by the U.S. Food and Drug Administration FDA, the Agency has not reached any new conclusions about safety risks with incretin mimetic drugs, and this early communication is intended only to inform the public and health care professionals that the Agency plans to obtain and evaluate this information. Patient safety is a top priority for Takeda, and we remain committed to ongoing clinical research to understand and investigate potential safety concerns.

**Have you analysed tissue samples from pancreata from humans who have been on alogliptin 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?**

Takeda has conducted extensive clinical research around NESINA (alogliptin), including placebo- and active-controlled clinical trials involving more than 13,000 patients. In the clinical trial program for NESINA, pancreatitis was reported in 11 of 5,902 (0.2%) patients receiving NESINA 25 mg daily, compared to 5 of 5,183 (<0.1%) patients receiving all comparators. No toxicology significant effects in the pancreas or pancreatic cell were observed in non-clinical studies of NESINA. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using NESINA and the fixed-dose combination therapies, OSENI (alogliptin and pioglitazone) and KAZANO (alogliptin and metformin HCl). For more information, please see the Full Prescribing Information for [NESINA](#), [KAZANO](#), and [OSENI](#).

Takeda worked with the FDA at the time of approval to develop the Warnings section of the labels for all NESINA-containing medicines and the patient Medication Guides for these products, which each include information relating to pancreatitis. We are confident in the therapeutic benefits and safety profile of NESINA and the FDC therapies, OSENI and KAZANO, and the importance of these therapies as treatment options for patients living with type 2 diabetes.
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 alogliptin, 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?

Takeda response 25/02/13

Takeda was not involved in the study or publication of “Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus A Population-Based Matched Case-Control Study” in the Journal of the American Medical Association (JAMA) Internal Medicine, which focused on sitagliptin and exenatide. All questions specific to this data should be directed to the study investigators.
Patient safety is a top priority for Takeda, and we remain committed to ongoing clinical research to understand and investigate potential safety concerns. Takeda has conducted extensive clinical research around Nesina (alogliptin), including placebo- and active-controlled clinical trials involving more than 13,000 patients, and we are confident in the therapeutic benefits and safety profile of Nesina and the FDC therapies, Oseni (alogliptin and pioglitazone) and Kazano (alogliptin and metformin HCl), and the importance of these therapies as treatment options for type 2 diabetes.

Takeda worked with the U.S. Food and Drug Administration (FDA) at the time of approval to develop the Warnings section of the labels for all Nesina-containing medicines and the patient Medication Guides for these products, which each include information relating to pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Nesina and the fixed-dose combination (FDC) therapies, Oseni and Kazano. In the clinical trial program for Nesina, pancreatitis was reported in 11 of 5,902 (0.2%) patients receiving Nesina 25 mg daily, compared to 5 of 5,183 (<0.1%) patients receiving all comparators. No toxicology significant effects in the pancreas or pancreatic cell were observed in non-clinical studies of Nesina.

It is worth noting that the study published in JAMA, “Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus A Population-Based Matched Case-Control Study,” has not looked at Takeda products.

DIALOGUE ENDS