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

Webappendix 7: Correspondence between the BMJ and the manufacturers or marketers of sitagliptin, a GLP-1 based drug

**DIALOGUE STARTS**

**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.

   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 sitagliptin? Please provide evidence

3. In 2007, Merck approached researchers at UCLA to study the effect of sitagliptin on rats. The UCLA team designed the study and Merck provided financial support and the drug. The researchers noted changes consistent with chronic pancreatitis in some of the animals in the treatment groups. One of the researchers, Professor Peter Butler says that he offered to look at slides of other animal tests carried out by Merck to look for proliferation, but Merck’s scientists did not respond to the offer.

   - why did you decide not to take him up on the offer?
- Have you published the findings from the studies in full?

4. The BMJ has received the preclinical monkey study reports you submitted to the regulators under FOI. The pathologists weighed many organs but not the pancreas. Other researchers have done that. Why did you take the decision not to weigh the pancreas?

5. On the 16 October 2009, the FDA asked Merck to conduct a further safety study in diabetic rats. After earlier warnings, this year you complied with this request. Have you published the results of this study?

6. Could you please explain why a glucagon antagonist Merck had in development did not make it through early phase trials?

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

Merck response 29/05/13

In response to your inquiry last week, Merck’s perspective on the weight of the scientific evidence has not changed. Our statement summarizing our perspective is provided below for your reference.

Since we last corresponded, additional perspectives on this subject have been published* – from Dr. Steven Kahn and Dr. Michael Nauck – which discuss some of the limitations of the Butler autopsy study and the Singh observational study. In addition, Merck has recently published an updated pooled analysis of our controlled clinical studies in Diabetes Therapy.

Merck will be participating in the NIDDK-NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer on June 12 and 13, as will others in the field. This type of open forum provides an important platform for scientific discourse on this subject. We are looking forward to the discussion and are encouraging reporters who are speaking to us about our diabetes medicines to attend to hear the full discussion where many of your questions will be addressed.

We are happy to provide you with the names of experts in the field, including pancreatitis and pancreatic cancer experts, should you be interested.

To your questions about Merck sharing its data, we have of course been continuing to share data on an on-going basis with regulatory agencies around the world. We also continue to work with leaders in the field in our continued assessment of the safety profile of our
diabetes medicines. Merck is in agreement with the recent proposal by Dr. Cefalu and co-authors in Diabetes Care[1] to pool patient-level data for meta-analysis by independent experts and to that end, Merck has offered to provide our patient level data to an independent third party organization. Merck is committed to carefully and regularly monitoring the safety of our medicines. We stand behind the safety profile of sitagliptin and will continue to work closely with regulatory authorities around the world to provide our data, including post marketing reports.

Should you wish to discuss this matter further, please look for me at the NIH meeting. If you continue to have questions after the NIH meeting, please send them to me via email.


* * *

Nothing is more important to Merck than the safety of our medicines and the people who take them, and we take this matter very seriously. Type 2 diabetes is a serious condition that can lead to serious complications including heart disease, stroke, kidney disease, blindness and nerve damage, if left untreated.

We appreciate and support the continued analysis of the safety of diabetes medicines, including sitagliptin. We have carefully reviewed all of the safety data from our preclinical studies and data from randomized clinical trials with sitagliptin in more than 14,000 patients (described below). We have also reviewed post marketing data, a number of independent observational studies and a meta-analysis conducted by an academic research group of clinical trials involving 33,881 patients (described below), that found no association between the use of DPP-4 inhibitors and pancreatic cancer. The weight of all available evidence supports the current safety profile of sitagliptin and we find no compelling evidence of a causal relationship between sitagliptin and pancreatitis or pancreatic cancer.

Randomized, controlled clinical trials continue to be the gold standard for rigorous evaluation of medication safety. We would note that there are substantial methodological issues with the designs of the Butler and Singh studies that limit interpretation of the authors’ observations and the ability to draw conclusions from their work, and we would encourage you to refer to recently published responses to their studies[2]

A published pooled analysis of 19 clinical trials of sitagliptin conducted in 2009 included data from 10,246 patients. (Williams-Herman, D. et al. BMC Endocrine Disorders 2010, 10:7). We updated our 2009 pooled analysis again in 2012 (Engel, S. et al. Diabetes Ther. 2013, 4:1) with data from six additional randomized controlled clinical studies that enrolled more than 4,000 patients. In this updated analysis that included data from more than 14,000 patients, there was no difference in the incidence of pancreatitis or pancreatic cancer between those who received sitagliptin and those who did not. Studies in the pooled analysis were not designed or powered to identify or adjudicate events of pancreatitis or pancreatic cancer.

In addition, a meta-analysis of 53 trials enrolling 20,312 and 13,569 patients for DPP-4
inhibitors and comparators, respectively, was conducted to assess the effect of DPP-4 inhibitors on the incidence of major cardiovascular events (MACE), all-cause and cardiovascular mortality, cancer, and pancreatitis. The study, published in Current Medical Research & Opinion (Vol. 27, No. S3, 2011, 57–64), did not find an increase in the incidence of pancreatitis (0.786 [0.357-1.734], p=0.55) or pancreatic cancer (0.586 [0.212-1.616], p=0.30) associated with the use of DPP-4 inhibitors.

Both DPP-4 inhibitors and GLP-1 analogues are incretin-based treatments; however, DPP-4 inhibitors and GLP-1 analogues have different mechanism of actions.

- DPP-4 inhibitors enhance the body’s own ability to lower blood sugar levels by increasing the levels of the body’s own active incretins, called GLP-1 and GIP.
- GLP-1 analogues are biological products that act as incretin mimetics by directly stimulating the GLP-1 receptors and have no known effect on GIP.

Additionally, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) is the largest randomized controlled clinical study with sitagliptin and includes more than 14,000 patients. This study, which began in 2008, is being led by an independent academic research collaboration between the University of Oxford Diabetes Trials Unit and the Duke University Clinical Research Institute. TECOS continues to be monitored through an independent Data and Safety Monitoring Board (DSMB), which has access to unblinded safety reports. The DSMB most recently reviewed data from TECOS in February 2013 and did not identify any safety concerns to Merck or make any recommendations to change the study.

Because nothing is more important to Merck than the safety of our medicines and the people who take them, we will continue to vigorously monitor the safety of sitagliptin in close collaboration with regulatory agencies and scientific experts. Merck actively monitors post-marketing reports we receive about sitagliptin, including those the company has received of pancreatitis and pancreatic cancer, and provides these to regulatory agencies around the world in accordance with each agency’s requirements.

We are confident in the safety profile of sitagliptin.

(1) Cefalu and associates. “Signals and Noise in Drug Safety Analyses” (Diabetes Care-May 21, 2013)


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 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?

**Merck response 24/03/13**

Upon initial review of the paper, we disagree with the authors’ conclusions. Definitive conclusions cannot be drawn from this small study. It is also important to note that there are inherent limitations to case-control studies. For example, in this small case-control study, there are meaningful differences noted in the average age, gender distribution, and duration of diabetes when comparing the group of patients with diabetes who were treated with incretin-based therapies versus the patients with diabetes in the control group. These differences may affect the results. The findings reported in this small study are in contrast with the data from randomized clinical trials with sitagliptin in more than 14,000 patients, results of a meta-analysis conducted by an academic research group of clinical trials involving 33,881 patients that found no association between the use of DPP-4 inhibitors and pancreatic cancer, and findings of epidemiological studies that have not found an association between pancreatic cancer, where evaluated, and the use of sitagliptin.

On a separate note, we would remind you that the FDA in their statement issued last week stated that they have not reached any new conclusions about safety risks with these medicines, and at this time patients should continue to take their medicine as directed until they talk to their HCP, and HCPs should continue to follow the prescribing information in the drug labels.

Please refer to the statement on merck.comat

**Merck further response 26/03/13**
Meta-analyses of DPP-4 inhibitors: A meta-analysis of 53 trials enrolling 20,312 and 13,569 patients for DPP-4 inhibitors and comparators, respectively, was conducted to assess the effect of DPP-4 inhibitors on the incidence of major cardiovascular events (MACE), all-cause and cardiovascular mortality, cancer, and pancreatitis. The study, published in Current Medical Research & Opinion (Vol. 27, No. S3, 2011, 57–64), did not find an increase in the incidence of pancreatitis ($0.786 [0.357-1.734]$, $p=0.55$) or pancreatic cancer ($0.586 [0.212-1.616]$, $p=0.30$) associated with the use of DPP-4 inhibitors.

**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 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?

**Merck response 18/03/13**

Thank you for your request for MSD’s opinion on the US FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes.

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

We appreciate and support continued analysis of the safety of diabetes medicines, including sitagliptin. As noted in the US FDA statement, the FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health care professionals that the Agency intends to obtain and evaluate this new information.
We are confident in the safety profile of sitagliptin, which is an important medicine to help adults with type 2 diabetes lower their blood glucose levels. MSD has reviewed all of the safety data on sitagliptin currently available to us and, based on that review, we find no compelling evidence establishing a causal relationship between the use of sitagliptin and pancreatic cancer.

As also noted in the US FDA statement, theWarnings and Precautions section of the US drug labels and the patient Medication Guides for incretin mimetic drugs, including sitagliptin, contain warnings about the risk of acute pancreatitis. The FDA issued a previous safety communication on sitagliptin and pancreatitis in 2009 2. The UK Summary of Product Characteristics (SmPC) also already contains warnings about the risk of acute pancreatitis 3.

Pancreatitis is a medical condition divided between an acute form, termed acute pancreatitis, and a chronic form, termed chronic pancreatitis. Acute pancreatitis refers to an episode of pancreatitis. Chronic pancreatitis refers to a progressive, destructive inflammatory condition of the pancreas. Both pancreatic cancer and pancreatitis are associated with a number of risk factors, including type 2 diabetes. While there are data indicating that chronic pancreatitis also appears to increase the risk for development of pancreatic cancer, the current scientific evidence does not establish a causal relationship between acute pancreatitis and pancreatic cancer 4,5.

It is important to note that there are two different types of medicines within the incretin-based medicines. Both DPP-4 inhibitors and GLP-1 analogues are incretin-based treatments; however, DPP-4 inhibitors and GLP-1 analogues have different mechanisms of actions 6.

- DPP-4 inhibitors enhance the body’s own ability to lower blood glucose levels by increasing the levels of the body’s own active incretins, called GLP-1 and GIP
- GLP-1 analogues are biological products that act as incretin mimetics by directly stimulating the GLP-1 receptors and have no known effect on GIP

Because nothing is more important to MSD than the safety of our medicines and the people who take them, we will continue to vigorously monitor the safety of sitagliptin in close collaboration with regulatory agencies and scientific experts.

Type 2 diabetes is a serious condition, and as the FDA said, “patients should not stop taking any medicine without speaking to their physician, and health care professionals should continue to follow the prescribing recommendations in the drug labels”.1

Additional information can be found in the SPC: http://www.medicines.org.uk/EMC/medicine/19609/SPC/JANUVIA+25mg%2c+50mg%2c+100mg+film-coated+tablets/ (17 March 2013)

2. Have you analysed tissue samples from pancreata from humans who have been on sitagliptin or any of the incretins?

No. We look forward to seeing the data referenced in the US FDA statement. As the FDA noted in their statement, the agency has asked the researchers to provide the methodology
used to collect and study these specimens and to provide the tissue samples for further evaluation.

We also look forward to participating in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute’s (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June, where more information may be made available.

3. What measures did you take to look for pancreatic damage in any of your clinical trials or post-marketing studies e.g. enzyme rises, scans etc.?

Randomised controlled clinical trials are the gold standard for evaluating the safety of medicines, and in the clinical trials of sitagliptin, there was no increase in the risk of pancreatitis/acute pancreatitis or in the risk of pancreatic cancer in patients taking sitagliptin compared to patients who did not take sitagliptin. A pooled analysis of 19 clinical trials of sitagliptin conducted in 2009 included data from 10,246 patients. [Patients were randomised to receive sitagliptin, the active component in Januvia, 100 mg/day (N=5,429) or corresponding (active comparator or placebo) control (N=4,817).] 7

• In this pooled analysis use of sitagliptin was not associated with an increase in the incidence of pancreatitis compared to those who did not take sitagliptin. For pancreatitis/acute pancreatitis, the incidence rate was 0.1 per 100 patient-years in each group.
• In this same analysis there was no imbalance in the number of cases of pancreatic cancer reported between those treated with sitagliptin and those not treated with sitagliptin: (two patients in the sitagliptin group and three patients in the group not exposed to sitagliptin).

We updated our 2009 pooled analysis again in 2012 (to be submitted for publication in March 2013 shortly) with data from six additional randomized controlled clinical studies that enrolled more than 4,000 patients. In this updated analysis that included data from more than 14,000 patients, there was no difference in the incidence of pancreatitis or pancreatic cancer between those who received sitagliptin and those who did not. There were 10 patients reported with pancreatitis/acute pancreatitis – five in the group treated with sitagliptin and five in the group that was not treated with sitagliptin – and six patients reported with pancreatic cancer -- three in the group treated with sitagliptin and three in the group that was not treated with sitagliptin 8.

The following are limitations of the pooled analysis: the results are from patients included in randomized, controlled clinical studies of up to 2 years in duration and, thus, may not be fully reflective of use in the general population; the analysis focused on sitagliptin 100 mg/day, the usual clinical dose; and there were multiple comparisons made without an adjustment for multiplicity, which increased the chance for spurious findings. The strengths of these analyses include: the ability to account for all reported adverse events using patient-level data; the large number of clinical trials and patients analysed; and the sensitivity analyses supporting the robustness of the findings 7.
Studies in the pooled analysis were not designed or powered to identify or adjudicate events of pancreatitis or pancreatic cancer, and do not allow for inference on the potential for long-term effects.

The safety of sitagliptin is also supported by an extensive pre-clinical safety program. This includes FDA-mandated studies to assess for potential genotoxicity and carcinogenicity studies in rodents. The latter are conducted over the lifetime of the animals and have been established to be highly predictive of tumour findings in humans. In these studies, sitagliptin was shown not to be genotoxic, and in the carcinogenicity studies conducted at exposures which exceed the clinical exposure of sitagliptin, no adverse effects on the pancreas were observed and sitagliptin was not associated with an increase in the incidence of pancreatic malignancies. In addition, we recently completed a three-month post-marketing rodent pancreatic safety study required by the FDA using a diabetic rat model of type 2 diabetes in which no adverse effects on the pancreas were observed. The totality of the currently available pre-clinical data does not demonstrate an association between sitagliptin treatment and pancreatitis or pancreatic cancer.

In addition, a number of additional clinical trials of sitagliptin are underway including TECOS, the largest randomized controlled clinical study with sitagliptin, which includes more than 14,000 patients and began in 2008. This study is being led by an independent academic research collaboration between the University of Oxford Diabetes Trials Unit and the Duke University Clinical Research Institute. Adverse events of pancreatitis are being adjudicated in TECOS.

- TECOS continues to be monitored through an independent Data and Safety Monitoring Board (DSMB), which has access to unblinded safety reports.
- The DSMB most recently reviewed data from TECOS in February 2013 and did not identify any safety concerns to Merck or make any recommendations to change the study.

We are happy to offer a company spokesperson for you to interview should you wish.

References:
1 FDA Sitagliptin – pancreatitis and pre-cancerous findings http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm
6 Deacon et al., Glycemic efficacy of GLP-1 receptor agonists and DPP-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes – a review and meta analysis. Diabetes, Obesity and Metabolism, in publication
7 Williams-Herman et al. BMC Endocrine Disorders 2010, 10:7
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?

Merck response 24/03/13

Upon initial review of the paper, we disagree with the authors’ conclusions. Definitive conclusions cannot be drawn from this small study. It is also important to note that there are inherent limitations to case-control studies. For example, in this small case-control study, there are meaningful differences noted in the average age, gender distribution, and duration of diabetes when comparing the group of patients with diabetes who were treated with incretin-based therapies versus the patients with diabetes in the control group. These differences may affect the results. The findings reported in this small study are in contrast with the data from randomized clinical trials with sitagliptin in more than 14,000 patients, results of a meta-analysis conducted by an academic research group of clinical trials involving 33,881 patients that found no association between the use of DPP-4 inhibitors
and pancreatic cancer, and findings of epidemiological studies that have not found an
association between pancreatic cancer, where evaluated, and the use of sitagliptin.

On a separate note, we would remind you that the FDA in their statement issued last week
stated that they have not reached any new conclusions about safety risks with these
medicines, and at this time patients should continue to take their medicine as directed until
they talk to their HCP, and HCPs should continue to follow the prescribing information in the
drug labels.

Please refer to the statement on merck.com at
profile-januvia-sitagliptin

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 sitagliptin, 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?

Merck response 26/02/13

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

Merck has reviewed all of the safety data on sitagliptin currently available to us and, based on that review, we find no compelling evidence establishing a causal relationship between the use of sitagliptin and pancreatitis or pancreatic cancer.

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?

Randomized clinical trials are the gold standard for evaluating the efficacy and safety of medicines. While there are no prospectively designed, randomized controlled clinical trials to date with pancreatitis as a primary outcome, in 2010, Merck published a thorough analysis of adverse event reports from 19 randomized controlled clinical trials based on data from 10,246 patients who were followed for up to two years; 5,429 of whom took sitagliptin 100 mg daily. In this analysis, the overall rate of acute pancreatitis in patients taking sitagliptin was low and was the same as the rate for patients who did not take sitagliptin and similar to rates that have been reported in the general diabetic population: 1 per 1000 patient-years in each group. Additionally, there were similar rates of chronic pancreatitis in the two treatment groups (0.4 and 0.3 per 1000 patient-years in the sitagliptin and non-sitagliptin groups, respectively). The references related to this analysis are: Engel SS, Williams-Herman DE, Golm GT, et al. Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. Int J Clin Pract. 2010;64(7):984-90; Williams-Herman D, Engel SS, Round E, et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. BMC Endocr Disord. 2010 22;10:7.

Since that time, we have continued to actively monitor the safety profile of sitagliptin. Subsequent to the pooled analysis published in 2010, Merck conducted a larger pooled analysis that included data from an additional six randomized controlled clinical studies that enrolled approximately 4,300 patients for a total of more than 14,000 patients. In this updated analysis, there were no differences in the incidence of pancreatitis or pancreatic cancer between patients taking sitagliptin and those who did not take sitagliptin. There
were six patients with reports of pancreatic cancer: three patients among those treated with sitagliptin and three patients among those who did not take sitagliptin. A manuscript describing this most recent analysis is to be submitted for publication shortly. In addition, the independent Data and Safety Monitoring Board (DSMB) that is overseeing an additional, long-term randomized clinical study of sitagliptin in more than 14,000 patients (which started in 2008) recently reviewed data from that study in February 2013. The DSMB did not identify any safety concerns to Merck or recommend any changes to the study.

There is also a recently published meta-analysis of randomized clinical trials comparing DPP-4 inhibitors to other treatments, which comprised fifty-three trials enrolling 33,881 patients. This analysis did not reveal an increase in risk of pancreatitis (Mantel-Haenszel odds ratio [95% CI] in patients allocated to DPP-4i treatment was 0.786 [0.357-1.734], p=0.55). The reference for this publication by independent investigators is: Monami M, Dicembrini I, Martelli, et al. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. CMRO. 2011:27(S3):57-64.

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?**

The safety of sitagliptin is also supported by an extensive pre-clinical safety program. This includes studies requested by the FDA to assess for potential genotoxicity and carcinogenicity studies in rodents. The latter are conducted over the lifetime of the animals and have been established to be highly predictive of tumor findings in humans (Sistare FD, Morton D, Alden C, et al. Toxicol Pathol 2011; 39:716-44). The studies included: in rats, separate 2-week, 3-month, 6-month and 2-year studies comprising approximately 600 rats exposed to sitagliptin; in mice, separate 3-month and 2-year studies comprising approximately 550 mice exposed to sitagliptin; in dogs, 2-week, 3-month, 6-month and 1-year studies comprising 96 dogs exposed to sitagliptin as well as a 3-month study comprising 45 dogs exposed to the combination of sitagliptin and metformin; and in monkeys, a 3-month study comprising 24 cynomolgus monkeys exposed to sitagliptin. At drug exposures well in excess of the expected human exposure, these preclinical studies did not reveal any evidence that administration of high doses of sitagliptin results in changes in the pancreas of non-diabetic rats, mice, dogs or monkeys. The reference for that publication is Engel et al (see response to question #2).

4. **What are the inclusion criteria that you require for a case of pancreatitis to be confirmed in your post marketing studies?**
In each randomized clinical trial that has been conducted since the initial approval of sitagliptin, investigators were to report adverse events (serious and non-serious) that occurred during the conduct of the study, as well as serious adverse events occurring within 14 days following the last dose of blinded study drug, in all randomized patients who took at least one dose of study treatment. These events are encoded in a uniform manner using the Medical Dictionary for Regulatory Activities (MedDRA). All such events are included in the assessment of the incidence of pancreatitis.

In the long-term randomized clinical study of sitagliptin in more than 14,000 patients described above, events of pancreatitis are being adjudicated by a blinded adjudication committee, using standard criteria for confirmation of the diagnosis of pancreatitis. These include the presence of symptoms of abdominal pain or vomiting, and the presence of objective evidence of pancreatic inflammation (either elevated pancreatic enzymes or radiographic evidence of pancreatitis).

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

See response to question #4.

Merck Research Laboratories perspective on the Singh et al. study

It should be noted that there are substantial methodological limitations to the Singh et al.1 case-control approach in an insurance claims database that should be considered when forming conclusions from the results of this study that include, but are not limited, to the following:

- Use of claims databases to create control populations, or to adjust for confounders, is limited by the absence of data on relevant baseline characteristics. In the study by Singh et al., the control population was developed using demographic and diabetes-related factors, but notably did not address factors associated with risk of developing pancreatitis. In addition, prevalence rates of risk factors for pancreatitis such as obesity, hypertriglyceridemia and alcohol use are typically substantially underestimated in claims databases such that residual confounding likely persists despite attempts to adjust for these confounding factors.
- There is the potential for channeling bias (or confounding by indication), where patients with certain baseline characteristics related to outcome are preferentially prescribed treatments with specific safety or efficacy profiles. For example, overweight patients may be preferentially prescribed GLP-1-based therapies due to
the absence of weight gain or weight loss associated with these therapies. Channeling bias associated with the use of sitagliptin has been previously reported due to its favorable safety profile, notably channeling to older patients and those with more advanced renal disease 2. In the analysis by Singh et al., the category of “recent users” also had an increased rate of hospitalization for acute pancreatitis despite not being exposed to either sitagliptin or exenatide treatment for a period of between 30 days and up to 2 years prior to the onset of the event, an observation consistent with channeling bias.

- There is a lack of confirmation/adjudication of the diagnosis of acute pancreatitis. In view of the notoriety bias related to the initial publication of case reports of pancreatitis with exenatide in 2006, and the FDA alert regarding post-marketing cases of pancreatitis in 2007, a differential rate of screening and potentially hospitalization for symptoms of abdominal pain may have contributed to a higher rate of hospitalization for non-specific abdominal pain in patients treated with GLP-1 based therapies (e.g., diagnostic bias). Additionally, the algorithm used to detect acute pancreatitis has a positive predictive value of only 50-60% in patients with type 2 diabetes3,4.
- A large number of case-control pairs (n=318) were excluded from the analysis because the diagnosis of pancreatitis occurred within 90 days of the start of the analysis period, which may introduce bias if these cases were less likely to be treated with sitagliptin or exenatide
- The exclusion of case-control pairs without drug enrollment (n=93), which may introduce bias as all of these are unexposed cases
- The grouping of both exenatide-treated and sitagliptin-treated patients into a single assessment group despite meaningful differences in both the magnitude and time course of effects on GLP-1 receptor activation, which are reflected in the different gastrointestinal profiles of the two drugs.

REFERENCES