Executive Highlights

Greetings from Bethesda, Maryland, where our team is reflecting on the absorbing second half of the NIDDK/NCI workshop on diabetes, pancreatitis, and pancreatic cancer. For background, our Day #2 mid-day report discuses highlights from this morning, as well as the general atmosphere of the meeting (it is available at http://close.cx/NIDDKpancreatitisDay2midday). We have little doubt that most people attended this workshop for the discussion of incretin therapies, and today's presentations did not disappoint.

A highlight was Dr. Peter Butler's (University of California at Los Angeles, Los Angeles, CA) talk, titled "GLP-1-based Therapies: Actions on Human Pancreas," which included a review of all his previous studies. Dr. Butler proposed that incretin therapies promote exocrine dysplasia and alpha cell hyperplasia, which can result in pancreatitis in some patients. Novo Nordisk's chief medical officer, Dr. Alan Moses, gave a talk entitled "no evidence of a risk of pancreatitis or PDAC with liraglutide therapy." He supported this position with an encouraging peek at an FDA-mandated prospective observational study, as well as Novo Nordisk's internal experiments using a new monoclonal antibody for the GLP-1 receptor (potentially a critical new research tool, as it seems to be more specific for the GLP-1 receptor than currently available antibodies). Dr. Samuel Engel (Merck Sharp & Dohme Corp., Whitehouse Station, NJ) gave an engaging presentation on Merck's sitagliptin, citing data from animal studies, pooled analyses of RCTs, and observational studies. In this talk, he concluded that these studies do not indicate an increased risk of pancreatitis or pancreatic cancer with sitagliptin. As noted in our mid-day report, we find it rather challenging to place Dr. Butler's findings in the context of the liraglutide and sitagliptin analyses (and vice versa). This is in part due to the different study designs, and of course the general lack of information on how animal models and subclinical abnormalities translate to real-world risks.

Discussing the FDA's interpretation of non-clinical safety signals, Dr. B. Timothy Hummer (Division of Metabolism and Endocrinology Products, FDA, Silver Spring, MD) said that experiments to date have not shown "definitive treatment-related adverse effect" with incretin therapies in healthy animals or models of diabetes. Given that different animal models sometimes show different results, however, he said that the FDA is still working to identify the best animal model for assessing the pancreatic risks of future diabetes drugs. As for clinical safety research, Dr. Solomon Iyasu (Division of Epidemiology, FDA, Silver Spring, MD) noted that studies to date all have methodological flaws, but he looked forward to the reports of pancreatitis and pancreatic cancer that will be included in incretin therapies' cardiovascular outcomes trials. He indicated that the FDA is exploring whether to request additional studies and/or conduct its own observational study, and the agency is also working to determine best practices for studying treatment-related cancer signals ("a perennial problem we face").

Dr. Butler (and many other attendees) departed before the end-of-day panel discussion, but we still got to hear several interesting debates, clarifications, and suggestions for future research. The meeting was concluded by Dr. Judith Fradkin, Director of the Division of Diabetes, Endocrinology, & Metabolic Diseases (NIDDK, Bethesda, MD), who sagely reminded the audience that we must step back and consider incretin therapies not in a vacuum, but as compared to other diabetes drugs and lifestyle intervention – exactly the kind of decision that patients and clinicians must make every day. Overall,

following this meeting, we suspect those following the controversy will be reassured that there is less to the "association" than may have been originally thought by some.

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Detailed Discussion and Commentary

Session 5: Surveillance of High-risk Populations and Early Detection of PDAC

IDENTIFICATION AND METHODS OF SURVEILLANCE OF HIGH-RISK POPULATIONS

Teri Brentnall, MD (University of Washington Medical Center, Seattle, WA)

Drawing on data from 100 patients screened for pancreatic cancer at the University of Washington, Dr. Teri Brentnall described her group's surveillance protocol. Roughly 10% of pancreatic cancer cases are thought to be hereditary, but most of these cancers are not associated with known genetic markers. Dr. Brentnall's group defines high-risk individuals as those who have two or more relatives with pancreatic cancer, at least one of whom is a first-degree relative. People at high risk are screened first with endoscopic ultrasound (EUS). If the EUS results are abnormal, the next step is a more invasive imaging test called endoscopic retrograde cholangiopancreatogrphy (ERCP). If the ERCP is abnormal, the next step is a biopsy to look for pancreatic intraepithelial neoplasia (PanIN) grade 2 or 3 (or intrapapillary mucinous neoplasia (IPMN), which is considered equivalent to PanIN-3). Patients who have PanIN-2 or PanIN-3 lesions are given a choice between continued surveillance or partial or full pancreatectomy. Dr. Brentnall emphasized the importance of counseling patients and training them in diabetes management and potential side effects (the worst, in her view, is hypoglycemia – a condition that has been fatal for at least one of her patients). Stepping back to consider which groups should be screened, she noted that smoking, diabetes, and impaired glucose tolerance are all key risk factors for pancreatic cancer. Dr. Brentnall reminded us that defining the at-risk population properly is critical: imaging tests are cost-effective only among patients with a pancreatic cancer risk of 15% or more.

- **Dr. Brentnall briefed the audience on how to interpret the grading of pancreatic intraepithelial neoplasm (PanIN) lesions.** PanIN-1 and/or PanIN-2 are seen in 16% of

normal pancreases, she said. She explained that PanIN-1 lesions are "no problem" and that interpretation of PanIN-2 lesions is fuzzier ("who knows"). However, PanIN-3 lesions are definitely worrisome. PanIN-3 lesions are not seen in normal pancreases in autopsy studies, but they are seen in roughly 40% of pancreatic ductal adenocarcinoma (PDAC). The progression of PanIN3 to PDAC has been described in clinical case studies; the process can take anywhere from 18 months to 12 years. Mouse models corroborate that PanIN lesions can worsen and eventually turn into deadly cancer ("stepwise neoplasia").

- **Dr. Brentnall described a set of 100 high-risk individuals who received endoscopic ultrasound (EUS) to screen for pancreatic cancer at the University of Washington.** Forty-eight people had normal EUS results initially; 10 of these people subsequently progressed toward higher risk, and 38 people underwent no detectable change during five or more years of follow-up. Among the fifty-two people with abnormal EUS, one had cancer detected by a subsequent imaging test called endoscopic retrograde cholangiopancreatogrphy (ERCP), 19 had normal ERCP, and 22 had abnormal ERCP. Twenty-one of those with abnormal ERCP underwent surgery. Four got partial pancreatectomies (three of these people had PanIN2 lesions, and one had cancer). The other 17 people got total pancreatectomies; five of them had PanIN2 lesions (all of these people had insulin-dependent diabetes), and 12 had PanIN3 lesions. It was unclear whether any were on incretins.

SUMMARY

Michael Goggins, MD (The Johns Hopkins University, Baltimore, MD)

Dr. Michael Goggins acknowledged that the surveillance and early detection of pancreatic ductal adenocarcinoma (PDAC) could be considered "quite complex" and full of unknowns, but he is optimistic: he said that current screening for pancreatic cancer resembles screening for colon cancer 25 years ago. To improve pancreatic cancer screening and treatment, Dr. Goggins called for better risk stratification, more precise interpretation of diagnostic findings, more useful biomarkers, clearer understanding of cancer development, and stronger consensus on clinical protocols. A critical part of achieving these goals will be getting more long-term data on patient outcomes, he noted.

Session 6: Effects of DM Treatment on PDAC

MECHANISMS OF THE TROPHIC EFFECTS OF GLP-1 AND DPP-4 INHIBITORS

Murray Korc, MD (Indiana University School of Medicine, Indianapolis, IN)

Filling in for Dr. Josephine Egan, session moderator Dr. Murray Korc presented Dr. Egan's conclusion slide about the trophic effects of GLP-1. The acute effect of GLP-1 is to stimulate glucose-dependent insulin release, but the peptide also has several chronic effects. It refills insulin stores, promotes beta-cell proliferation and survival, and suppresses beta cell apoptosis. Lest beta cells grow out of control, GLP-1 also seems to constrain its own effects through four negative feedback loops. In the synopsis included in the meeting handbook, Dr. Egan adds that the role of DPP-4 inhibition is more complicated, because DPP-4 has many substrates besides GLP-1 (and some of them, such as GLP-2, are known to have their own trophic effects).

INCRETIN MIMETICS ASSOCIATIONS WITH PDAC?

Peter Butler, MD (University of California at Los Angeles, Los Angeles, CA)

Dr. Peter Butler gave a straightforward review of his previous work on incretins and pancreatitis, offering possible mechanisms that could explain the potential interaction. Focusing mainly on the data, he refrained from making broader statements about the use of incretin therapies in clinical practice. Dr. Butler spent the majority of his presentation describing his animal studies, as well as his recent study of human pancreases. During this review, he highlighted that in rodents, GLP-1 therapy induces ductal proliferation, and the changes are most notable in the head of the pancreas. He proposed that GLP-1 may accelerate chronic pancreatitis and dysplasia and noted that it may have no affect in the absence of dysplasia. Dr. Butler asserted that data from human pancreases suggests that GLP-1 may accelerate exocrine dysplasia and induce alpha cell hyperplasia, which can both intrude into the pancreatic ducts – to him, this finding offers a plausible mechanism for how incretin therapy promotes acute pancreatitis.

- **Dr. Butler offered a mechanistic explanation of why type 2 diabetes is associated with an increased risk of pancreatic cancer.** He noted that since type 2 diabetes is marked by ongoing beta cell apoptosis (cell death) and local inflammation, the pancreas needs to replenish its supply of beta cells. Dr. Butler reminded the audience of two facts: 1) islet cells make up only 1% of the entire pancreas; and 2) progenitor cells are typically programmed to repopulate the organ in which they reside. Thus, if the pancreas does harness progenitor cells, only 1% of these cells would differentiate into beta cells, and the remaining 99% would target exocrine cells. Notably, type 2 diabetes does not involve an exocrine deficiency; thus the disease drives a proliferation of cells in an area where such growth is not needed (i.e., the exocrine pancreas).
- **Dr. Butler then recounted "the incretin story," noting that his first animal study was commissioned by Merck.** Specifically, Merck asked Dr. Butler to use his HIP rat model of type 2 diabetes to evaluate whether sitagliptin (Januvia) could prevent beta cell loss. Dr. Butler's group found that while sitagliptin conferred beneficial effects to the beta cells, it appeared to have harmful effects on the exocrine pancreas – mice treated with sitagliptin had more acinar-to-ductal metaplasia and higher rates of ductal cell replication compared to mice treated with metformin or metformin plus sitagliptin. At the time, Dr. Butler concluded that "because the apparent adverse effects of DPP-4 inhibitors are at least to some extent offset by the concurrent use of metformin, it is perhaps judicious to use DPP-4 inhibitors only in addition to metformin until the potential long-term adverse effects of these therapies can be ruled out in humans." In describing his reaction to this initial rat experiment, Dr. Butler remarked "we felt obliged to continue to sort out what was going on."
- **Dr. Butler explained that he subsequently examined the effects of exendin-4 on other rodent and found results consistent with his initial study.** Rats treated with exendin-4 exhibited an increased proliferation of pancreatic ductal cells. Dr. Butler remarked that this observation is consistent with the finding that exocrine duct cells express the GLP-1 receptor, as well as the finding that rodents treated with GLP-1 have larger pancreases. He highlighted that exendine-4 only increased cell proliferation in specific parts of the pancreas – he also implied that other researchers who found no effect for incretin therapies likely failed to conduct a thorough analysis of the entire pancreas. Dr. Butler's subsequent study in mice found that mice treated with exendin-4 had a "striking increase" in chronic pancreatitis compared to those given saline.

- **Dr. Butler ended by reviewing his recently published morphological study of human pancreases.** He began with an enthusiastic endorsement of JDRF's nPOD, the Network of Pancreatic Organ Donors with Diabetes (he remarked this was perhaps the most important part of his talk). Dr. Butler's group studied 34 human pancreas: 14 from individuals who did not have diabetes (referred to as "ND"), 12 from people who had lived with diabetes (DM), and eight from diabetes patients who had taken incretin therapies for more than one year (DM-I; seven for sitagliptin, one for exenatide). Dr. Butler detailed the results: 1) DM-I pancreases were statistically significantly heavier than the DM and ND pancreases; 2) DM-I pancreases showed marked ductal cell proliferation and dysplasia; 3) DM-I pancreases had a greater number of PanIN 1 and PanIN 2 lesions, thought on this point, he acknowledged that the numbers in his study were small; 4) DM-I pancreases exhibited alpha cell hyperplasia. Dr. Butler also highlighted that three of the eight DM-I pancreases had microadenomas and that one DM-I pancreas had a neuroendocrine tumor that expressed glucagon.
    - **Dr. Butler addressed several critics of his study:** 1) He responded to the criticism that the DM group and the DM-I would not matched well: "anyone who thinks you can do a RCT that ends in brain death with have a hard time." He noted that while his study was not a randomized study, it represented a unique opportunity to use the first nPOD pancreases available to the endocrinology community; 2) Dr. Butler highlighted the critique that some pancreases in the DM group came from patients with diabetes ketoacidosis who likely had type 1 diabetes. He stated "I can assure you that none of the patients had type 1 diabetes" and reasoned that DKA is now often associated with type 2 diabetes; 3) he noted that while one pancreas had GAD antibodies, the ratio was consistent with that observed in type 2 diabetes; and 4) Dr. Butler remarked that some pancreases did have anti-insulin antibodies; however, this finding is common in people who use insulin – i.e., those with long-standing type 2 diabetes.
- **Turning to biological mechanisms, Dr. Butler proposed that incretin therapies promote PanIN lesions and alpha cell hyperplasia, which can intrude into the pancreatic ducts and cause pancreatitis.** He noted that this finding is not surprising since incretin therapies are known to prevent glucagon and since reducing glucagon has been found to promote alpha cell hyperplasia in certain models. Dr. Butler explained that this problem is cyclic, since alpha cells secret glucagon, which ultimately increases levels of GLP-1. He emphasized that incretin therapy likely accelerates dysplasia, and probably does not have an effect in the absence of dysplasia.
- **Dr. Butler provided four recommendations for the future study of incretins and pancreatitis:** 1) he urged investigators to screen patients randomized to incretin therapy vs. other therapies for a variety of markers, including pancreatic enzymes, chromogranin A, glucagon, and GLP-1; 2) he asked the CTSA to help expand the nPOD program; 3) he noted that ongoing clinical studies should attempt to clarify the temporal relationship between drug discontinuation and subsequent events; and 4) he called for mechanistic studies in models of chronic pancreatitis, as well as in adult non-human primates with type 2 diabetes.

Questions and Answers

Q: You do see a lot of variation in the acinar-to-ductal metaplasia and the timing. I'm curious about the number of animals you used. Also, were the effects reversible?

A: That's a great question. Remember that this has been an unfunded hobby of mine since the first study. We did not repeat the study and didn't do the reversibility study. The numbers were small, but the

difference was so striking in every animal who had the drug. A pathologist who has worked with mice a lot said it was the most striking thing he's seen.

NO EVIDENCE OF A RISK OF PANCREATITIS OR PDAC WITH LIRAGLUTIDE THERAPY

Alan Moses, MD (Novo Nordisk, Bagsvaerd, Denmark)

Dr. Alan Moses energetically discussed published and unpublished studies of liraglutide, from rodent toxicology studies to ongoing epidemiologic analyses. He concluded that "no animal or human data support any increased risk of pancreatic cancer following exposure to liraglutide," and he forecasted that liraglutide's ongoing cardiovascular outcomes trial, LEADER, will provide "the best evidence for a relationship to pancreatitis if there is one." The data shown by Dr. Moses were generally in contrast to Dr. Butler's findings, but we think that differences in study design make comparisons challenging at best.

- **In pre-approval toxicology and carcinogenicity studies in normal rodents and non-human primates, liraglutide did not induce histopathological changes in the endocrine or exocrine pancreas.** Drawing an implicit contrast to Dr. Butler's small, short studies in mice, Dr. Moses emphasized the liraglutide studies' large sizes, long duration, and high dosage. (For example, rodent toxicology studies included 50-to-80 animals per group per dose; non-human primates received up to 63-fold the equivalent human dose; and carcinogenicity studies lasted the full 104-week lifetime of rats.) Dr. Moses noted that more islet-cell adenomas were actually seen in the control group than in liraglutide-treated rodents – a result that he said highlights the need to use a sufficient number of animals.
    - **In one 52-week study of cynomolgus monkeys, absolute pancreas weight increased in females.** However, in a subsequent 87-week study in monkeys, absolute pancreas weight did not change. Histopathology in the monkey studies reportedly did not indicate between-group differences in any area or cell type of the pancreas. Dr. Moses drew particular attention to slides from a monkey in the 52-week study, showing that glucagon-positive cells were expressed to a similar extent in liraglutide and control animals, and no marked proliferation of glucagon-positive cells was observed in either group.
- **In completed randomized controlled trials of liraglutide, pancreatic cancer and acute pancreatitis were numerically more common with liraglutide than control therapy, but Dr. Moses pointed out that the absolute numbers were low,** and the rates were not more common than anticipated based on historical data from the general population of type 2 diabetes (see table below). Altogether, 6,628 patients were exposed to liraglutide, and 1,877 patients were treated with active comparators. The total liraglutide exposure was over 5,000 patient years. However, during Q&A Dr. Moses acknowledged that only a "relatively small" number of patients in the trial were exposed to liraglutide for two years, limiting this analysis' implications for long-term exposure.
    - **Two events of pancreatic cancer were reported in liraglutide-treated patients (compared to zero in the active comparator group and one case that was detected prior to randomization).** However, one of these patients was diagnosed with stage 4 pancreatic cancer just one week after admission (exonerating liraglutide of a causative effect in this patient, as Dr. Moses explained it).

- **The completed liraglutide trials included 13 cases of pancreatitis that were diagnosed and coded: nine cases of acute pancreatitis (eight of them with liraglutide) and four cases of chronic pancreatitis (all with liraglutide).** Dr. Moses did not hypothesize why pancreatitis might have been more frequent with liraglutide use. However, during Q&A he remarked that it was interesting that liraglutide-treated patients started to report pancreatitis around the time that exenatide-associated pancreatitis was publicized. He said that he had "no idea" how many patients may have had type 3c diabetes, but that among the 24 patients in LEAD-1 through LEAD-5 who had a history of pancreatitis, none re-developed symptoms. A similar finding was reported in EVIDENCE, an observational study required by French regulators. Of roughly 3,000 patients in EVIDENCE, 36 liraglutide users a past history of pancreatitis, and none of them developed symptoms of pancreatitis while taking the drug.

	Observed rate with liraglutide (per 1,000 PYE)	**Observed rate with active comparators (per 1,000 PYE)**	**"Anticipated rate" in type 2 diabetes (per 1,000 patient years observation)**
Pancreatic cancer*	0.4	0	0.55-1.37
Acute pancreatitis	1.8	0.7	0.5-4.2

- PYE = patient years of exposure. *Two events of pancreatic cancer were seen in liraglutide-treated patients, one was found prior to randomization, and none were seen in patients receiving active comparators

- **Dr. Moses said that Novo Nordisk researchers developed their own monoclonal antibody to the GLP-1 receptor, which they have found to be more specific than the GLP-1-receptor antibodies that are conventionally used.** With this antibody, studies of nonhuman primates suggest that duct cells do not express GLP-1 receptor (though Dr. Moses said that acinar cells do show "background staining"; as we understand it, this would leave open the possibility that GLP-1 receptor agonists could promote acinar-to-ductal metaplasia). During Q&A, Dr. Moses expressed confidence that the antibody performs well, but he also emphasized that it still needs to be shown effective in peer-reviewed research. He said that Novo Nordisk probably would not commercialize the antibody, but that the company might make it available to some investigators.

- **A wealth of new clinical data on liraglutide will become available in the next few years,** with the completion of the drug's cardiovascular outcomes trial and two prospective observational studies that Novo Nordisk is conducting to meet the FDA's post-marketing requirements.

    - **The leadership of Novo Nordisk believes that liraglutide's cardiovascular outcomes trial, LEADER, "will provide the best evidence for a relationship to pancreatitis if there is one."** Dr. Moses said that he is not sure if LEADER will shed any light on carcinogenicity, however, given pancreatic cancer's long latency period. As a reminder, LEADER is a prospective, blinded, placebo-controlled trial for liraglutide that includes acute pancreatitis and pancreatic cancer as endpoints. The study includes 9,340 subjects and has been underway for roughly three years; completion is anticipated in early 2016.

- **Dr. Moses shared an early, "highly favorable" report from a prospective epidemiological study using a large claims database in the US (OptumInsight).** This five-year study includes ~25,000 patients who initiated liraglutide between February 2010 and September 2012; each liraglutide user was matched to a control patient based on age, duration of diabetes, and concomitant medications. Compared to four other types of medications (pioglitazone, metformin, sulfonylureas, and DPP-4 inhibitors), GLP-1 receptors had relative risks that were neutral-to-beneficial both for pancreatitis and for pancreatic cancer. However, Dr. Moses noted that the numbers of events were still low, the confidence intervals still wide, and the study still only halfway complete.
- **Novo Nordisk's other post-marketing epidemiological study does not yet include enough cases for the researchers to make any determinations.** This study uses a clinical practice research database in the United Kingdom.

- **In ongoing clinical trials, Novo Nordisk is measuring patients' lipase and amylase as potential indications of pancreatic problems.** Lipase did increase with liraglutide treatment, but Dr. Moses said that he has "no idea" whether this reflects underlying disease, and he emphasized that lipase values are known to "fluctuate wildly over time." Median lipase rose by roughly 10 U/l to remain below the upper limit of normal (60 U/l), but 10-20% of patients with diabetes had elevated lipase activity. Studies of liraglutide in obese patients suggested that the elevation disappeared once drug was discontinued, and lipase elevation did not predict the development of pancreatitis or other clinical symptoms. Dr. Moses admitted that the mechanism of lipase elevation is unclear but said that it does not seem to be helpful as a monitoring tool. Median amylase levels did not increase with liraglutide treatment.
- **Dr. Moses reviewed 13-week post-marketing studies of liraglutide and exenatide in a rat model of diabetes (ZDF),** in which neither of the two drugs induced pancreatitis, affected biochemical or histopathological markers of pancreatitis, increased pancreas weight, or promoted exocrine or ductal cell proliferation or mass.

Questions and Answers

Q: In liraglutide's clinical development program, there was an excess of pancreatitis. These patients were randomized to receive liraglutide, yes? How do you explain the result?

A: Yes, the trials were randomized. Exposure was 3:1 for liraglutide vs. control, the number of cases was small, and events were not adjudicated. They started to appear around the time that the literature suggested relationship between pancreatitis and exenatide – interesting. We will be able to tell the risk relationship only from prospective studies designed to look at pancreatitis.

Q: Why are there differences between various groups in finding histopathological changes? Another company showed some drug-related histopathological effect on a high background effect.

A: Different animal models will give different results. For normal animals, I can show only the data that I have and cannot explain differences.

Q: How many patients in the completed liraglutide trials were exposed to drug for more than two years?

A: We now have half of the 9,300 patients in the CVOT taking lira for more than two years. The randomized controlled studies that have been completed were of relatively short duration. Some patients were exposed for up to 2 years, and we have 1.3-million patient-years of data in the real world.

Q: How many patients took liraglutide for two years?

A: The number was relatively small – I don't want to mis-quote it but can look it up and tell you before the panel.

INCIDENCE OF PANCREATITIS AND PDAC IN CLINICAL STUDIES OF SITAGLIPTIN

Samuel Engel, MD (Merck Sharp & Dohme Corp., Whitehouse Station, NJ)

In a balanced presentation, Dr. Samuel Engel discussed current evidence on sitagliptin and pancreatitis. He began with animal studies, noting that Merck investigated sitagliptin in a range of animal models with doses far in excess of those used for human studies. He next cited two pooled analyses of randomized controlled trials that did not find an increased risk of pancreatitis or pancreatic cancer with sitagliptin or with other DPP-4 inhibitors (details below). Dr. Engel next pointed out that the FDA AERS database has found that reporting rates for pancreatitis and pancreatic cancer are higher for sitagliptin compared to other medications. However, he highlighted the well-established point that while the FAERS database is useful for detecting a potential safety signal, it cannot establish a casual relationship due to its many limitations. Dr. Engel also noted that while a case-controlled study found a potential signal for pancreatitis (Singh et al., JAMA Intern Med *2013), a self-controlled case study – which he noted is more rigorous in design – found no evidence of an increased risk. Dr. Engel concluded that while these studies come with limitations, the "preponderance of evidence from real-world clinical practice does not indicate an increased risk."*

- **Dr. Engel reviewed the results of two pooled analyses of randomized controlled trials.** First, Merck conducted a pooled analysis of data from 25 RCTs, which included roughly 14,000 patients. Merck found that the combined incidence rate of pancreatitis and acute pancreatitis was similar between the sitagliptin group (which had 5 events) and the non-exposure group (which also had 5 events). Similarly, the two groups had comparable incidence rates of pancreatic cancer (both groups had three cases). Monami et al. also conducted an independent analysis using data from 53 clinical trials of DPP-4 inhibitors (n= ~33,000 patients) and found that the use of DPP-4 inhibitors was not associated with an increased incidence of pancreatitis or pancreatic cancer. In concluding this part of his presentation, Dr. Engel acknowledged that such pooled analyses have limitations. Specifically, the duration of these studies do not allow investigators to infer the potential for long-term treatment effects. Furthermore, the size of the studies may limit their ability to detect rare events.
- **Dr. Engel cited three limitations of the FDA AERS database:** 1) it contains spontaneous and voluntary reports drawn from a population of unknown size; 2) stimulated reporting caused by publicity has been known to affect reporting rates (i.e., notoriety bias); and 3) reporting rates are generally higher for newer drugs compared to older medications.
- **Interestingly – but perhaps not surprisingly – Merck has seen an increase in the volume of pancreatic cancer reports regarding sitagliptin;** however, the company does not believe that this trend indicates a new safety concern, for several reasons. For example, reporting rates have increased only in the US. Furthermore, the increase in cancer reports has paralleled the heightened focus on pancreatic cancer in the scientific literature and popular media.

- **Dr. Engel asserted that a wide range of cohort-designed studies have not indicated that sitagliptin increases the risk of pancreatitis or pancreatic cancer.** However, as expected, these studies have several limitations: 1) the possibility of preferential prescribing to specific patients; 2) the potential of differential rates of diagnostic testing based on the drug used; 3) a limited ability to adjust for potentially confounding risk factors. We very much appreciated Dr. Engel's balanced viewpoint.

PITFALLS OF STUDIES OF ADVERSE DRUG EFFECTS

Yu-Xiao Yang, MD (Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA)

Using both diabetes-related and humorous examples, Dr. Yu-Xiao Yang discussed approaches to assessing adverse events, as well as the limitations of these methods. Pre-marketing clinical trials have several drawbacks – most notably small sample sizes – that limit their ability to detect safety signals. Thus the FDA and companies rely mainly on post-marketing surveillance, which includes adverse event reporting systems as well as formal studies. Dr. Yang focused on observational studies, which are easier to conduct and far more prevalent than phase 4 RCTs. He explained that the emergence of electronic health records has allowed observational studies to look at a large number of real-life patients, typically using either a retrospective cohort or case-controlled design. Dr. Yang noted that such post-marketing studies can have a significant impact on clinical practice, and astutely argued that "the amount of scientific rigor of these studies should match their potential impact." Dr. Yang then detailed the methodological challenges related to observational studies of adverse drug effects. The definition of "drug exposure" can have important implications, and Dr. Yang recommended that studies only look at new drug users (this avoids prevalent user bias). Observational studies also suffer from potential confounding, though propensity scores can help resolve this issue. Lastly, observational studies can suffer from protopathic bias (if you use a drug to treat the early signs of a disease, it may seem like the drug is causing that disease), as well as immortal time bias (a span of cohort follow-up during which, because of exposure definition, the outcome under study could not occur).

FDA SURVEILLANCE OF ADVERSE DRUG EFFECTS

B. Timothy Hummer, PhD, DABT (Division of Metabolism and Endocrinology Products, FDA, Silver Spring, MD)

Dr. B. Timothy Hummer explained that the FDA's Division of Metabolism and Endocrinology Products has taken three main "non-clinical actions" in response to concerns about pancreatitis and pancreatic cancer with incretin therapies: re-evaluating pre-approval studies, requiring manufacturers of marketed incretin therapies to perform new pancreatic safety toxicology studies in rodent models of diabetes, and requesting the FDA's Division of Drug Safety Research to conduct its own rodent studies. The resulting data have not ended the controversy or ambiguity, but they seem to have allayed the FDA's worst fears. Dr. Hummer concluded that the non-clinical development programs for incretin drugs have not shown a "definitive treatment-related adverse effect in the pancreas," and that incretin therapies in a diabetic rodent model "did not result in a definitive adverse treatment-related effect." He also noted that additional research is "warranted" to identify a widely available, reproducible animal model for future studies of drugs with potential pancreatic issues.

- **The Division of Metabolism and Endocrinology Products requested that the FDA's Division of Drug Safety Research conduct tests of incretin safety in several animal**

models, including: chemical-induced pancreatitis in mice, Zucker Diabetic Fatty rats, and C57BL/6 mice fed either a normal or high-fat diet. The incretins studied included sitagliptin and exenatide, which were given for three, six, or 12 weeks. Data from the pancreatitic mice and ZDF rats did not confirm a treatment-related pancreatic signal, but high-fat-fed c57BL/6 mice did experience "time- and dose-dependent exacerbation of acinar cell hyperplasia, atrophy, fibrosis, and increased periductal inflammation" – changes that thankfully "were not associated with animal morbidity or mortality." Dr. Hummer noted that this mouse model needs further evaluation for its utility in pancreatic safety tests.

FDA'S APPROACH TO ADDRESSING A PANCREATIC SAFETY SIGNAL WITH INCRETIN MIMETICS: PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY

Solomon Iyasu, MD, MPH (Division of Epidemiology, FDA, Silver Spring, MD)

After reviewing the limitations of pre-approval randomized trials and post-marketing observational studies, Dr. Solomon Iyasu discussed the FDA's efforts to study the pancreatic safety of incretin drugs in patients with diabetes. He acknowledged that the relationship of incretin therapies with pancreatitis and pancreatic disease remains unclear due to methodological limitations in studies to date, and he noted that the FDA has asked companies to report these diseases as "adverse events of special interest" in their CV outcomes trials. Meanwhile, the agency is reviewing a required, post-marketing epidemiological study of pancreatic cancer and exenatide use (though Dr. Iyasu said that the study's statistical power is limited). The FDA is also exploring whether to request additional studies and whether to conduct its own observational study using medical data. In his conclusion, Dr. Iyasu indicated that the agency is starting to develop a guidance document on best practices in assessing potential cancer risks of drug therapy. We think that this document could be of great help to regulators, companies, and the general public, because – as Dr. Iyasu observed – "this is a perennial problem we face, and many study approaches have been limited."

GENERAL DISCUSSION AND OVERVIEW OF DAY 2

Judith Fradkin, MD (Division of Diabetes, Endocrinology, & Metabolic Diseases, NIDDK, Bethesda, MD); Donghui Li, PhD (The University of Texas MD Anderson Cancer Center, Houston, TX); Alan Moses, MD (Novo Nordisk, Bagsvaerd, Denmark); Samuel Engel, MD (Merck Sharp & Dohme Corp., Whitehouse Station, NJ); Yu-Xiao Yang, MD (Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA); B. Timothy Hummer, PhD, DABT (Division of Metabolism and Endocrinology Products, FDA, Silver Spring, MD); Solomon Iyasu, MD, MPH (Division of Epidemiology, FDA, Silver Spring, MD)

Dr. Fradkin: Consider Dr. Butler's recommendations before he left. One was to do MRIs of the pancreas in randomized controlled trials of incretin therapies. I wonder about that, given the prevalence of pancreatic cysts in the general population, their likely greater prevalence in diabetes, and the concerns associated with identifying unimportant lesions to patients.

Dr. Moses: Sometimes you have to be careful what you ask for because of unintended consequences. This would have to be done in a careful way. The study should be designed specifically for that, and

measurements would need to be very accurate. I agree with you that with a large sample-size study, the use of imaging could raise major concerns.

Dr. Engel: I must say that Dr. Butler dismissed the difference between the incretin-treated patients and the control group in his autopsy study, but there is 20-yer difference between those populations. That 20-year difference may actually result in substantial differences in pancreas volume and weight, as he himself has published. One of the co-authors has shown that the presence of pancreatic antibodies results in smaller pancreas size, and pancreatic antibodies were present in the non-incretin-treated people with diabetes. There is so much confounding, it really becomes problematic. It's about pancreatitis and cancer and looking at the right data set.

Q: Dr. Yang, I have a question on protopathic bias. Thank you for bringing up the gastrin situation. My lab has described gastrin's effects on CCK receptors in pancreas. It is not gastrin that causes cancer, but it does stimulate growth in vitro. Dr. Yang, if you see new-onset cancer in patients given incretins, could it be that those patients already had lesions or cancer, and then the drugs exacerbate it? Maybe the "egg" is already there, but something has to come along and incubate it and make it grow? We know that it is safe to take proton pump inhibitors. Could we learn something from that with regard to incretins? Maybe we should be very careful using them in type 3c diabetes, though.

Dr. Yang: Determining the existence of protopathic bias requires knowledge about biological and clinical aspects. What you proposed is a possible mechanism whereby short-term, recent exposure could be biologically linked to increased risk. At that point you can't dismiss a safety signal as protopathic bias, if there's reason to believe it could be treatment-related from a biological standpoint.

Q: This is for Dr. Moses and Dr. Engel. We have been thinking about pancreatitis and pancreatic cancer. In clinical studies you excluded patients with pancreatitis. But one of our concerns is this group of people with type 3c diabetes. Now that drugs are widely used and openly marketed, it may be possible to identify patients who harbor type 3c diabetes and to analyze them as a separate cohort for whom special surveillance may be valuable. Will you try to identify these patients, and if so how?

Dr. Engel: In the sitagliptin development program, we did not exclude patients with a prior history of acute or chronic pancreatitis. That said, among the 14,000 patients in the program, 40 had a history of acute pancreatitis, and 20 or so had a history of chronic pancreatitis. Moving forward, I think that sensitivity analyses of people who potentially fall into that category certainly seem appropriate. While there may be a potential relationship between type 3c diabetes and pancreatic cancer, I think that many of these issues go beyond that specific patient population, so I don't think we would restrict.

Dr. Moses: Until the reports in 2008-09, acute pancreatitis was not an exclusion criterion in liraglutide studies. None of the people with history of pancreatitis developed pancreatitis during exposure in clinical trial. Clearly there is a lot of controversy still in terms of type 3c diabetes' total impact in the population. I think that it is time to look more carefully and determine not if they should be excluded but if a signal can be identified. The question that I would put back to you is how to diagnose type 3c diabetes. I don't know the answer – I would love to hear from an expert about whether we can define an answer from available data.

Q: What have we learned about the effects of bariatric surgery, which seems to be cancer-protective, and how might this shed light on incretin therapies' effects?

Dr. Moses: I can cleverly avoid giving an answer, because I don't have one. Dr. Dana Andersen and I talked about this recently. It's very different to give a GLP-1 receptor agonist vs. the hormonal changes post-gastric-bypass.

Dr. Dana Andersen (NIDDK, Bethesda, MD): My suspicion is that the reason bariatric surgery is cancer-protective is simply that patients lose weight. Thus their incidence of mortality due to obesity-related cancers goes down. But no studies have been large enough to detect a signal in pancreatic cancer per se. Another interesting part of this story is relevant to Dr. Butler's findings. Post-RYGB, some patients get hyperinsulinemic hypoglycemia, and they are referred for pancreatic resection. 100-200 patients have been referred for this rare complication (maybe 5%). We no longer recommend pancreatectomy, but patients who did have pancreatectomies typically showed nesidioblastosis when resected. Using hematoxylin-and-eosin histology, we knew that these patients were hyper-secretors of GLP-1. Then we looked at actual cell types in the expanded endocrine cell mass, and the real surprise was that the alpha cell mass was dramatically expanded. We had no answer until now – this next observation. Dr Hummer, you've done these beautiful studies – have you looked for glucagon in normal or diseased animal models? If Dr. Butler's observations and the bariatric observations are correct, perhaps there is a relationship between prolonged GLP-1 exposure and alpha-cell mass.

Dr. Hummer: I personally haven't done any studies; I review studies conducted by industry. I did ask a veterinary pathologist about this, though. I asked whether hematoxylin-and-eosin staining could distinguish between alpha cells and beta cells. He basically said that you need to do special staining; as far as I know none of the standard toxicology studies have done that staining. We do have ~22 carcinogenicity studies, and treatment-related increase in glucagon was not noted. If you do see increase in alpha cells with short duration of treatment, when you treat rat or mouse for two years, the lesion does not progress to anything that looks pre-neoplastic or like a tumor. I wonder about this whole mechanism that Dr. Butler has proposed. My understanding is that insulin that is produced shuts down glucagon. If the patient is normoglycemic, they shouldn't be producing a lot of insulin even if GLP-1 is around; therefore I am not sure how excess GLP-1 shuts down glucagon, if insulin is involved. I may not be right on this.

Dr. Moses: In our 52-week monkey studies, we saw no expansion of glucagon cells. In ZDF rat cells, we looked at insulin, glucagon, and pancreatic polypeptide with staining. We saw no evidence of expansion of that cell mass for liraglutide or exenatide.

Dr. Engel: In a previously published autopsy series, researchers found a dramatic expansion of both alpha- and beta-cell mass, correlated with the amount of time that individuals had been on a respirator or in the ICU. The mechanism there remains unclear, but it occurred in the absence of antidiabetic treatment. It could be related to the extent of premorbid illness, or hypoxia pre-death. I think that this is critical in interpreting the whole concept of alpha-cell hyperplasia. It is true that there are a number of models of glucagon receptor antagonism, but to my knowledge alpha-cell hyperplasia has been demonstrated only in cases of hyperglucagonemia – not glucagon suppression.

Comment: GLP-1 lowers glucagon levels but does not shut down production totally. People talk about a rise in insulin, with GLP-1 treatment. Actually, insulin levels during GLP-1 treatment are often lower compared to no GLP-1; what's higher is the relative increase of insulin at a particular glucose level.

Comment: As to the PanIN story with Dr. Butler's findings – my conclusion is that it is consistent with the null hypothesis. We don't know a lot about PanIN prevalence, and there are limitations to doing this properly; it requires rigorous sampling and multivariate modeling. It is completely undeveloped as a field. Certainly, 10-20 years between groups is enough to cause radical differences in PanINs.

Comment: Also, Dr. Butler suggests that duct obstruction could lead to pancreatitis. If it leads to anything, atrophy and acinar dropout would seem more likely. To link it to the clinical endpoint of pancreatitis is too premature.

Comment: We shouldn't use lipase as a way to determine whether someone has acute or chronic pancreatitis. But you see elevated levels in some patients, Dr. Moses. You could stratify a subset of these patients and compare them to people exposed to the drug without presence of lipase elevation – simply endoscopically measure fluid levels of all the hormones secreted from the pancreas. This would be a small study, and it would rule out whether the lipase elevations appear in secretory function of those people's pancreases. It would probably take in about 60 patients, matched. I am assuming that the lipase overflow is due to overstimulation of acinar cells. Another possibility is that GLP-1 is interacting with stellate cells. Still, you will have opportunity to look at that – stellates can be a mechanism for lighting up PanINs that somehow get out into other tissues and are waiting to become cancer. I don't think that any pancreatologist would suggest that lipase elevations are diagnostic of acute pancreatitis. But I hear them talking about whether lipase and amylase levels are up; we need other criteria before acute pancreatitis and chronic pancreatitis. The whole trick is to design a little study with the exposed patients you already have, and take a look – it's just a physiological question. At least then you'll know if the acinar and ductal cells are involved in the lipase elevations.

Dr. Moses: I have insufficient expertise to make an intelligent comment. We need to look more closely. The challenge is that lipase levels are evanescent and that they are already elevated in type 2 diabetes.

Q: PDX-1 is a transcription factor, and it regulates so many things. GLP-1 up-regulates PDX-1 – which promotes beta cell growth – and it also assures the stability of insulin mRNA. What is it doing up-regulating glucagon-secreting cells? What if this relates to the finding that alpha cells can be re-programmed to become beta cells?

Dr. Engel: I feel reluctant to rebut Dr. Butler's work so profoundly without him here, but I will do it anyway. Alpha- and beta-cell mass were calculated based on pancreatic weight. All the calculations and comparisons to the non-diabetic control group were based on the pancreas weight in the control group. Data on pancreatic weights were available for all the patients with diabetes, but only 50% of the normal non-diabetic controls. Also, when you look at the ages, the people for whom weights were available were 20 years younger – 34 vs. 56 years old. It has been well described that in that age range, pancreas weight increases. You need to go back to the basic observation that pancreas weight normalizations could have been substantially impacted by 50% missing data and a 20-year age difference. I'm not sure that this is actually a finding.

Q: First, I think that the very specific antibody to the GLP-1 receptor is critically important. Was it true that the antibody was to beta cells and not alpha cells? If so, why do we see alpha-cell hyperplasia and not beta-cell hyperplasia?

Dr. Moses: The interrelationship between the beta and alpha cells is controversial. It is a hot topic of debate; I am not an expert. Our antibody is against GLP-1R, and it clearly identifies the beta cell based on dual staining. The alpha cell hasn't been looked at as carefully for this, but this is an area where we are just now beginning to probe how this new agent can be used to define tissue distribution of GLP-1r in the pancreas and elsewhere.

Q: Any plans to make the new GLP-1 receptor antibody commercially available?

Dr. Moses: Unlikely. I am sure that for appropriate studies we could make it available to investigators. First we need to have independent peer review of our data on the antibody, however.

Comment: Considering Dr. Butler's concern for acute and chronic pancreatitis – I don't think that there was any evidence for acute or chronic pancreatitis in the autopsy study that he did. If he were here I would ask him to confirm that.

Comment: Unfortunately autopsy rates have gone down in the US, but I think that Dr. Butler's suggestion to expand organ donation by people with diabetes was good.

Dr. Fradkin: We have been focused on pancreatic disease and diabetes – clearly we have to take a broader view. No drug for any condition is without adverse effects, and this is especially true for treatments of diabetes. We are comparing possible risks to the pancreas vs. hypoglycemia – a side effect whose severity we heard about from Dr. Brentnall – vs. weight gain, vs. TZDs' effects on bone. We have to put this in the perspective of other choices for the treatment of diabetes. This is why NIDDK has invested a fair amount of money in the Diabetes Prevention Program and also Look AHEAD, which has shown that once you have diabetes, with weight loss you can get equally good metabolic control using fewer drugs. NIDDK also has a study just launching: GRADE, in which four different classes of diabetic medications will be compared in conjunction with metformin – GLP-1 receptor agonists, DPP-4 inhibitors, sulfonylureas, and insulin. This study will provide an opportunity to follow people in a comparative effectiveness design. It is not powered for hard endpoints like cardiovascular or pancreatic disease, but – to the extent that we have validated biomarkers – it might be a venue for ancillary studies.

-- by Nina Ran, Joseph Shivers, and Kelly Close