OPEN Comment on
Andersen et al, Pancreatitis–
Diabetes–Pancreatic Cancer
Summary of an
NIDDK-NCI Workshop

To the Editor:

We have read the summary of the National Cancer Institute/National Institutes of Diabetes and Digestive and Kidney Diseases-sponsored workshop on Pancreatitis, Diabetes, and Pancreatic Cancer held in June 2013, written by Andersen et al,¹ with considerable interest. Novo Nordisk was as industry representative invited by the organizers to present the current evidence around pancreatic cancer and type 2 diabetes in the liraglutide development program. We commend the organizers for having organized a conference of high scientific merit and for thoroughly summarizing the proceedings in this article. There are a few statements in the section concerning the Novo Nordisk data that should be clarified.

The publication states that the incidence rate of acute pancreatitis in type 2 diabetes is 0.55 to 1.37 cases per 1000 patient-years. As quoted in our presentation, based on work by several authors,^{2–5} the incidence rate can be estimated to be 0.5 to 5.6 cases per 1000 patient-years, that is, up to 3 times higher than in a population of individuals without diabetes. These estimates place the incidence rate of acute pancreatitis observed in the clinical development program of liraglutide in type 2 diabetes within the range seen in the background type 2 diabetes population.⁶ Based on available data, Novo Nordisk can neither confirm nor exclude a causal relationship for liraglutide and pancreatitis because of the low number of adjudicated events reported in our trials. The labeling for Victoza (Novo Nordisk A/S, Bagsvaerd, Denmark) includes a warning for pancreatitis and describes the symptoms of this condition to assist clinicians in their decision making.

Importantly, based on the totality of information available to Novo Nordisk, there is no evidence that liraglutide increases the risk of pancreas cancer in humans or induces dysplasia or precancerous lesions in animal models. Using a new monoclonal antibody for immunohistochemistry, we detected the GLP-1 receptor (GLP-1R) in the non-human primate pancreas. The GLP-1R was predominantly localized in beta cells

with a markedly weaker expression in acinar cells. Pancreatic ductal epithelial cells did not express GLP-1R, in agreement with results using in situ ligand binding in samples from pancreatic ductal adenocarcinomas.⁷

To generate more definite evidence to assess the association between liraglutide administration and pancreatic disease, Novo Nordisk is conducting a large-scale, double-blind cardiovascular outcome study (LEADER; NCT01179048) that will prospectively evaluate the overall safety of liraglutide. The trial has enrolled 9340 patients with type 2 diabetes. Adjudication of all adverse reactions related to pancreatitis and any neoplasm is an integral part of the protocol.⁸ While Novo Nordisk also is pursuing prospectively designed pharmacovigilance studies,⁹ randomized, controlled, large, long-duration trials with independent adjudication provide the most objective way to evaluate infrequent adverse effects, as also mentioned by Drucker recently.¹⁰ The LEADER study will be reported in 2016.

Conflicts of Interest and Source of Funding: All authors are employees of Novo Nordisk A/S and hold employee shares in the company. The work was funded by Novo Nordisk A/S.

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially. <http://creativecommons.org/licenses/by-nc-nd/3.0>.

Alan Charles Moses, MD

Global Chief Medical Office, Research & Development, Novo Nordisk A/S, Bagsvaerd Denmark

Lotte Bjerre Knudsen, BSc

Diabetes Research Unit, Research & Development, Novo Nordisk A/S, Måløv Denmark

Claus Bo Svendsen, MD, PhD

Global Medical Affairs GLP-1 Diabetes, Novo Nordisk A/S, Denmark
cbstv@novonordisk.com

REFERENCES

- Andersen DK, Andren-Sandberg A, Duell EJ, et al. Pancreatitis–diabetes–pancreatic cancer: summary of an NIDDK-NCI workshop. *Pancreas*. 2013;42:1227–1237.
- Noel RA, Braun DK, Patterson RE, et al. Increased risk of acute pancreatitis and biliary disease observed in patients with type

2 diabetes: a retrospective cohort study. *Diabetes Care*. 2009;32:834–838.

- Girman CJ, Kou TD, Cai B, et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes Obes Metab*. 2010;12:766–771.
- Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care*. 2010;33:2349–2354.
- Gonzalez-Perez A, Schlienger RG, Rodriguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care*. 2010;33:2580–2585.
- Jensen TM, Saha K, Steinberg WM. Assessment of acute pancreatitis in liraglutide type 2 diabetes trials. *Pancreas*. 2012;41:1370.
- Korner M, Stockli M, Waser B, et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. *J Nucl Med*. 2007;48:736–743.
- Marso SP, Poulter NR, Nissen SE, et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J*. 2013;166:823–830.
- Funch D, Gydesen H, Tornøe K, et al. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. *Diabetes Obes Metab*. 2014;16:273–275.
- Drucker DJ. Incretin action in the pancreas: potential promise, possible perils, and pathological pitfalls. *Diabetes*. 2013;62:3316–3323.

**Pancreas Volume With
Obesity in Asians
Comparison With Whites**

To the Editor:

Although it has been reported that pancreas mass or volume quantified by anatomical or imaging study is increased with obesity in both white and Asian subjects,^{1–5} there has been no report conducting a direct comparison. We have recently developed a population data for pancreas volume determined by computed tomography (CT) from birth to age 100 years.⁵ Here, we have conducted a subanalysis of our prior study to clarify ethnic difference in the effect of obesity