

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-341

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review - Addendum

Date	December 3, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review - Addendum
NDA #	22-341
Applicant	Novo Nordisk
Date of Submission	May 23, 2008
PDUFA Goal Date	March 23, 2009
Proprietary Name / Established (USAN) names	Victoza (liraglutide)
Dosage forms / Strength	6 mg/mL formulation administered subcutaneously via 3 mL — as 0.6 mg, 1.2 mg, or 1.8 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	<i>Approval, pending agreement on labeling.</i>

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This document is an addendum to the Cross Discipline Team Leader (CDTL) memorandum for Victoza (liraglutide). The purpose of this document is to summarize the following information that has become available after the CDTL memorandum was finalized.

1. A postmarketing case of liver failure in a liraglutide-treated patient
2. Two postmarketing cases of gastric perforation in liraglutide-treated patients
3. Updated calcitonin shift analyses, including follow-up information on the liraglutide-treated patient who had an increase in serum calcitonin to >50 ng/L as well as a postmarketing case of “suspected C-cell carcinoma”
4. Recommendations from the recently completed immunology consult describing the need for better characterization of immunogenicity in a postmarketing clinical trial

The information contained in this addendum does not alter my previous recommendation that liraglutide be approved.

1. Postmarketing case of liver failure

The sponsor submitted a safety report of liver failure regarding a 53-year old woman treated with liraglutide during an ongoing clinical trial. The patient was hospitalized with hepatic failure and encephalopathy after presenting with disorientation, visual hallucinations, aphasia, and asterixis approximately 3 years after starting treatment with liraglutide. She had mildly elevated serum alanine aminotransferase (ALT), alkaline phosphatase, and gamma glutamyl transferase (GGT) at screening and throughout the trial. Her ALT, alkaline phosphatase, and GGT values upon hospitalization were comparable to her screening and on-treatment values. Total bilirubin was 2.1 mg/dL (1.9x ULN). During the 3 years of liraglutide treatment, the patient’s total bilirubin values were mostly within normal limits, although on 5 occasions, her total bilirubin exceeded the upper limit of normal (maximum value prior to hospitalization was 1.5x ULN at Week 92). The patient was treated with lactulose, improved within 72 hours and was discharged after a 9-day hospital stay. The cause for the liver failure is unknown – the patient did not have a history of alcohol abuse, was not taking any culprit medications, and tested negative for various causes of hepatitis, including hepatitis B and C, autoimmune hepatitis, alpha-1-antitrypsin, and Wilson’s disease. Of note, the transferrin saturation was 56% suggesting hemochromatosis as a possible cause, although this condition was not further evaluated with genetic testing, there is no information on family history, and the patient was from Mexico (most cases of hemochromatosis occur in Caucasians). Liver biopsy confirmed cirrhosis but there is no mention of whether there was staining for iron. Liraglutide is not a likely explanation for the liver failure based on the fact that the patient had abnormal liver test measurements at screening that did not appreciably change during the treatment period. There is no signal for hepatotoxicity in the liraglutide new drug application, as discussed in the CDTL memorandum.

2. Postmarketing cases of gastric perforation

The sponsor submitted a 7-day safety report of a 52 year-old man in Germany who developed gastric perforation approximately two weeks after starting liraglutide. He was treated with laparotomy and oversewing of a gastric ulcer. The sponsor submitted another 7-day safety report of a 52 year-old man in Germany who developed gastric perforation and peritonitis approximately 1 week after starting liraglutide. The liraglutide dose at the time of both of these events was 1.2 mg. There are several similarities in the descriptions of these reports (same patient age, gender, country) and the sponsor is attempting to determine whether these 2 reports pertain to the same patient. One of these reports describes the presence of an ulcer, which may have predisposed the patient to gastric perforation. Liraglutide's effects on delaying gastric emptying could conceivably cause greater distension/pressure in the stomach, leading to perforation in susceptible individuals. However, such a conclusion would be premature based on limited information involving two (or possibly one) postmarketing cases. In addition, this has not been identified as a safety concern with the currently marketed glucagon-like peptide (GLP-1) agonist. The clinical reviewer for liraglutide should monitor for cases of gastric perforation post-approval via submitted 15-day Adverse Event Reporting System (AERS) cases and summary data in Periodic Update Safety Reports (PSURs).

3. Calcitonin data

The patient with an elevation in serum calcitonin to >50 ng/L:

In the CDTL memorandum, there is mention of one liraglutide-treated patient (and no comparator-treated patients) who developed a treatment-emergent elevation in serum calcitonin to >50 ng/L. As mentioned in the CDTL memorandum, this 48 year-old man was treated with liraglutide 1.8 mg as add-on to glimepiride and had serum calcitonin values of 10.7 ng/L at Week 0, 30.7 ng/L at Week 12 and 53.5 ng/L at Week 26. The patient did not report any thyroid-related adverse events. After finalization of the CDTL memorandum, we received updated information on this patient. He had a follow-up serum calcitonin of 22.3 ng/L obtained more than 2.5 years after the last dose of liraglutide with an estimated glomerular filtration rate of 56 mL/min suggesting mild renal impairment. The sponsor recommended that the patient be referred to an endocrinologist for further evaluation.

The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104.

7-day report of "suspected C-cell carcinoma":

On November 26, 2009, the sponsor submitted a 7-day report of "suspected C-cell carcinoma" in a patient receiving liraglutide 1.8 mg and insulin Detemir in an ongoing clinical trial. This diagnosis is based solely on serum calcitonin values – the patient has not yet undergone

thyroidectomy. Of note, this patient had a baseline (pre-liraglutide) serum calcitonin of 15.8 pg/mL. Approximately 7 months later, while on liraglutide, the patient underwent pentagastrin stimulation testing. The peak serum calcitonin during this test was 128 pg/mL, prompting referral for thyroidectomy. However, the serum calcitonin was 16.1 pg/mL immediately prior to pentagastrin administration, which is similar to the baseline value of 15.8 pg/mL. Therefore, I agree with the sponsor's assessment that the condition causing the calcitonin elevation was present prior to initiation of liraglutide and that it is unlikely that the exposure to liraglutide played a causal role in the underlying thyroid abnormality.

Updated shift data for serum calcitonin:

Table 1 summarizes calcitonin shift data and is virtually identical to Table 15 included in the CDTL memorandum. The only difference between Table 1 here and Table 15 in the CDTL memorandum is the inclusion of data shown in the shaded rows. These data were requested for completeness after the CDTL memorandum was finalized. The previously available data show the rates for patients meeting various calcitonin shift criteria over selected time periods (e.g., first 20/24/26/28 weeks, first 52 weeks, 104 weeks) using last-observation-carried forward for missing data. The newly available data show the rates for patients meeting the calcitonin shift criteria at any point during their treatment with study medication.

The bolded numbers in Table 1 correspond to rates that are numerically higher for liraglutide compared to the corresponding rates for placebo and active comparators. The liraglutide 0.6 mg dose and the 1.2 mg dose were not more likely than comparators to meet the calcitonin shift criteria shown in Table 1. Each column in Table 1 contains 16 incidence rates and there are only 2/16 incidence rates for 0.6 mg and 1/16 incidence rates for 1.2 mg that are numerically higher for liraglutide compared to control. There are 10/16 incidence rates for 1.8 mg that are numerically higher for liraglutide compared to control. However, it is noteworthy that the patients with the longest exposure to liraglutide (e.g., Week 104 data) did not have higher rates of calcitonin shifts compared to control. Lastly, a majority of the incidence rates (9/16) for total liraglutide were numerically lower than the corresponding incidence rates for control.

The one liraglutide-treated patient with an increase in serum calcitonin to ≥ 50 ng/L is discussed above and the patients with an increase in serum calcitonin to ≥ 20 ng/L are discussed in the original CDTL memorandum. Note that the CDTL memorandum counts 11 patients with a serum calcitonin increase to ≥ 20 ng/L when in fact there were 12 such patients (the twelfth patient is the patient described above who had an increase to ≥ 50 ng/L). This is clarified in the text below:

A total of 11 liraglutide-treated patients (two with 0.6 mg, one with 1.2 mg, and eight with 1.8 mg), five active comparator-treated patients, and one placebo-treated patient developed at least one treatment-emergent serum calcitonin ≥ 20 ng/L and < 50 ng/L. One additional liraglutide-treated patient had an increase in serum calcitonin to ≥ 50 ng/L and is discussed separately above. One of the 11 liraglutide-treated patients with an increase in serum calcitonin to ≥ 20 ng/L and < 50 ng/L had an increase in serum calcitonin from 2.1 ng/L at baseline to 22.4 ng/L at Week 12. There are no additional calcitonin data because the patient was discontinued

prematurely due to nausea and diarrhea. For the remaining 10 liraglutide-treated patients with an increase in serum calcitonin to ≥ 20 ng/L and < 50 ng/L, four had serum calcitonin values < 20 ng/L at the last clinic visit despite continued treatment with liraglutide and the other six had increases in serum calcitonin from baseline to endpoint of only 2.1-7.1 ng/L with serum calcitonin at endpoint ranging from 20.2-25.8 ng/L (the patient with the 7.1 ng/L increase to 25.8 ng/L at Week 26 was diagnosed with Hashimoto's thyroiditis based on positive anti-TPO antibodies but had a normal thyroid ultrasound). For the six comparator-treated patients, four had serum calcitonin ≥ 20 ng/L at the last clinic visit, with endpoint values ranging from 20.2-38.1 ng/L. In summary, eight liraglutide-treated patients (one on 0.6 mg, one on 1.2 mg, and six on 1.8 mg) and four comparator-treated patients had treatment-emergent serum calcitonin values ≥ 20 ng/dL at the last clinic visit, which is consistent with the overall patient-year exposures to liraglutide and control.

In summary, the available shift data for serum calcitonin do not provide evidence of a convincing relationship to treatment assignment.

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**Table 1. Calcitonin shift analyses using last observation carried forward
(updates Table 15 in the CDTL memorandum)**

Shift from baseline	Liraglutide				Comparator		
	0.6 mg	1.2 mg	1.8 mg	Total ¹	Placebo	Active	Total
N (safety dataset)							
Week 20/24/26/28	563	991	1455	3551	710	1412	2122
Week 52	272	497	479	1741	216	630	846
Week 104	184	327	328	839	61	320	381
<ULN to persistently ≥ULN²	6 (1.1)	10 (1.0)	27 (1.9)	46 (1.3)	6 (0.8)	15 (1.1)	21 (1.0)
Per 1,000 patient-years (PY)	11.2	10.9	24.2	15.1	14.0	13.1	13.4
Week 20/24/26/28, n (%)	6 (1.1)	10 (1.0)	27 (1.9)	46 (1.3)	6 (0.8)	15 (1.1)	21 (1.0)
Per 1,000 PY	23.2	22.9	41.8	29.4	20.7	23.7	22.7
Week 52, n (%)	0	3 (0.6)	6 (1.3)	9 (0.5)	0	6 (1.0)	6 (0.7)
Per 1,000 PY	0	6.9	14.1	5.7	0	10.9	8.1
Week 104, n (%)	0	1 (0.3)	2 (0.6)	3 (0.4)	0	2 (0.6)	2 (0.5)
Per 1,000 PY	0	1.7	3.4	2.0	0	3.5	3.0
From <ULN to ≥1.5x ULN	1 (0.2)	5 (0.5)	9 (0.6)	15 (0.4)	3 (0.4)	7 (0.5)	10 (0.5)
Per 1,000 patient-years (PY)	1.9	5.4	8.1	4.9	7.0	6.1	6.4
Week 20/24/26/28, n (%)	1 (0.2)	2 (0.2)	7 (0.5)	10 (0.3)	3 (0.4)	5 (0.4)	8 (0.4)
Per 1,000 PY	3.9	4.6	10.8	6.4	10.3	7.9	8.7
Week 52, n (%)	0	4 (0.8)	1 (0.2)	5 (0.3)	0	2 (0.3)	2 (0.2)
Per 1,000 PY	0	9.2	2.4	3.2	0	3.6	2.7
Week 104, n (%)	0	1 (0.3)	2 (0.6)	3 (0.4)	0	2 (0.6)	2 (0.5)
Per 1,000 PY	0	1.7	3.4	2.0	0	3.5	3.0
From <20 ng/L to ≥20 ng/L	2 (0.4)	1 (0.1)	9 (0.6)	12 (0.3)	1 (0.1)	5 (0.4)	6 (0.3)
Per 1,000 patient-years (PY)	3.7	1.1	8.1	3.9	2.3	4.4	3.8
Week 20/24/26/28, n (%)	1 (0.2)	1 (0.1)	8 (0.5)	10 (0.3)	1 (0.1)	3 (0.2)	4 (0.2)
Per 1,000 PY	3.9	2.3	12.4	6.4	3.4	4.7	4.3
Week 52, n (%)	1 (0.4)	0	3 (0.6)	4 (0.2)	0	2 (0.3)	2 (0.2)
Per 1,000 PY	3.8	0	7.1	2.5	0	3.6	2.7
Week 104, n (%)	1 (0.5)	0	0	1 (0.1)	0	1 (0.3)	1 (0.3)
Per 1,000 PY	3.1	0	0	0.7	0	1.8	1.5
From <50 ng/L to ≥50 ng/L	0	0	1 (0.1)	1 (<0.1)	0	0	0
Week 20/24/26/28, n (%)	0	0	1 (0.1)	1 (<0.1)	0	0	0
Per 1,000 PY	0	0	1.5	0.6	0	0	0
Weeks 52 and 104	0	0	0	0	0	0	0

¹includes liraglutide doses >0.6 to <1.2 mg and >1.8 mg (used in the two Japanese trials and in the obesity trial)

²all values (even if only one is available) after baseline ≥ULN

Week 20/24/26/28 – phase 3 diabetes trials, 20-week obesity trial, 24-week Japanese trials, 26-week exenatide trial

Week 52 – monotherapy trial and extensions for the add-on to metformin trial, Japanese trials and obesity trial

Week 104 – monotherapy and add-on to metformin extensions

4. Immunogenicity

In the clinical development program, some patients developed anti-liraglutide antibodies that cross-reacted with native glucagon-like peptide (GLP)-1 (see CDTL memorandum for details). The sponsor has not yet developed an assay to assess whether these cross-reacting antibodies are neutralizing. Dr. Rosebraugh, Director, Office of Drug Evaluation II, requested an immunogenicity consultation from the Division of Pulmonary and Allergy Products (DPAP) based on these findings. DPAP noted that cross-reactivity to endogenous GLP-1 carries a potential risk of inactivation of the native protein and antigen-antibody complex-mediated disease. Therefore, DPAP is recommending that the sponsor evaluate the rate of anti-liraglutide antibody formation and potentially related adverse events after long-term dosing with liraglutide. DPAP stated that this assessment could be performed in a subset of patients in the required postmarketing cardiovascular trial or as a separate trial. In addition to antibody titers, DPAP recommended that the immunogenicity assessment include ongoing screening for laboratory parameters and adverse events related to inactivation of the native protein and possible antibody complex-mediated disease (e.g. cutaneous and musculoskeletal manifestations, complement levels, hepatic transaminases, and renal function). See Dr. Brian Porter's review for further details.

5. Recommendations

I uphold my previous recommendation that liraglutide can be approved. As per the DPAP recommendations, immunogenicity must be further assessed in the postmarketing setting. This requirement will be communicated to the sponsor and will be reflected in the postmarketing requirements section of the approval letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

HYLTON V JOFFE
12/03/2009

MARY H PARKS
12/03/2009
I concur with Dr. Joffe's addendum

Cross-Discipline Team Leader Review

Date	October 14, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA #	22-341
Applicant	Novo Nordisk
Date of Submission	May 23, 2008
PDUFA Goal Date	March 23, 2009
Proprietary Name / Established (USAN) names	Victoza (liraglutide)
Dosage forms / Strength	6 mg/mL formulation administered subcutaneously via 3 mL injection as 0.6 mg, 1.2 mg, or 1.8 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	<i>Approval, pending agreement on labeling and a satisfactory response to the outstanding information request</i>

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Cross Discipline Team Leader Review

1. Introduction

Glucagon-like peptide (GLP)-1 is released from the gastrointestinal tract during meals and stimulates insulin release from the pancreatic beta-cell in a glucose-dependent manner. GLP-1 also reduces hepatic glucose production (by lowering glucagon secretion from the pancreatic alpha-cell) and slows gastric emptying. Endogenous GLP-1 has a short half-life (<2 minutes) due to rapid degradation by dipeptidyl peptidase (DPP)-4. Because patients with type 2 diabetes have reduced GLP-1 concentrations, GLP-1 receptor agonists resistant to DPP-4 degradation have been developed for the treatment of type 2 diabetes. Currently, Byetta (exenatide) is the only FDA-approved GLP-1 receptor agonist. Novo Nordisk has subsequently submitted a new drug application (NDA) for liraglutide (proposed tradename Victoza), a new GLP-1 receptor agonist, that is the focus of this memorandum.

2. Background

GLP-1 receptor agonists are protein-based therapies that are typically administered via the subcutaneous route. Other routes of administration under investigation include intranasal and skin (patch). Byetta is administered twice daily by subcutaneous injection. Byetta is currently not indicated for use as monotherapy because there were inadequate efficacy and safety data for this setting at the time of approval. The monotherapy indication is currently under review and will likely be approved in the near future. An NDA for a once-weekly formulation of Byetta (Exenatide LAR) is also under review.

Safety concerns with Byetta include:

- Postmarketing reports of acute pancreatitis, including the more severe hemorrhagic or necrotizing forms with deaths
- Worsened renal function, sometimes requiring hemodialysis, that may be attributed to dehydration due to gastrointestinal side effects
- Increased incidence of hypoglycemia when used in combination with a sulfonylurea

In addition, high titers of anti-exenatide antibodies may reduce efficacy.

In July 2008, the Division convened a public, 2-day advisory committee meeting to discuss cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. After considering the recommendations of the advisory panel and other data, the Division published a December 2008 Guidance for Industry entitled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. This guidance document recommends that sponsors of new pharmacologic therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. Of note, the liraglutide NDA _____ for the treatment of type 2 diabetes were submitted to FDA prior to the July 2008 advisory committee meeting and prior to the

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December 2008 guidance. Nonetheless, FDA has requested that the sponsors for these _____ products provide adequate evidence of cardiovascular safety in accordance with the guidance to support approvability. Therefore, cardiovascular safety was a major focus of the clinical and statistical reviews for liraglutide. Another major focus of the liraglutide review pertains to findings of benign and malignant thyroid C-cell tumors in rodents. Both of these issues were discussed at a public advisory committee meeting on April 2, 2009 and the tumor issue was discussed at a regulatory briefing on June 26, 2009.

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3. CMC/Device

Liraglutide is produced by recombinant DNA technology in the yeast *Saccharomyces cerevisiae*. The drug substance for liraglutide is the 7-37 peptide fragment of human GLP-1 with two modifications: Substitution of lysine by arginine at position 34 and addition of a glutamic acid-spaced palmitic acid to the lysine residue at position 26.

The drug product consists of _____ liraglutide, _____ disodium phosphate dihydrate (_____), _____ propylene glycol (_____), and _____ phenol (_____) and is supplied in a multiple-dose prefilled pen-injector. Each pen-injector contains 3 mL of drug product at a concentration of 6 mg/mL. _____

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_____ Part-way through the review cycle, the sponsor requested to also market a pen that can be used to administer _____. The Office of Surveillance and Epidemiology recommends that only this newly proposed pen be marketed because having _____ is unnecessary and may lead to confusion. The sponsor has subsequently agreed to market only _____.

The sponsor states that the liraglutide pens are modified versions of the previously cleared _____ for insulin. The Center for Devices and Radiological Health (CDRH) review by Sajjad Syed dated February 13, 2009, raised concerns that the changes to the _____ may introduce confusion when liraglutide users work with the modified pen-injector, prompting a request for a Human Factors study to show safe and effective use of the liraglutide pen-injector by the intended users. The sponsor conducted a Human Factors study, the design and results of which were found to be acceptable by CDRH to support approvability.

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Based on the results of stability testing, the Chemistry/Manufacturing/Controls (CMC) reviewers recommend a shelf-life for the drug product of 24-months at 2-8 degrees Celsius and 32 days at 28-32 degrees Celsius.

The drug product is photo-labile. The CMC reviewers note that the pen-injector adequately protects the drug product from degradation due to light.

CMC has determined that the application qualifies for a categorical exclusion from an environmental assessment report because the expected introduction concentration of the active moiety at the point of entry into the aquatic environment is less than 1 part per billion.

The Office of Compliance issued an acceptable recommendation on the manufacturing facilities of the drug product.

CMC deficiencies identified during the review have been adequately resolved. The CMC reviewers have determined that the drug product is acceptable and recommend approval of the NDA. Please see reviews by Drs. Joseph Leginus, Ali Al-Hakim, Suong Tran, and Christine Moore for further details.

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology reviewers recommend not approving this NDA based on findings of thyroid C-cell tumors in mice and rats during the 2-year lifetime exposure carcinogenicity studies. Please see reviews by Drs. Anthony Parola and Karen Davis-Bruno for details. The finalized tertiary review by Dr. Paul Brown is pending at this time. The reviewers have concluded that the human relevance of these tumors is unknown. In the original NDA submission, the sponsor proposed that liraglutide-induces calcitonin secretion and synthesis driving C-cell hyperplasia and C-cell tumor formation in rodents, but not in primates. Dr. Parola did not agree that the conducted mechanistic studies support this proposed mode-of-action in rodents. For example, he notes that the proposed mechanism would be expected to first result in physiological, diffuse C-cell hyperplasia that precedes focal C-cell hyperplasia, but this did not occur. Our Executive Carcinogenicity Assessment Committee (ECAC) concurred that the sponsor did not provide adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans as did 12 of 13 panel members at the April public advisory committee meeting. At the advisory committee meeting and in a subsequent face-to-face meeting, the sponsor abandoned the above-described mode-of-action, and instead, based human relevance on the absence of liraglutide effects on thyroid C-cells in primates, including the absence of treatment-related medullary thyroid carcinoma in clinical studies and the fact that liraglutide did not increase plasma calcitonin or proliferative C-cell lesions in monkeys treated for up to 20 months.

Liraglutide tested negative in a standard battery of genotoxicity studies. Table 1 summarizes the findings from the rodent 2-year carcinogenicity studies. There is a dose-related effect of liraglutide on thyroid C-cell tumors in both genders in rats and mice. In rats, thyroid C-cell adenomas and carcinomas occurred at low multiples of clinical exposure. In mice, thyroid C-cell adenomas occurred at 10-times the clinical exposure and carcinomas occurred in 2/76 (3%) females at 45-times the clinical exposure. Despite the thyroid C-cell tumor findings, liraglutide did not reduce survival in these studies.

As discussed by Dr. Davis-Bruno, monkeys dosed with liraglutide for up to 20 months at ~60 times human exposure did not develop proliferative C-cell lesions. However, Dr. Davis-Bruno recommends caution in interpreting these findings because monkey studies are not powered or designed to evaluate carcinogenicity and the duration of treatment was only 5% of the monkey lifespan, which may not mimic long-term use of liraglutide in humans. In addition, liraglutide was immunogenic in monkeys, but not in rodents.

With regard to the rodent C-cell tumor findings, Dr. Parola notes that there is no direct evidence showing GLP-1 receptors on thyroid C-cells, but states that indirect evidence suggests co-localization in rodents (e.g., GLP-1 regulates bone resorption in mice through a calcitonin-dependent mechanism) and humans. In one study¹ using autoradiography with ¹²⁵I-GLP-1(7-36)amide, there was binding in 12/12 normal thyroid samples from rats, 3/5 normal thyroid samples from mice, and 1/18 normal thyroid samples from humans (the authors were unable to determine whether the binding occurred on thyroid follicular cells or on thyroid C-cells). This study also reported binding in 5/18 medullary thyroid cancer samples from humans. The sponsor attempted to directly evaluate whether the GLP-1 receptor is expressed in C-cells from thyroid tissue in rodents, monkeys and humans, but Dr. Parola has concluded that the findings are equivocal because of methodological issues. A summary of an autoradiographic ligand binding study submitted part-way through the NDA review cycle states that GLP-1 receptor binding occurred on C-cells in thyroid from rats, but not humans. A report for this study was not submitted for review. Nonetheless, it appears that rodent C-cell tumors are a pharmacologic class effect due to persistent GLP-1 receptor activation. As discussed by Dr. Parola, there is preliminary evidence that other long-acting GLP-1 agonists (dosed less frequently than once-daily) have a similar propensity to cause rodent C-cell tumors like liraglutide whereas short-acting GLP-1 agonists are less tumorigenic. For example, exenatide, which is dosed twice daily, caused C-cell adenomas in female rats (no-observed-adverse-effect level <5x) but did not cause C-cell tumors in male rats or in mice (one potential limitation of the Byetta carcinogenicity studies is that dosing was once-daily whereas Byetta is clinically dosed twice-daily). In contrast, continuous subcutaneous infusion of exenatide in mice caused focal C-cell hyperplasia and the exenatide LAR formulation, which is intended for once-weekly dosing in humans, appears to have considerably more tumorigenic effects on the thyroid C-cell than Byetta in rats (tumorigenicity with the exenatide LAR formulation has not yet been evaluated in mice).

As discussed by Dr. Parola, there are six other approved medications that cause C-cell tumors in rats. Five of these drugs do so in only one gender. The seventh does so in both genders but at a no-observed-adverse-effect level of 20-times clinical exposure. None of these drugs cause C-cell tumors in mice.

Diffuse and focal C-cell hyperplasia and C-cell tumors are common in rats (incidence >1%) but rare in mice (incidence <1%). C-cell carcinoma is rare (incidence <1%) in both species. In rats, the incidence of diffuse C-cell hyperplasia, focal C-cell hyperplasia, and C-cell adenomas increases with age. This increase in C-cell mass results in an increase in calcitonin with age. Dr. Parola has concluded that plasma calcitonin is a biomarker for liraglutide-induced C-cell tumors in mice, but not in rats. This means that in rats, liraglutide did not lead to consistent increases in calcitonin beyond the increases seen with age (which are due to increased C-cell mass). Therefore, calcitonin could still be a biomarker for increased C-cell mass in humans, even if caused by liraglutide, assuming these C-cells remain adequately differentiated to continue expressing calcitonin.

¹ Körner M, et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. J Nucl Med. 2007; 48: 736-43.

Dr. Parola calculated a time course for the C-cell tumor findings in rodents integrating data from control and high-dose groups from toxicity studies, mechanistic studies, and the carcinogenicity studies. In high-dose groups, the earliest appearance of thyroid C-cell carcinoma occurred after 64 weeks of treatment in mice (~60% of their lifespan) with liraglutide exposures 45-times the clinical exposure and after 86 weeks of treatment in rats (~70% of their lifespan) with liraglutide exposures 8-times clinical exposure. In young adult rats treated with liraglutide at exposures 8-times clinical exposure, liraglutide increased the incidence of focal C-cell hyperplasia after 43 weeks of treatment and increased the incidence of C-cell adenomas after 30 weeks of treatment. In mice, focal C-cell hyperplasia occurred after only 4 weeks of treatment with liraglutide at 88-times the clinical exposure and C-cell adenomas occurred as early as 47 weeks of treatment with liraglutide exposures 45-times the clinical exposure. There are at least two important limitations of these time-course data. First, toxicity studies are not designed or powered to evaluate carcinogenicity. Therefore, the absence of tumors in animals that complete toxicity studies should be interpreted in this context. Second, animals in the carcinogenicity studies are not sacrificed until dosing has been completed. Therefore, findings of tumors at earlier timepoints were detected in animals that died early for unrelated reasons. It is not possible to know when C-cell tumors first appeared in those animals that developed tumors but did not die early.

Liraglutide has been approved by the European Medicines Agency (EMA). Dr. Parola has reviewed the EMA-assessment of the non-clinical thyroid C-cell tumors and agrees with their assessment that the findings in rodents are caused by a non-genotoxic mechanism that is probably GLP-1 receptor-mediated, but disagrees that there are sufficient data to conclude that the relevance to humans was adequately assessed. Dr. Parola's conclusion is that the relevance to humans is unknown at the present time.

Based on the above findings, Dr. Parola is recommending that the sponsor determine the mode-of-action for these tumors and evaluate the human relevance based on this mode-of-action. Activating mutations in the rearranged during transfection (RET) proto-oncogene account for most cases of familial medullary thyroid cancer (the human form of C-cell carcinoma) and account for approximately one-half of patients with sporadic medullary thyroid carcinoma. RET mutations have not been identified in rat strains susceptible to C-cell carcinoma. Dr. Parola recommends that the sponsor evaluate the effect of liraglutide on RET signaling in thyroid C-cells in rodents and determine whether liraglutide alters phosphorylation of RET residues involved in C-cell proliferation and transformation. Dr. Parola also recommends that the sponsor assess whether the thyroid GLP-1 receptor is required for liraglutide's proliferative effects and whether liraglutide-induced C-cell tumors occur in GLP-1 receptor knockout animals or rodents treated with a GLP-1 receptor antagonist.

Table 1. C-cell tumors and dorsal skin/subcutis fibrosarcomas in the 2-year rodent carcinogenicity studies										
RATS	Males					Females				
	Dose (mg/kg/day)	0	0.075	0.25	0.75	0	0.075	0.25	0.75	
Human exposure multiple ^a	-	0.5	2.2	7.6	7.6	-	0.5	2.2	7.6	
N	50	49	50	50	50	50	49	49	50	
Focal hyperplasia ^b	11 (22%)	14 (29%)	20 (40%)	24 (48%)	24 (48%)	14 (28%)	14 (29%)	27 (55%)	24 (48%)	
C-cell adenoma (common) ^c	6 (12%)	8 (16%)	21 (42%)	23 (46%)	23 (46%)	5 (10%)	13 (27%)	16 (33%)	28 (56%)	
C-cell carcinoma (rare) ^c	1 (2%)	4 (8%)	3 (6%)	7 (14%)	7 (14%)	0	0	2 (4%)	3 (6%)	
C-cell adenoma or carcinoma (common) ^c	7 (14%)	11 (22%)	21 (42%)	28 (56%)	28 (56%)	5 (10%)	13 (27%)	18 (37%)	29 (58%)	
Dorsal skin/subcutis fibrosarcoma (common) ^c	2 (4%)	1/50 (2%)	2/49 (4%)	0	0	0	2/50 (4%)	0	0	
MICE										
MICE	Males					Females				
	Dose (mg/kg/day)	0	0.03	0.2	1	3	0	0.03	0.2	1
Human exposure multiple ^a	-	0.2	1.8	10.0	45.0	45.0	-	0.2	1.8	10.0
N	79	66	65	67	79	75	66	67	66	76
Focal hyperplasia (rare) ^b	0	0	1 (2%)	11 (16%)	30 (38%)	0	0	7 (10%)	10 (15%)	22 (29%)
C-cell adenoma (rare) ^c	0	0	0	9 (13%)	15 (19%)	0	0	0	4 (6%)	15 (20%)
C-cell carcinoma (rare) ^c	0	0	0	0	0	0	0	0	0	2 (3%)
C-cell adenoma or carcinoma (rare) ^c	0	0	0	0	0	0	0	0	0	17 (22%)
Dorsal skin/subcutis fibrosarcoma (common) ^c	0	2/67 (3%)	1/67 (2%)	2 (3%)	7 (9%)	1 (1%)	1/67 (2%)	1 (2%)	0	2/79 (3%)

^a=based on area under the time-concentration curve relative to the 1.8 mg dose

^b=Diffuse C-cell hyperplasia cannot be adequately assessed without specialized staining

^c=tumor considered common or rare based on incidence in historical control groups of >1% or <1%, respectively

Other findings from the pharmacology/toxicology review are summarized below.

As shown in Table 1, there were liraglutide treatment-related skin and subcutis fibrosarcomas in male mice but not in female mice or in rats. Dr. Parola attributed the fibrosarcomas (which occurred at or near the injection sites) to high local concentrations of liraglutide. Of note, mice were injected with a liraglutide formulation that was 10-fold more dilute than the clinical formulation. ECAC considered the fibrosarcomas to be drug-related but, per Dr. Davis-Bruno, ECAC questioned the clinical relevance of this finding because the signal was isolated to male mice only.

Dr. Parola notes that liraglutide was well tolerated in chronic repeat-dose toxicity studies with 8-fold safety margins in rats and 72-fold safety margins in monkeys relative to clinical exposures. He reports that mice did not have dose-limiting toxicity. In rats, clinical signs of toxicity and reduced food consumption were dose-limiting. Reduced food consumption and decreased body weight gain were dose-limiting in rabbits and monkeys.

Dr. Parola notes that liraglutide caused irreversible injection site reactions (necrosis, fibrosis) in monkeys using drug formulations that were at least 3-times more dilute than the clinical formulation. Dr. Parola requests that the sponsor provide evidence that local toxicity after repeat subcutaneous injection with liraglutide has been adequately assessed in non-clinical studies. Dr. Parola also notes that the sponsor used drug substance and drug product acceptance criteria based on impurity groups and not on individual impurities. He requests that the sponsor evaluate the *in vitro* genotoxicity of liraglutide impurities at impurity levels consistent with drug substance and drug product acceptance criteria. Dr. Davis-Bruno further addresses these two issues in her supervisory memorandum. She agrees that local toxicity of liraglutide may not have been thoroughly assessed in the nonclinical program because of dilute formulations used relative to the clinical formulation. Nonetheless, Dr. Davis-Bruno concludes that additional nonclinical testing of local toxicity may not be necessary, because of extensive experience in the trials with the clinical formulation and the expectation that injection reactions will be self-limiting because patients with significant injection reactions will discontinue liraglutide. Dr. Davis-Bruno also notes that different drug lots used in various nonclinical studies may have diverse impurity profiles. However, she comments that the sponsor has identified the grouped impurities components as _____ and she concludes that these are unlikely to have a structural alert for genotoxicity, noting that _____ are generally exempt from genotoxicity testing based on International Conference on Harmonisation (ICH) guidelines. b(4)

Dr. Parola states that liraglutide was not immunogenic in mice or rats, but noted the formation of anti-liraglutide antibodies that cross-reacted with native GLP-1 in some chronically dosed monkeys. The sponsor did not assess neutralizing effects of these anti-liraglutide antibodies. Dr. Parola notes that immunogenicity in animal studies is not predictive for immunogenicity in humans.

Dr. Parola states that mild anemia occurred at clinically relevant exposures in some repeat-dose studies in mice, rats, and monkeys. He states that the anemia in the 13-week mouse toxicity study was likely due to hemolysis.

With regard to cardiovascular effects, in rats, single doses of liraglutide increased blood pressure and heart rate, and repeat dosing decreased heart weight at clinically relevant exposures. In contrast, liraglutide increased heart weight in male monkeys at clinically relevant exposures. No histopathological changes accompanied the changes in heart weight. There is no evidence of ischemic cardiovascular toxicity based on non-clinical testing in healthy animals.

Dr. Parola is recommending Pregnancy Category C based on fetal abnormalities in rats and rabbits that are generally not dose-related, but that occur at doses yielding clinically relevant maternal plasma exposures. Teratogenic effects included misshapen oropharynx, displaced kidneys, displaced azygous vein, and irregular skull ossification in rats and abnormalities of the skeleton, blood vessels, and gallbladder in rabbits.

Exposure in human milk is possible because liraglutide is detected in rat milk.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers recommend approval of the NDA. Please see the joint review co-authored by Drs. Manoj Khurana, Ritesh Jain, Wei Qui, Rajanikanth Madabushi, and Christoffer Tornøe for details.

Liraglutide's duration of action is prolonged by self-association (which slows absorption), binding to albumin, and resistance to degradation by DPP-4. Liraglutide is cleaved by the ubiquitous DPP-4 enzyme and by neutral endopeptidases. There is minor excretion of closely related metabolites in the feces and urine in all animal species and humans. No unchanged liraglutide was detected in urine or feces.

The sponsor conducted 26 clinical pharmacology trials. Liraglutide is dose-proportional up to 20 mcg/kg (equivalent to the 1.8 mg dose for a 90 kg person). Median time to maximal concentration is 12 hours. Mean half-life with subcutaneous dosing is 13 hours, which is longer than the 8-hour half-life observed after intravenous dosing, suggesting that subcutaneous absorption is slower than elimination. There is slight accumulation (R_A of 1.4-1.5) based on area under the time-concentration (AUC)_{0-24h} curve after multiple once daily subcutaneous administration, but the clinical pharmacology reviewers did not flag this as a concern. Absolute bioavailability is approximately 55%. Relative bioavailability of a 0.6 mg subcutaneous dose was 78% in the thigh vs. abdomen, 87% in the upper arm vs. abdomen, and 110% in the upper arm vs. thigh without a differential effect on T_{max} . These differences were not considered clinically meaningful and the clinical pharmacology reviewers agree that liraglutide can be administered interchangeably at these injection sites.

According to the clinical pharmacology reviewers, no dosage adjustment is needed based on gender, age, race, renal impairment, or hepatic impairment. Mean AUC_{0-inf} was decreased approximately 20-35% in renally impaired patients compared to subjects with normal renal function. Mean AUC_{0-inf} was decreased approximately 10-15% in patients with mild or

moderate hepatic impairment. Mean AUC_{0-inf} was decreased by approximately 40% with a two-fold increase in clearance in patients with severe hepatic impairment.

There is no effect of body mass index on liraglutide clearance. However, increasing body weight was associated with increases in liraglutide clearance and decreases in liraglutide exposure in the population pharmacokinetic analysis. For example, mean steady state exposures were approximately 40% lower in patients weighing 160 kg compared to patients weighing 70 kg. Nonetheless, clinical pharmacology has determined that the proposed clinical doses achieve sufficient exposures in the 40-160 kg range of body weight without the need for weight-based dose adjustment. These conclusions are consistent with the data from the phase 3 program, which did not show a consistent interaction between baseline body weight and change from baseline in HbA1c in the placebo-controlled phase 3 trials (see the clinical efficacy section of this memorandum for further details).

The clinical pharmacology reviewers also note a 30% lower weight-adjusted clearance in women compared to men but have concluded that this effect does not appear to be clinically meaningful to warrant a dose adjustment. This recommendation is substantiated by the phase 3 data, which do not show an interaction between gender and change from baseline in HbA1c.

Liraglutide has minimal, if any, inhibitory effects on the cytochrome P450 system and is not expected to cause drug-drug interactions related to CYP450 inhibition. The sponsor conducted drug interaction studies with atorvastatin, paracetamol, digoxin, lisinopril, and griseofulvin. The clinical pharmacology reviewers concluded that findings from these studies were generally consistent with liraglutide's slowing of gastric emptying. The reviewers have determined that none of the drug interactions are clinically relevant and are not recommending dosage adjustment in these settings. A drug interaction study with an oral contraceptive showed bioequivalence based on AUC_{0-inf} for ethynylestradiol but not for levonorgestrel (mean 1.18; 90% confidence interval 1.04-1.34). This finding will be labeled but the clinical pharmacology reviewers did not flag this as a clinically relevant change.

The pivotal bioequivalence study demonstrated bioequivalence of the phase 3 formulation and the to-be-marketed formulation. However, the Division of Scientific Investigations (DSI) identified several deficiencies involving the clinical and analytic portions of this trial potentially impacting the reliability of the data. The clinical pharmacology reviewers have evaluated the sponsor's responses to the deficiencies and have subsequently determined that the data from the trial are adequate to support a conclusion of bioequivalence (see Section 11). The Division also communicated its concern to the sponsor regarding other clinical pharmacology studies that have used the same laboratory to perform the liraglutide assay. Please see reviews by Ms. Lisa Capron, Dr. Sriram Subramaniam, and Dr. Manoj Khurana for details.

The pharmacometric reviewers note considerable overlap in pharmacokinetic exposures for the 1.2 mg and 1.8 mg liraglutide doses.

The Interdisciplinary Review Team (IRT) for QT Studies reviewed the sponsor's Thorough QT Study and has concluded that liraglutide does not prolong the QT interval. The largest

treatment arms each had twice as many patients compared to the placebo arm. Two of the trials (see below) have ongoing, voluntary, open-label extensions (study medication was unblinded after the last patient completed the corresponding six-month core phase 3 trial and the phase 3 database was unlocked).

Study medication could be injected subcutaneously in the upper arm, abdomen, or thigh and was administered using the FlexPen. The injection could be administered any time of day, but the protocols stated it was preferable that liraglutide be injected during the same overall time period on a day-to-day basis.

The phase 3 clinical trials evaluated liraglutide in the following settings:

Monotherapy (Study 1573) – 52-week trial

- Compared liraglutide (1.2 mg and 1.8 mg) vs. glimepiride 8 mg
- This trial has an ongoing 4-year, voluntary, open-label extension

Add-on to one oral antidiabetic medication (Study 1572 and 1436) – 26-week trials

- Add-on to metformin (Study 1572)
 - Compared add-on liraglutide (0.6, 1.2, and 1.8 mg) vs. add-on placebo and vs. add-on glimepiride 4 mg
 - This trial has a 1.5-year, voluntary, open-label extension
- Add-on to sulfonylurea (Study 1436)
 - Compared add-on liraglutide (0.6, 1.2, and 1.8 mg) vs. add-on placebo and vs. add-on rosiglitazone 4 mg

Add-on to two oral antidiabetic medications (Study 1574 and 1697) – 26-week trials

- Add-on to metformin+rosiglitazone (Study 1574)
 - Compared add-on liraglutide (1.2 and 1.8 mg) vs. add-on placebo
- Add-on to metformin+glimepiride (Study 1697)
 - Compared add-on liraglutide 1.8 mg vs. add-on placebo and vs. add-on insulin glargine

As discussed by Dr. Yanoff, the washout and/or run-in periods for all phase 3 trials were generally not ideal. For example, the monotherapy trial permitted enrollment of patients treated with metformin 1500 mg, pioglitazone 30 mg, or less than one-half the maximal dose of other antidiabetic medications and these medications were only discontinued upon randomization at Week 0. In these patients, the baseline HbA1c reflects residual effects of preceding antidiabetic therapy and would be higher if sufficient washout had occurred. Therefore, the within-group change from baseline in HbA1c may underestimate the true effect. However, the between-group change from baseline in HbA1c should be unaffected, assuming that patients were well-balanced between treatment groups as a result of randomization.

In the add-on to metformin trial, patients were titrated to metformin 2000 mg during the run-in phase but were only required to be taking this dose for as little as 3 weeks prior to randomization at Week 0. Similar findings are noted for the other phase 3 trials (Table 2). HbA1c reflects overall glycemic control during the preceding 8-12 weeks. Therefore, the short duration of maintenance doses of background therapy during the run-in period will not be fully reflected in the baseline HbA1c measurement (for this reason, we typically recommend run-in periods of 6-12 weeks at maximal/near-maximal doses of background anti-diabetic medications). In these patients, the baseline HbA1c would have been lower if sufficient run-in occurred. As a result, the within-group changes from baseline in HbA1c may overestimate the true effect, although the between-group changes from baseline in HbA1c should be unaffected, assuming patients were well balanced between treatment groups as a result of randomization.

The sponsor stated that the duration of the run-in period was chosen to ensure that fasting plasma glucose, one of the criteria for randomization, had reached steady state levels.

Trial	Background therapy	Duration of run-in once at maintenance dose of background therapy
1572	Metformin 2,000 mg	3 weeks
1436	Glimepiride 4 mg	2 weeks
1574	Met 2,000 mg; Rosi 4 mg BID	6 weeks
1697	Met 2,000 mg; Glimepiride 4 mg	3 weeks

All add-on trials used near-maximal or maximal doses of background antidiabetic medications. The usual maintenance dose of glimepiride is 2-4 mg daily; therefore the use of glimepiride 4 mg is acceptable as background therapy in studies 1436 and 1697 and as an active comparator in the add-on to metformin trial. However, the maximal dose of rosiglitazone in the United States is 8 mg but only 4 mg of rosiglitazone was used as the active comparator in the add-on to sulfonylurea trial. The sponsor justified the lower dose of rosiglitazone because 8 mg is not an approved dose in some of the foreign countries participating in this trial (this was not an issue for Study 1574, which was conducted only in the United States and Canada where the 8 mg dose is approved). Nonetheless, for patients in the United States (who will use liraglutide if approved here), the comparative efficacy conclusions in the add-on to sulfonylurea setting are limited because full-dose liraglutide is compared to only half-maximal dose rosiglitazone.

In the clinical trials that included background glimepiride therapy (Study 1436 and 1697), the protocol permitted a reduction in the glimepiride dose after randomization if there was unacceptable hypoglycemia.

In the add-on to metformin+glimepiride trial, the insulin glargine arm was open-label with titration managed by patients after instruction by investigators. The starting dose of glargine was equivalent to the mean fasting plasma glucose (in mmol/L) obtained by glucometer for randomization. During the first 8 weeks of treatment, glargine was to be titrated twice weekly based on self-measured fasting plasma glucose on the day of titration. Target fasting plasma glucose was ≤ 100 mg/dL. After Week 8, the frequency of insulin glargine titration was left to

the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. There was minimal titration of glargine during the last 12 weeks of the trial (the endpoint HbA1c value obtained at Week 26 would not have fully reflected changes in glycemic control if there had been substantial insulin adjustments during this latter part of the trial).

In the intent-to-treat dataset, the median glargine dose was 10 units (range 6-22 units) during Week 0 and 18 units (range 6-90 units) at study end. Approximately 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤ 100 mg/dL.

The phase 3 trials had similar inclusion and exclusion criteria. Entry criteria included age between 18-80 years and type 2 diabetes with inadequate glycemic control (baseline HbA1c 7-10%, 7-11%, or 7.5-10% depending on the trial and prior anti-diabetic medication use). Exclusion criteria for all trials included insulin use within the 3 months prior to screening, ALT and/or AST ≥ 2.5 x ULN, and elevated serum creatinine (exact cutoff varied by trial and ranged from 1.4-1.7 mg/dL for men and 1.2-1.7 mg/dL for women). Other exclusion criteria included history of significant cardiovascular disease, such as myocardial infarction, within the 6 months prior to study entry or Class III or IV New York Heart Association heart failure. These trials also excluded patients with recurrent major hypoglycemia and all trials except the add-on to metformin trial excluded patients with hypoglycemia unawareness.

The add-on trials required patients to be taking at least one anti-diabetic medication (at any dose) for at least 3 months prior to screening. In the add-on to metformin+rosiglitazone trial, exenatide was also permitted prior to screening for patients enrolled in the United States. At the start of the run-in period, all prior anti-diabetic medications that differed from the background therapy to be used during the randomized treatment periods were discontinued.

The sponsor prespecified fasting plasma glucose cutpoints (e.g., fasting plasma glucose >240 mg/dL at Week 8 in some trials) that would trigger the need for glycemic rescue therapy. Patients meeting these criteria were discontinued from the phase 3 trials.

The primary efficacy endpoint for all phase 3 trials was the change in HbA1c from baseline to Week 52 (monotherapy) or Week 26 (add-on combination trials). Other efficacy endpoints included change from baseline in fasting plasma glucose (FPG), HbA1c responder analyses, self-measured plasma glucose profiles, blood pressure, and lipids. In all trials, patients were stratified by previous diabetes treatment (diet/exercise vs. oral anti-diabetic medication for the monotherapy trial; prior monotherapy vs. prior combination therapy for the add-on trials).

HbA1c was measured by a National Glycohemoglobin Standardization Program (NGSP) certified high-performance liquid chromatography assay. As discussed by Dr. Yanoff, Level I NGSP certification expired at _____ (where all samples from _____ were processed) part-way through the add-on to metformin trial and the add-on to metformin+glimepiride trial. When possible, affected samples were reanalyzed in _____ contributed 51 patients in the add-on to metformin trial ($<5\%$ of the efficacy dataset) and 52 patients ($<10\%$ of the efficacy dataset) in the add-on to metformin+glimepiride trial. The effect of NGSP certification expiration appears to have had no meaningful effect on

b(4)

the efficacy conclusions. For example, excluding the 52 patients from the primary efficacy analysis in the add-on to metformin+glimepiride trial yielded virtually identical results to the original analysis. Specifically, in the new analysis, the mean reduction in HbA1c was -1.29% with liraglutide (vs. -1.33% in the original analysis), -1.10% with glargine (vs. -1.09% in the original analysis), and -0.25% with placebo (vs. -0.24% in the original analysis). Therefore, the efficacy analyses summarized in this memorandum include data from these patients.

As discussed by Dr. Janice Derr, the biostatistics reviewer, the primary statistical population for each trial consisted of all randomized patients exposed to at least 1 dose of study medication with a baseline (could be imputed from screening for the monotherapy trial) and at least one post-baseline assessment of the parameter of interest. The last-observation-carried-forward (LOCF) method was used for patients with missing data and for patients who were discontinued early because of needing glycemic rescue therapy. The primary efficacy analysis was conducted using analysis of covariance (ANCOVA) with study treatment, country, and previous antidiabetic treatment stratification categories as fixed effects and baseline HbA1c as a covariate. The sponsor used a gate-keeping strategy to control type 1 error within each study for comparisons of the liraglutide arms (tested in descending doses) against comparators. Liraglutide would need to be shown to be superior to placebo at a 2-sided alpha of 0.05 before being tested for non-inferiority against active comparator with a 1-sided alpha of 0.025. If non-inferiority was shown against active comparator then that dose of liraglutide was tested for superiority to the active control. Body weight analyses were tested conditional on the outcome of the tests of the primary efficacy endpoint, with prespecified comparisons of liraglutide to active comparator using Dunnett's method to protect the family-wise error rate.

The sponsor used a prespecified margin of 0.4% for all non-inferiority comparisons, which is the usual margin used in these settings. As discussed by Dr. Derr, the choice of a 0.4% margin for glimepiride is based predominantly on 14-week data and assumes that the effect of glimepiride does not decline appreciably between 14 weeks and 52 weeks of therapy (the duration of the liraglutide monotherapy trial). Of note, this issue is moot because liraglutide was subsequently shown to be superior to glimepiride in this trial.

Demographics: Drs. Yanoff and Derr discuss the patient demographics in detail. Briefly, the mean age across the five phase 3 trials was approximately 52-53 years in the monotherapy trial and 55-57 years in the add-on trials. Most patients (approximately 80-85%) were <65 years old. Men and women were equally represented in the monotherapy and add-on to glimepiride trials, whereas there was a slight male predominance (56-58%) in the other three trials. Most patients were Caucasian (64%-87%) with blacks comprising 2-13% of the randomized patients. Asian/Pacific Islander representation was reasonable in the add-on to metformin (9%), add-on to metformin+glimepiride (16%), and add-on to glimepiride (32%) trials, but Asians accounted for only 2-4% of patients in the remaining two trials. As expected, median duration of diagnosed diabetes was shortest in the monotherapy trial (3.8 years), intermediate in the add-on to single-agent trials (6.5-6.6 years), and longest in the add-on to dual-agent trials (7.9-8.4 years). Mean body mass index ranged from 29.4-33.6 kg/m², with the highest values in the monotherapy and add-on to metformin+rosiglitazone trials. In the monotherapy trial, approximately one-third of patients were treated only with diet and exercise at the time of screening and the remaining two-thirds were treated with anti-diabetic monotherapy. For the

single-agent trials, approximately one-third of patients were treated with anti-diabetic monotherapy at screening with the remainder treated with anti-diabetic combination therapy. For the dual-agent trials, most patients were treated with anti-diabetic combination therapy at screening (83-94%). Mean baseline HbA1c was 8.2-8.6% across the phase 3 trials.

Efficacy Results:

HbA1c: Table 3 shows the primary efficacy results using the intent-to-treat population with LOCF. In the four placebo-controlled phase 3 trials, liraglutide 1.8 mg resulted in a statistically significant ($p < 0.0001$) mean reduction in HbA1c of 0.9%-1.4% relative to placebo.

Although the studies were not powered for comparison between liraglutide dose arms, as discussed by Drs. Derr and Yanoff, and as shown in Table 3, the 1.2 mg and 1.8 mg doses had comparable efficacy in three of the four phase 3 trials that evaluated both doses.

The liraglutide 0.6 mg dose was included in the add-on to metformin and add-on to glimepiride trials, and also resulted in a statistically significant ($p < 0.0001$) mean reduction in HbA1c compared to placebo, although the effect size was somewhat smaller than that seen with the 1.2 mg and 1.8 mg doses.

In the active-controlled monotherapy trial, both the 1.2 mg and 1.8 mg doses of liraglutide resulted in a statistically significantly greater reduction from baseline in HbA1c compared to maximal dose glimepiride.

In the add-on to metformin trial, both the liraglutide 1.2 mg and 1.8 mg doses were non-inferior to glimepiride 4 mg. In contrast, the 0.6 mg dose was inferior to glimepiride. The sponsor notes that the 0.6 mg dose is non-inferior to glimepiride in the per protocol analysis (patients who completed the trials with HbA1c values at endpoint and no major protocol violations) and when LOCF is not used in the intent-to-treat analysis, with 95% confidence intervals for the treatment difference of (0.01, 0.36) and (0.04, 0.38), respectively. However, as noted by Dr. Derr, these confidence intervals are entirely in the region of inferiority of liraglutide 0.6 mg to glimepiride even though the upper bound is less than the margin of 0.4.

In the add-on to glimepiride trial, both the liraglutide 1.2 mg and 1.8 mg doses were superior to rosiglitazone 4 mg; however, this dose of rosiglitazone is only one-half the maximal FDA approved dose of 8 mg. In this trial, the 0.6 mg dose was non-inferior to rosiglitazone 4 mg. In the add-on to metformin+glimepiride trial, liraglutide 1.8 mg was superior to insulin glargine, with the caveats discussed above regarding the adequacy of glargine titration.

As discussed by Dr. Derr, the primary HbA1c results are supported by sensitivity analyses using the per-protocol analysis and a modified intent-to-treat analysis that did not use LOCF.

Table 3. Change from baseline in HbA1c (%) (intent-to-treat population with last-observation-carried-forward)							
	N	Baseline±SD	Adjusted mean change±SE	Change with lira relative to change with placebo		Change with lira relative to change with comparator	
				Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Monotherapy (Study 1573) – 52 weeks							
Lira 1.2 mg	236	8.2±1.1	-0.8±0.1	N/A		-0.3 (-0.5, -0.1)	0.001
Lira 1.8 mg	234	8.2±1.1	-1.1±0.1			-0.6 (-0.8, -0.4)	<0.0001
Glimep 8 mg	241	8.2±1.1	-0.5±0.1				
Add-on to metformin (Study 1572) – 26 weeks							
Lira 0.6 mg	239	8.4±0.9	-0.7±0.1	-0.8 (-1.0, -0.6)	<0.0001	+0.3 (0.1, 0.5)	<0.001
Lira 1.2 mg	232	8.3±1.0	-1.0±0.1	-1.1 (-1.3, -0.9)	<0.0001	0.0 (-0.2, 0.2)	0.88
Lira 1.8 mg	236	8.4±1.0	-1.0±0.1	-1.1 (-1.3, -0.9)	<0.0001	0.0 (-0.2, 0.2)	0.86
Placebo	120	8.4±1.1	0.1±0.1				
Glimep 4 mg	234	8.4±1.0	-1.0±0.1				
Add-on to glimepiride (Study 1436) – 26 weeks							
Lira 0.6 mg	224	8.4±1.0	-0.6±0.1	-0.8 (-1.1, -0.6)	<0.0001	-0.2 (-0.4, 0.0)	0.09
Lira 1.2 mg	223	8.5±1.1	-1.1±0.1	-1.3 (-1.5, -1.1)	<0.0001	-0.6 (-0.8, -0.5)	<0.0001
Lira 1.8 mg	226	8.5±0.9	-1.1±0.1	-1.4 (-1.6, -1.1)	<0.0001	-0.7 (-0.9, -0.5)	<0.0001
Placebo	107	8.4±1.0	0.2±0.1				
Rosi 4 mg	224	8.4±1.0	-0.4±0.1				
Add-on to metformin+rosiglitazone (Study 1574) – 26 weeks							
Lira 1.2 mg	174	8.5±1.2	-1.5±0.1	-0.9 (-1.1, -0.8)	<0.0001	N/A	
Lira 1.8 mg	177	8.6±1.2	-1.5±0.1	-0.9 (-1.1, -0.8)	<0.0001		
Placebo	167	8.4±1.2	-0.5±0.1				
Add-on to metformin+glimepiride (Study 1697) – 26 weeks							
Lira 1.8 mg	224	8.3±0.9	-1.3±0.1	-1.1 (-1.3, -0.9)	<0.0001	-0.2 (-0.4, -0.1)	<0.01
Placebo	110	8.3±0.9	-0.2±0.1				
Glargine	225	8.2±0.9	-1.1±0.1				

Fasting plasma glucose: In the four placebo-controlled trials, all tested doses of liraglutide resulted in significantly greater mean reductions in fasting plasma glucose relative to placebo (Table 4). The 1.2 mg and 1.8 mg doses resulted in comparable reductions in fasting plasma glucose in three of the four trials that evaluated both doses. Liraglutide 1.2 mg and 1.8 mg were superior to glimepiride in the monotherapy trial (although the p-value for the 1.2 mg comparison was nominal) and was superior to rosiglitazone 4 mg (see above regarding the caveat of this rosiglitazone dose) in the add-on to glimepiride trial. In contrast, liraglutide was not superior to glimepiride in the add-on to metformin trial or to glargine in the add-on to metformin+glimepiride trial.

Table 4. Change from baseline in fasting plasma glucose (mg/dL) (intent-to-treat population with last-observation-carried-forward)							
	N	Baseline±SD	Adjusted mean change±SE	Change with lira relative to change with placebo		Change with lira relative to change with comparator	
				Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Monotherapy (Study 1573) – 52 weeks							
Lira 1.2 mg	234	168±47	-15±3	N/A		-9 (-19, -1)	0.03
Lira 1.8 mg	230	172±47	-26±3			-20 (-29, -12)	<0.0001
Glimep 8 mg	242	172±47	-5±3				
Add-on to metformin (Study 1572) – 26 weeks							
Lira 0.6 mg	238	173±44	-20±3	-28 (-38, -17)	<0.0001	3 (-6, 12)	0.81
Lira 1.2 mg	234	179±42	-29±3	-37 (-47, -26)	<0.0001	-6 (-15, 3)	0.30
Lira 1.8 mg	235	181±41	-30±3	-38 (-48, -27)	<0.0001	-7 (-16, 2)	0.18
Placebo	116	181±41	7±4				
Glimep 4 mg	234	180±46	-24±3				
Add-on to glimepiride (Study 1436) – 26 weeks							
Lira 0.6 mg	230	180±43	-13±3	-31 (-43, -20)	<0.0001	3 (-7, 12)	0.88
Lira 1.2 mg	218	177±48	-28±3	-46 (-58, -35)	<0.0001	-12 (-22, -3)	<0.01
Lira 1.8 mg	227	174±44	-29±3	-47 (-58, -35)	<0.0001	-13 (-22, -3)	<0.01
Placebo	109	171±37	18±4				
Rosig 4 mg	226	179±45	-16±3				
Add-on to metformin+rosiglitazone (Study 1574) – 26 weeks							
Lira 1.2 mg	175	181±43	-40±4	-32 (-41, -23)	<0.0001	N/A	
Lira 1.8 mg	174	185±43	-44±4	-36 (-44, -27)	<0.0001		
Placebo	164	180±47	-8±4				
Add-on to metformin+glimepiride (Study 1697) – 26 weeks							
Lira 1.8 mg	225	165±38	-28±4	-37 (-46, -30)	<0.0001	4 (-2, 11)	0.20
Placebo	111	170±36	10±4				
Glargine	226	164±35	-32±4				

HbA1c responder analyses: As expected, the proportion of patients achieving HbA1c <7% (American Diabetes Association treatment goal) was greater with liraglutide and active comparators compared to placebo (Table 5). Liraglutide 1.8 mg resulted in a numerically greater proportion of patients achieving HbA1c <7% compared to liraglutide 1.2 mg in three of the four trials that compared these doses. In general, the liraglutide 1.2 mg and 1.8 mg doses resulted in a numerically greater proportion of patients achieving HbA1c <7% compared to the active comparators.

Table 5. Patients achieving HbA1c <7% (intent-to-treat population with last-observation-carried-forward)	
Monotherapy (Study 1573) – 52 weeks	
Lira 1.2 mg	101/236 (43%)
Lira 1.8 mg	119/234 (51%)
Glimep 8 mg	67/241 (28%)
Add-on to metformin (Study 1572) – 26 weeks	
Lira 0.6 mg	68/242 (28%)
Lira 1.2 mg	84/240 (35%)
Lira 1.8 mg	101/242 (42%)
Placebo	13/121 (11%)
Glimep 4 mg	87/242 (36%)
Add-on to glimepiride (Study 1436) – 26 weeks	
Lira 0.6 mg	54/23 (23%)
Lira 1.2 mg	77/228 (34%)
Lira 1.8 mg	94/234 (40%)
Placebo	8/114 (7%)
Rosi 4 mg	49/231 (21%)
Add-on to metformin+rosiglitazone (Study 1574) – 26 weeks	
Lira 1.2 mg	100/174 (58%)
Lira 1.8 mg	95/177 (54%)
Placebo	47/167 (28%)
Add-on to metformin+glimepiride (Study 1697) – 26 weeks	
Lira 1.8 mg	119/230 (52%)
Placebo	17/114 (15%)
Glargine	103/232 (44%)

Subgroup analyses for HbA1c: Dr. Derr conducted subgroup analyses for each of the five phase 3 trials and noted that the HbA1c findings were not consistently affected by age (<65 years vs. ≥65 years), gender, race/ethnicity (Caucasian vs. non-Caucasian) and body mass index, with most p-values for the interactions >0.1. Three interaction p-values, one for race, one for age group, and one for body mass index were <0.1, but these findings were each isolated to only a single trial. Dr. Derr noted that, across the five phase 3 trials, patients with higher baseline HbA1c values had greater mean reductions in HbA1c compared to patients with lower baseline HbA1c values, but this finding was present in all treatment arms, including the active comparator and placebo groups. This is a common finding with other antidiabetic medications and is no longer being permitted in labeling for several reasons. First, a greater proportion of patients with higher baseline HbA1c typically requires glycemic rescue compared to patients with lower baseline HbA1c, which limits conclusions. Second, as mentioned above, there were similar findings in the comparator groups.

As discussed in Section 5 of this memorandum, the clinical pharmacology reviewers noted a reduction in liraglutide exposures with increasing body weight in the population pharmacokinetic analysis (but no relationship to body mass index). Dr. Derr conducted a test for interaction between baseline body weight and change from baseline in HbA1c using the

four placebo-controlled phase 3 trials. The p-value for the interaction was <0.1 for only one of these four trials (add-on to glimepiride). In this trial, there was some evidence for a decreasing effect of liraglutide vs. placebo with increasing baseline body weight for the 0.6 mg and 1.2 mg doses but not for the 1.8 mg dose. The isolated finding in this trial is likely of no clinical significance given the lack of an interaction in the other three trials (one of which also includes a 0.6 mg dose arm and two of which also include a 1.2 mg dose arm). One possibility is that there may be a pharmacokinetic interaction between liraglutide and glimepiride that may contribute to the findings in the add-on to glimepiride trial, although the clinical pharmacology reviewers note there is no mechanistic basis for such an interaction.

Other analyses: Please see Dr. Yanoff's review of other efficacy endpoints such as metabolic syndrome and self-measured postprandial glucoses. The results from these analyses should not be included in labeling. The Division has permitted labeling of postprandial glucose, particularly when related to mechanism of action, but these data have been based on oral glucose tolerance testing or mixed-meal tolerance testing conducted at clinic visits where testing is standardized, appropriate timing of measurements are assured, and more accurate data are obtained from venous samples as opposed to patient glucometers. The Division has not labeled changes in metabolic syndrome for any anti-diabetic drug. There are various definitions for this syndrome and improvement may be due to one or more of the components, such as glucose or lipids.

Head-to-head trial against exenatide: In preparation for a face-to-face meeting after the April advisory committee meeting, the sponsor submitted summary data for a 26-week phase 3 trial comparing liraglutide 1.8 mg once daily to exenatide 10 mcg twice daily. The sponsor reported superior glycemic efficacy for liraglutide over exenatide with an adjusted mean change from baseline in HbA1c of -0.3% (95% confidence interval -0.5, -0.2; p-value <0.0001). However, the full study report has not been submitted to FDA. Therefore, these findings are considered preliminary and labeling of this information should not be entertained until after the study has been submitted and has undergone full FDA review.

8. Safety

Dr. Karen Mahoney conducted the primary clinical safety review for liraglutide. This section of the memorandum will focus on potential safety signals identified by Dr. Mahoney and adverse events of interest, including findings potentially related to the non-clinical thyroid C-cell tumors and cardiovascular safety.

The safety dataset consists of all randomized patients who received at least one dose of study medication. The integrated summary of safety submitted with the NDA used MedDRA version 10.1 and the 120-day safety update used MedDRA version 11.0.

Table 6 summarizes patient exposures in the liraglutide development program at the time of NDA submission and in the 120-day safety update. At the Pre-NDA meeting on February 5, 2008, the Division mentioned that the expected minimum patient exposure required at the time of NDA submission is evolving and that the Division now expects at least 1,300 patients exposed to investigational agent for ≥ 1 year at the time of NDA submission. The Division

Deaths: As discussed by Dr. Mahoney, there were a total of 7 treatment-emergent deaths in the clinical program (including the 120-day safety update database), with 4 occurring on liraglutide (renal cell carcinoma, cirrhosis/hepatocellular carcinoma, acute pancreatitis, and cardiorespiratory arrest after presenting with gastroenteritis) and 3 occurring on comparator (traffic accident with no suspicion for hypoglycemia and 2 cases of acute myocardial infarction).

The liraglutide-treated patient who died of hepatocellular carcinoma was diagnosed with cirrhosis and hepatocellular carcinoma after approximately 4 months of therapy making a relationship to liraglutide unlikely. Alcohol may have been a contributing factor but there are inadequate data to definitively say so.

There have been postmarketing reports with Byetta of acute pancreatitis, including severe necrotizing and hemorrhagic forms associated with some deaths. Therefore, the liraglutide-treated patient who died of acute pancreatitis is of interest. The patient received liraglutide 1.8 mg for 668 days and was last known to be alive on the evening of the day before the body was found. The autopsy report lists acute and chronic pancreatitis and cholelithiasis as major diagnoses. On gross autopsy there were gallbladder stones (no mention of bile duct involvement), white areas on the pancreas (consistent with fat necrosis) and dark red/black areas, raising the possibility of necrotizing pancreatitis. The death certificate notes acute pancreatitis as the cause of death with cholelithiasis as a contributing cause. Blinded consultative review of 3 autopsy slides (without prior knowledge of the clinical history or gross autopsy findings) did not identify pancreatic tissue, noted advanced autolytic changes, and concluded that tissues were poorly preserved suggesting a long post-mortem interval and possible delay in refrigeration of the body. After the pathologist was informed of the clinical history and gross autopsy findings, he stated that no identification of pancreatic tissue in the blinded review is not surprising based on the combined effects of antemortem necrosis (an expected finding in acute pancreatitis) and accelerated postmortem autolysis (due to high content of digestive enzymes). The consultant pathologist identified three potential risk factors for pancreatitis: cholelithiasis, hyperlipidemia, and administration of propofol for colonoscopy within 3 days of death (no endoscopic retrograde cholangiopancreatography performed). Interpretation of this case is limited because of the features described above.

In summary, I concur with Dr. Mahoney that there is no concerning signal for death with liraglutide, although event rates are low.

Serious adverse events: Dr. Mahoney reviewed all serious adverse events occurring in completed liraglutide trials included in the NDA submission. The overall incidence of serious adverse events was numerically lower in the liraglutide group (3.8%; 86.6 per 1000-patient years) than in the comparator group (4.0%; 97.5 per 1000-patient years). Dr. Mahoney notes that pancreatitis, thyroid cancer, thyroid disorders in general, events of immune etiology, stroke or cerebral hemorrhage events, angina, and overall malignancies occurred at a somewhat greater numerical incidence among liraglutide-treated patients than among comparators (Table 8). Pancreatitis, angioedema, major adverse cardiovascular events, and papillary thyroid cancer are discussed under Adverse Events of Interest.

Dr. Mahoney's review contains narratives and an assessment of the serious events that may be immune-related. Upon review of the narratives, I concur with Dr. Mahoney's assessment that the serious immune system events were either exacerbations of pre-existing conditions, not clearly immune-mediated, or with inadequate information to assign causality.

Dr. Mahoney notes an imbalance not favoring liraglutide in serious adverse events in the "Neoplasms, Benign, Malignant, and Unspecified" System Organ Class for both the original NDA (8.9 vs. 5.3 events per 1000 patient-years) and the 120-day safety update (12.3 vs. 8.1 events per 1000 patient-years). Of note, most of the events in Table 8, including the neoplasm events, were reported in only one liraglutide-treated patient and the lack of similar reported events in the comparator group may simply be related to the liraglutide group being nearly two times larger than the comparator group. Furthermore, as noted by Dr. Mahoney, 9 of the 17 serious malignant neoplasms in the liraglutide group in the original NDA and 2 of the 6 serious malignant neoplasms in the comparator group occurred within the first 6 months of treatment with study medication. This timeframe is unlikely to reflect drug-related carcinogenesis, even if the drug is a tumor promoter. When these 11 patients are excluded, the frequency of serious malignant neoplasms in the original NDA is 3.6 events per 1000 patient-years with liraglutide vs. 3.5 events per 1000 patient-years with comparator.

Neoplasms are discussed further under Common Adverse Events.

Table 8. Serious adverse events identified by Dr. Mahoney as occurring at a somewhat greater numerical incidence among liraglutide-treated patients than among comparators (all completed trials at NDA submission)				
Preferred Term	Liraglutide N=4211 (2241 PY)		Comparator N=2272 (1139 PY)	
	n (%)	Per 1000 PY	n (%)	Per 1000 PY
Pancreatitis events				
Pancreatitis	2 (<0.1)	0.9	0	0
Edematous pancreatitis	1 (<0.1)	0.4	0	0
Pancreatitis chronic	1 (<0.1)	0.4	0	0
Pancreatitis acute	0	0	1 (<0.1)	0.9
Thyroid disorders				
Papillary thyroid cancer	4 (0.1)	1.8	1 (<0.1)	0.9
Benign neoplasm of thyroid gland	1 (<0.1)	0.4	0	0
Thyroid disorder	1 (<0.1)	0.4	0	0
Goiter	3 (0.1)	1.3	0	0
Immune-related events				
Crohn's disease	1 (<0.1)	0.4	0	0
Collagen disorder	1 (<0.1)	0.4	0	0
Myositis	1 (<0.1)	0.4	0	0
Rheumatoid arthritis	1 (<0.1)	0.4	0	0
Adrenocortical insufficiency acute	2 (<0.1)	0.9	0	0
Cryptogenic organizing pneumonia	1 (<0.1)	0.4	0	0
Uveitis	1 (<0.1)	0.4	0	0
Angioedema	1 (<0.1)	0.4	0	0
Strokes and cerebral hemorrhage				
Cerebrovascular accident	3 (0.1)	1.3	0	0
Cerebral hemorrhage	1 (<0.1)	0.4	0	0
Hemorrhage intracranial	1 (<0.1)	0.4	0	0
Subarachnoid hemorrhage	1 (<0.1)	0.4	0	0
Ischemic stroke	0	0	1 (<0.1)	0.9
Angina events				
Angina pectoris	7 (0.2)	3.1	3 (0.1)	2.6
Myocardial ischemia	2 (<0.1)	0.9	0	0
Acute coronary syndrome	1 (<0.1)	0.4	0	0
Angina unstable	1 (<0.1)	0.4	0	0
Neoplasms benign, malignant and unspecified				
Papillary thyroid cancer	4 (0.1)	1.8	1 (<0.1)	0.9
Prostate cancer	4 (0.1)	1.8	1 (<0.1)	0.9
Breast cancer	2 (<0.1)	0.9	1 (<0.1)	0.9
B-cell lymphoma	1 (<0.1)	0.4	0	0
Benign neoplasm of thyroid gland	1 (<0.1)	0.4	0	0
Colon adenoma	1 (<0.1)	0.4	0	0
Gastrointestinal carcinoma	1 (<0.1)	0.4	0	0
Hepatic neoplasm malignant	1 (<0.1)	0.4	0	0
Lung carcinoma cell type unspecified recurrent	1 (<0.1)	0.4	0	0
Malignant lymphoma unclassifiable high grade	1 (<0.1)	0.4	0	0
Nasopharyngeal cancer	1 (<0.1)	0.4	0	0
Renal cell carcinoma stage unspecified	1 (<0.1)	0.4	1 (<0.1)	0.9
Uterine leiomyoma	1 (<0.1)	0.4	0	0
Colon cancer	0	0	1 (<0.1)	0.9
Glioblastoma multiforme	0	0	1 (<0.1)	0.9

Withdrawals due to adverse events: Dr. Mahoney has reviewed the adverse events associated with patient withdrawal pooled across all completed clinical trials included in the NDA submission. She notes that withdrawals due to adverse events occurred in 5.9% of all liraglutide-treated patients and in 3.0% of comparator treated patients, with this difference driven by withdrawals due to gastrointestinal events, particularly nausea (1.9% vs. 0.1%), vomiting (1.1% vs. <0.1%), and diarrhea (0.7% vs. 0.2%). Dr. Mahoney also discusses narratives for potentially important adverse events associated with patient withdrawal, such as preferred terms of “hepatic enzyme increased” and “blood creatinine phosphokinase increased”. None of these patients had severe drug-induced liver injury, Hy’s Law, or rhabdomyolysis.

Dr. Mahoney notes that all withdrawals due to injection site reactions (8 vs. 0 events) occurred among liraglutide-treated patients. Injection site reactions are discussed below under Adverse Events of Interest.

Dr. Mahoney notes that all withdrawals due to hepatobiliary disorders (5 [1.2%] vs. 0 events) occurred among liraglutide-treated patients. The 5 hepatobiliary disorders were cholelithiasis (n=2), cholecystitis, hepatic cirrhosis (see the section on deaths), and hepatic function abnormal. However, including relevant events from “Investigations”, such as aspartate aminotransferase increased (1 vs. 0 events), hepatic enzyme increased (1 vs. 1 event), liver function test abnormal (0 vs. 1 event), and transaminases increased (0 vs. 1 event), yielded more comparable findings between the liraglutide group (7 events) and comparator group (3 events), which is consistent with the randomization scheme.

Table 9 summarizes the most common adverse events associated with patient withdrawal in the phase 3 trials and includes data by liraglutide dose. Nausea, vomiting, and diarrhea were the only adverse events associated with patient withdrawal that occurred in >1% of the pooled liraglutide-treated patients. There is an apparent dose-response relationship for nausea and vomiting, but not for diarrhea. Based on Kaplan-Meier plots, most of the withdrawals due to gastrointestinal adverse events occurred within the first 14 weeks of the phase 3 trials.

Table 9. Most common adverse events (>1% of the pooled liraglutide-treated patients) associated with patient withdrawal in the phase 3 trials (NDA database)							
	Liraglutide				Comparator		
	0.6 mg N=475 387 PY n (%)	1.2 mg N=896 724 PY n (%)	1.8 mg N=1130 825 PY n (%)	All N=2501 1936 PY n (%)	Placebo N=524 265 PY n (%)	Active N=953 738 PY n (%)	Total N=1477 1003 PY n (%)
Events leading to withdrawal	21 (4.4)	74 (8.3)	100 (8.8)	195 (7.8)	14 (2.7)	36 (3.8)	50 (3.4)
Gastrointestinal disorders	8 (1.7)	48 (5.4)	70 (6.2)	126 (5.0)	3 (0.6)	5 (0.5)	8 (0.5)
Nausea	3 (0.6)	26 (2.9)	41 (3.6)	70 (2.8)	0	0	0
Vomiting	3 (0.6)	12 (1.3)	23 (2.0)	38 (1.5)	1 (0.2)	0	1 (0.1)
Diarrhea	0	13 (1.5)	14 (1.2)	27 (1.1)	0	2 (0.2)	2 (0.1)

PY = patient-years

acknowledged the need to balance this changing policy with the patient exposure numbers that were agreed upon during the end-of-phase 2 meeting. Therefore, the Division requested complete data be available for $\geq 2,500$ patients exposed to liraglutide with approximately 850 of these patients exposed to liraglutide for ≥ 1 year and approximately 350 of these patients exposed to liraglutide for at least 18 months. Although the NDA includes data on over 4,200 patients exposed to liraglutide, the sponsor has marginally satisfied the request for 1-year data (Table 6). These sample sizes do not meet the exposures recommended in the February 29, 2008 draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*, which was published after the Pre-NDA meeting.

	Lira 0.6 mg	Lira 1.2 mg	Lira 1.8 mg	All lira	Placebo	Active comparator
At NDA filing	802	1151	1408	4211	1122	1165
≥ 24 weeks	413	735	937	2086	380	803
≥ 52 weeks	167	325	324	816	47	309
≥ 76 weeks	110	200	187	497	29	169
Patient-years (all trials)	418	758	870	2241	353	786
At 120-day safety update						
≥ 24 weeks	479	735	937	2412	438	905
≥ 52 weeks	167	325	324	816	47	309
≥ 76 weeks	110	199	186	495	29	167
Patient-years (all trials)	456	758	869	2434	391	843

Patient disposition: As discussed by Dr. Mahoney, the placebo group had the highest rate of withdrawal, driven predominantly by ineffectiveness of therapy (Table 7). Withdrawals due to adverse events were more common with liraglutide than with comparator, particularly for the 1.2 mg and 1.8 mg dose groups with ineffectiveness of therapy being the most common reason for withdrawal in the 0.6 mg group. The proportion of patients who completed the 6-month trials and entered the voluntary extension periods was approximately 40% in the liraglutide and active-comparator groups and approximately 15% in the placebo group.

	Liraglutide				Comparator		
	0.6 mg	1.2 mg	1.8 mg	All	Placebo	Active	Total
Randomized and exposed	475	896	1130	2501	524	953	1477
Completers, n (%)	416 (88)	708 (79)	917 (81)	2041 (82)	374 (71)	775 (81)	1149 (78)
Withdrawal, n (%)	59 (12)	188 (21)	213 (19)	460 (18)	150 (29)	178 (19)	328 (22)
Adverse event	16 (3.4)	69 (7.7)	93 (8.2)	178 (7.1)	15 (2.9)	35 (3.7)	50 (3.4)
Protocol non-compliance	5 (1.1)	24 (2.7)	22 (2.0)	51 (2.0)	11 (2.1)	19 (2.0)	30 (2.0)
Ineffective therapy	31 (6.5)	34 (3.8)	34 (3.0)	99 (4.0)	91 (17)	50 (5.3)	141 (10)
Other	7 (1.5)	61 (6.8)	64 (5.7)	132 (5.3)	33 (6.3)	74 (7.8)	107 (7.2)
Entered extension	184	327	328	839	61	320	381
% of original randomized	39%	36%	29%	34%	12%	34%	26%
% of core completers	44%	46%	36%	41%	16%	41%	33%

Common adverse events: Dr. Mahoney has summarized treatment-emergent adverse events occurring across all completed liraglutide trials included in the NDA submission. Table 10, adapted from Dr. Mahoney's review, shows adverse events occurring in >1% of the pooled liraglutide-treated patients and occurring with an incidence >0.2% higher in the pooled liraglutide group than in the pooled placebo group. Several of the adverse events occurring more frequently with liraglutide in this analysis are consistent with the pharmacologic mechanism of action of the drug (e.g., nausea, vomiting, decreased appetite, anorexia) and these events appear dose-related. Constipation, diarrhea, and fatigue were also increased with liraglutide and also appear dose-related. An association with liraglutide for some of the other adverse effects is more questionable. For example, the three listed infections in Table 10 each occur more frequently with liraglutide than with placebo but occur with comparable or lower numerical frequency with liraglutide than with active comparator and none have a clear relationship to liraglutide dose. Dizziness and back pain occur somewhat more frequently with liraglutide than with placebo but there is no dose-response relationship for either of these events.

Neoplasms:

Dr. Mahoney notes that neoplasms were reported at an overall incidence of 1.3% (23.7 per 1000 patient-years) for liraglutide vs. 0.5% (10.5 per 1000 patient-years) for comparator based on all completed trials included in the original NDA. As discussed by Dr. Mahoney, no particular cancer cell type predominated with many of the reported preferred terms occurring in isolated liraglutide-treated patients. In addition, the clinical trials were not prospectively designed to rigorously assess neoplasms (e.g., events were identified based on investigator reporting without adjudication). Nonetheless, to further explore this imbalance, the sponsor conducted updated analyses using all phase 2 and phase 3 clinical trials up until a cutoff date of May 30, 2008. For this analysis, the sponsor classified neoplasm events as benign or malignant based on reported verbatim term, medical history, pathology reports and surgery reports. Of the 115 treatment-emergent neoplasm adverse events, 45 (39%) were classified as malignant.

As shown in Table 11, the overall incidence rate of neoplasms as well as the incidence rates for serious neoplasms, non-serious neoplasms, and benign neoplasms with liraglutide compare favorably to the corresponding incidence rates with placebo, although these incidence rates are higher than those with active comparator.

The incidence rate for malignant neoplasms (per 1,000 patient-years) was 10.9 for liraglutide, 6.3 for placebo, and 7.2 for active comparator. A total of 15 malignant neoplasms were detected >6 months after initiation of study medication, with 12 (0.3%) events in liraglutide-treated patients, 0 events in placebo-treated patients, and 3 (0.2%) events in active comparator-treated patients. Among these 15 events, there were 4 breast cancers (3 with liraglutide vs. 1 with active comparator), 2 prostate cancers (both with liraglutide), and 4 colon cancers (3 with liraglutide vs. 1 with active comparator) - the incidence of these events is consistent with the randomization scheme. However, seven malignant neoplasm events were reported beyond 1

year of exposure to study medication, six occurring with liraglutide and only 1 occurring with active comparator.

The sponsor states that the incidence of malignant neoplasms with liraglutide is comparable to the reported neoplasm frequency in the United States based on the United States Surveillance, Epidemiology and End Results (SEER) database from 1998-2002. However, there remains an unexplained numerical imbalance of malignant neoplasms not favoring liraglutide in the clinical trials. Therefore, this imbalance should be described under Adverse Reactions in the package insert. The sponsor is including neoplasms as an Adverse Event of Interest in the cardiovascular trial and will be adjudicating these events.

Table 10. Most common adverse events (all completed liraglutide trials included in the NDA) (>2% of the pooled liraglutide-treated patients and occurring >0.2% more frequently with pooled liraglutide compared to pooled placebo)												
System Organ Class Preferred Term	Liraglutide dose group (mg)							Comparator				
	<0.6 N=401 n (%)	0.6 N=641 n (%)	>0.6 - <1.2 N=416 n (%)	1.2 N=993 n (%)	1.8 N=1408 n (%)	>1.8 N=288 n (%)	All N=4211 n (%)	Placebo N=1122 n (%)	Active N=1165 n (%)	Total N=2272 n (%)		
Any	220 (55)	451 (70)	209 (50)	785 (79)	1082 (77)	236 (82)	3015 (72)	675 (60)	767 (66)	1437 (63)		
Gastrointestinal disorders												
Nausea	65 (16)	209 (33)	109 (26)	447 (45)	658 (47)	173 (60)	1682 (40)	212 (19)	246 (21)	455 (20)		
Diarrhea	21 (5.2)	53 (8.3)	60 (14)	210 (21)	341 (24)	96 (33)	788 (19)	56 (5.0)	48 (4.1)	102 (4.5)		
Vomiting	15 (3.7)	51 (8.0)	24 (5.8)	108 (11)	183 (13)	46 (16)	437 (10)	54 (4.8)	72 (6.2)	126 (5.5)		
Constipation	5 (1.2)	20 (3.1)	23 (5.5)	76 (7.7)	124 (8.8)	28 (9.7)	285 (6.8)	25 (2.2)	20 (1.7)	45 (2.0)		
Dyspepsia	11 (2.7)	22 (3.4)	11 (2.6)	67 (6.7)	86 (6.1)	34 (11.8)	234 (5.6)	25 (2.2)	32 (2.7)	57 (2.5)		
Abdominal pain upper	6 (1.5)	20 (3.1)	5 (1.2)	40 (4.0)	91 (6.5)	26 (9.0)	191 (4.5)	10 (0.9)	22 (1.9)	32 (1.4)		
Infections and infestations												
Influenza	3 (0.7)	9 (1.4)	3 (0.7)	28 (2.8)	39 (2.8)	12 (4.2)	94 (2.2)	9 (0.8)	18 (1.5)	27 (1.2)		
Gastroenteritis	69 (17)	214 (33)	49 (12)	381 (38)	465 (33)	98 (34)	1281 (30)	302 (27)	389 (33)	691 (30)		
Urinary tract infection	0	16 (2.5)	0	41 (4.1)	61 (4.3)	10 (3.5)	130 (3.1)	23 (2.0)	54 (4.6)	77 (3.4)		
Nervous system disorders												
Dizziness	1 (0.2)	17 (2.7)	1 (0.2)	32 (3.2)	41 (2.9)	16 (5.6)	108 (2.6)	13 (1.2)	30 (2.6)	43 (1.9)		
Musculo/connective tissue												
Back pain	3 (0.7)	12 (1.9)	1 (0.2)	42 (4.2)	27 (1.9)	3 (1.0)	88 (2.1)	13 (1.2)	21 (1.8)	34 (1.5)		
General disorders/admin site												
Fatigue	63 (16)	90 (14)	73 (18)	195 (20)	295 (21)	58 (20)	786 (19)	189 (17)	184 (16)	371 (16)		
Metabolism/nutrition	19 (4.7)	19 (3.0)	27 (6.5)	35 (3.5)	61 (4.3)	8 (2.8)	172 (4.1)	36 (3.2)	25 (2.1)	60 (2.6)		
Decreased appetite	23 (5.7)	84 (13)	23 (5.5)	163 (16)	204 (15)	30 (10)	532 (13)	117 (10)	188 (16)	304 (13)		
Anorexia	5 (1.2)	24 (3.7)	6 (1.4)	43 (4.3)	59 (4.2)	9 (3.1)	147 (3.5)	27 (2.4)	50 (4.3)	77 (3.4)		
	36 (9.0)	64 (10)	28 (6.7)	132 (13)	199 (14)	50 (17)	514 (12)	99 (8.8)	97 (8.3)	195 (8.6)		
	11 (2.7)	12 (1.9)	4 (1.0)	27 (2.7)	63 (4.5)	17 (5.9)	136 (3.2)	19 (1.7)	17 (1.5)	36 (1.6)		
	24 (6.0)	47 (7.3)	10 (2.4)	145 (15)	230 (16)	26 (9.0)	483 (12)	75 (6.7)	81 (7.0)	156 (6.9)		
	1 (0.2)	5 (0.8)	1 (0.2)	46 (4.6)	96 (6.8)	3 (1.0)	152 (3.6)	9 (0.8)	1 (0.1)	10 (0.4)		
	4 (1.0)	9 (1.4)	3 (0.7)	35 (3.5)	77 (5.5)	9 (3.1)	137 (3.3)	8 (0.7)	7 (0.6)	15 (0.7)		

Data from the >1.2 - <1.8 mg group is included in the "All liraglutide" group. A separate column is not shown because this group had only 64 patients.

Table 11. Neoplasm Adverse Events in the Phase 2 and Phase 3 Clinical Trials (data cutoff date May 30, 2008)								
	Liraglutide N=4257		Placebo N=907		Active Comparator N=1474		Total Comparator N=2381	
	n (%)	Per 1000 PY	n (%)	Per 1000 PY	n (%)	Per 1000 PY	n (%)	Per 1000 PY
All neoplasms	78 (1.8)	26.9	12 (1.3)	25.3	17 (1.2)	17.0	29 (1.2)	19.5
Serious	38 (0.9)	12.5	5 (0.6)	10.5	8 (0.5)	7.2	13 (0.5)	8.2
Non-serious	43 (1.0)	14.4	7 (0.8)	14.8	9 (0.6)	9.8	16 (0.7)	11.3
Benign neoplasms reported in >1 liraglutide-treated patient								
All	48 (1.1)	16.0	9 (1.0)	19.0	9 (0.6)	9.8	18 (0.8)	12.6
Thyroid neoplasm	21 (0.5)	7.0	3 (0.3)	6.3	1 (0.1)	0.9	4 (0.2)	2.5
Uterine leiomyoma	5 (0.1)	1.6	1 (0.1)	2.1	1 (0.1)	0.9	2 (0.1)	1.3
Lipoma	4 (0.1)	1.3	0	0	0	0	0	0
Skin papilloma	3 (0.1)	1.0	0	0	1 (0.1)	0.9	1 (<0.1)	0.6
Lung neoplasm	3 (0.1)	1.0	0	0	1 (0.1)	0.9	1 (<0.1)	0.6
Colon adenoma	2 (<0.1)	0.6	1 (0.1)	2.1	1 (0.1)	0.9	2 (0.1)	1.3
Melanocytic nevus	2 (<0.1)	0.6	1 (0.1)	2.1	2 (0.1)	1.8	3 (0.1)	1.9
Malignant neoplasms reported in >1 liraglutide-treated patient								
All	34 (0.8)	10.9	3 (0.3)	6.3	8 (0.5)	7.2	11 (0.5)	6.9
Prostate cancer	5 (0.1)	1.6	1 (0.1)	2.1	0	0	1 (<0.1)	0.6
Papillary thyroid ca.	5 (0.1)	1.6	1 (0.1)	2.1	0	0	1 (<0.1)	0.6
Breast cancer	3 (0.1)	1.0	0	0	2 (0.1)	1.8	2 (0.1)	1.3
Colon cancer	2 (<0.1)	0.6	0	0	1 (0.1)	0.9	1 (<0.1)	0.6
Rectal cancer	2 (<0.1)	0.6	0	0	0	0	0	0
Basal cell carcinoma	2 (<0.1)	0.6	0	0	0	0	0	0
PY = patient-years								
Benign vs. malignant determination based on reported verbatim term, medical history, pathology, surgery reports								

Adverse events of interest:

Major adverse cardiovascular events: As discussed in Section 2, the Division has requested that sponsors of new pharmaceuticals for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. The 2008 guidance on this topic asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a pre-specified meta-analysis of major cardiovascular events can reliably be performed.
- Enroll patients at increased cardiovascular risk, such as elderly patients and those with renal impairment.

The guidance states that to support approvability from a cardiovascular standpoint, the sponsor should compare the incidence of major adverse cardiovascular events (MACE) with the investigational agent to the incidence of MACE occurring with the control group and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio or hazard ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.

Although the liraglutide development program was completed well in advance of this guidance, the Division has requested that all pending NDAs be held to the 1.3 and 1.8 goalposts described above. This decision affected two other NDAs (alogliptin and saxagliptin) submitted to FDA prior to the publication of the guidance. To standardize the approach for assessing cardiovascular safety for all three products, the Division requested that the sponsors of these applications perform similar post-hoc analyses of cardiovascular events, as summarized below and discussed in detail in Dr. Mahoney's clinical review. Of note, none of the programs had pre-specified definitions or prospective adjudication of major cardiovascular events and, because of the retrospective nature of these analyses, some events have insufficient information to definitively determine whether a cardiovascular event of interest had occurred.

The Division requested two cardiovascular endpoints. The first endpoint, termed "Broad SMQ MACE" was defined as a composite endpoint of cardiovascular death and all preferred terms in the Standardised MedDRA Queries (SMQs) for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents." Although the preferred terms in the "Broad SMQ MACE" could be consistent with cardiovascular events of interest, there may be an alternate explanation in some patients. For example, "blood creatine phosphokinase increased" is a preferred term in the Myocardial Infarction SMQ, but could be related to exercise, muscle trauma, medications, or a variety of other causes. Therefore, this analysis will detect all patients with reported preferred terms that could be consistent with, but not necessarily diagnostic of, the condition of interest.

A second endpoint, called "Custom MACE", was also analyzed. The "Custom MACE" endpoint is a subset of "Broad SMQ MACE" and was created as follows. Without considering which events had occurred, the three clinical reviewers for saxagliptin, alogliptin, and liraglutide independently reviewed the list of all preferred terms included in the "Broad SMQ MACE" endpoint with the following question in mind: "If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?" The goal was to select only those preferred terms that seemed more likely to represent events of myocardial infarction or stroke as reported by investigators.

The lists generated by the three clinical reviewers were compared and consensus was reached regarding inclusion or exclusion for all preferred terms. A listing of the preferred terms included in the "Broad SMQ MACE" and "Custom MACE" endpoints is shown in Dr.

Mahoney's review and in the January 2009 information request in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS).

As noted by Dr. Mahoney, reports of "blood creatine phosphokinase increased" accounted for approximately one-half of the Broad SMQ MACE events. This finding is likely explained by routine measurement of creatine phosphokinase in the clinical trials. As discussed above, elevated creatine phosphokinase is non-specific; therefore, the proportion of such events that truly represent myocardial infarction is unknown (because of limited data collection) but probably low. Dr. Mahoney notes that only one of the patients with blood creatine phosphokinase increased had another reported MACE event (transient ischemic attack occurring 4 months later).

Table 12 summarizes the MACE results for the liraglutide controlled phase 2/3 database. Results are presented for the short-term population (randomized, controlled portions of all phase 2/3 trials up to the primary efficacy timepoint) and for the long-term population (short-term population plus data from the controlled, open-label, voluntary extensions). The incidence ratios and 95% confidence intervals for MACE were calculated using three different comparators – placebo, active comparator, and total comparator (placebo + active comparator). As discussed by Dr. Mahoney, three statistical methods were used to calculate each incidence ratio and 95% confidence interval as summarized below:

- The sponsor used an asymptotic, stratified, Mantel-Haenszel analysis, which is a well-established method for calculating incidence ratios. However, studies are excluded if there are zero MACE events in the comparator group. Also, this method assumes the variance of the estimated ratio is normally distributed, which may not apply well when event rates are low.
- Dr. Derr conducted two analyses for the incidence ratios and 95% confidence intervals. The first approach is an exact, stratified analysis. Like the sponsor's analysis, this method excludes studies with zero MACE events in the comparator group. Also, this method is conservative, yielding 95% confidence intervals that may be wider than necessary.
- Dr. Derr's second analysis used a stratified, fixed-effects Mantel-Haenszel meta-analysis with a continuity correction of 0.5 applied to studies with zero MACE events in one or both groups. This approach allows studies with zero events to be included in the estimate, but the continuity correction can be influential when events are rare.

These different approaches were used to assess the sensitivity of the MACE results to statistical analyses, with one approach not necessarily favored over another approach.

A total of 36 incidence ratios with 95% confidence intervals were calculated – 18 for Broad MACE and 18 for Custom MACE. Results are summarized below.

When liraglutide was compared to total comparator, all 6 Broad MACE analyses and all 6 Custom MACE analyses yielded point estimates for the incidence ratio <1.0 (range 0.63-0.90) and all upper bounds for the corresponding 95% confidence intervals were less than 1.8 (range

1.24-1.74). Similarly, when liraglutide was compared to active comparator, all 6 Broad MACE analyses and all 6 Custom MACE analyses yielded point estimates for the incidence ratio <1.0 (range 0.60-0.85). For the comparison to active comparator, all upper bounds for the corresponding 95% confidence intervals were less than 1.8 (range 1.27-1.72), except for the upper bound for Custom MACE for the short-term population, which was 1.83.

When liraglutide was compared to placebo, two of the 6 Broad MACE analyses and all 6 of the Custom MACE analyses yielded point estimates for the incidence ratio <1.0 . For the comparisons to placebo, the incidence ratio was >1.0 (range 1.02-1.10) for 4 Broad MACE analyses (both the short-term and long-term populations using the sponsor's analysis and the FDA exact analysis). The upper bound of the corresponding 95% confidence intervals were <1.8 for the 4 analyses calculated using FDA's fixed-effects approach with continuity correction. The eight results obtained with the two other analytical approaches yielded upper bounds for the 95% confidence intervals ranging from 1.92-4.76.

Eight of the 36 calculated 95% confidence intervals had an upper bound below 1.3 (range 1.24-1.29).

Based on the above data, the advisory committee was asked to vote on the following question: "...[H]as the applicant provided appropriate evidence of cardiovascular safety to conclude that liraglutide rules out unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?" The vote tally was 8 "yes" and 5 "no". As noted by Dr. Mahoney, both cardiologists and the statistician on the committee voted "no". One of the cardiologists noted the low risk population, the unblinded long-term extensions, upper bounds of the 95% confidence intervals close to 1.8, and apparent sensitivity to analytical method. The other cardiologist was concerned with the low event rates, lack of adjudication, unblinded long-term extensions, and inconsistent point estimates/confidence intervals depending on comparator used. The statistician noted the increased risk relative to placebo and some of the above stated limitations of the data, such as lack of adjudication.

As discussed above, the incidence of MACE events was low, ranging from 1.0-2.2% for Broad MACE and 0.3-0.9% for Custom MACE; depending on the patient population (short-term vs. long-term). This is an important limitation of the data. The phase 3 trials excluded patients at high cardiovascular risk. As a result, there are only 26 events for Custom MACE for liraglutide vs. total comparator during the phase 2/3 trials up to the primary efficacy timepoint and a total of 38 events when Custom MACE events are included from the controlled, but open-label and voluntary extensions. The number of MACE events is lowered further when liraglutide is compared to a subset of total comparator, particularly placebo. For example, there are only 3 patients treated with add-on placebo who developed a Custom MACE event during the phase 2/3 trials up to the primary efficacy timepoint (vs. 13 patients for total comparator) and only 4 add-on placebo patients when Custom MACE is included from the extension periods (vs. 17 for total comparator). The particularly low number of MACE events with placebo is most likely due to the smaller placebo exposures (328 patient-years vs. 718 patient-years for active comparator). This low number of placebo events adds uncertainty to the point estimate for the incidence ratios, as reflected by the wider 95% confidence intervals. Of note,

all point estimates for Custom MACE are less than 1.0 regardless of whether liraglutide is compared to placebo, active comparator (combined rosiglitazone, glimepiride, glargine), or total comparator.

One caveat of these analyses is that the active comparators have unknown cardiovascular profiles. Rosiglitazone increased myocardial ischemic events in a meta-analysis of short-term clinical trials that were not prospectively designed to assess cardiovascular risk. Long-term trials have not confirmed these findings and a definitive cardiovascular trial comparing rosiglitazone and pioglitazone to placebo is ongoing. All sulfonylurea package inserts contain a bolded warning describing increased cardiovascular mortality with the first-generation sulfonylurea, tolbutamide, in the University Group Diabetes Program (UGDP) trial. There have been numerous criticisms of UGDP, and it remains unknown whether the findings are real – and if real, whether the findings extend to other sulfonylureas. Despite these caveats, the favorable point estimates (0.60-0.85) for all comparisons of liraglutide to active comparator are reassuring and provide a comparison to real-world alternatives in the treatment armamentarium for type 2 diabetes.

Based on the above considerations and the fact that the liraglutide NDA was submitted prior to the publication of the diabetes cardiovascular guidance, I concur with the majority vote of the advisory committee panel that liraglutide has fulfilled the spirit of this guidance. I base this conclusion on the comparison of liraglutide to total comparator. There are too few placebo comparator events to permit a meaningful comparison to placebo, particularly for the preferred endpoint of Custom MACE. If liraglutide is approved, a definitive cardiovascular safety trial should be required, as described in the guidance.

Table 12. Major adverse cardiovascular events (MACE) in the liraglutide phase 2/3 program (bolded values exceed the 1.8 goalpost described in the FDA diabetes cardiovascular guidance)

	Liraglutide events n (%)	Comparator events n (%)	Novo Nordisk Incidence ratio ¹ (95% CI)	FDA exact Incidence ratio ² (95% CI)	FDA fixed-effects Incidence ratio ³ (95% CI)
Total comparator	N=4257	N=2381			
Broad MACE					
Short-term population	51 (1.20)	35 (1.47)	0.87 (0.57, 1.34)	0.86 (0.55, 1.41)	0.83 (0.55, 1.27)
Long-term population	69 (1.62)	45 (1.89)	0.88 (0.61, 1.28)	0.90 (0.60, 1.36)	0.86 (0.59, 1.24)
Custom MACE					
Short-term population	13 (0.31)	13 (0.55)	0.72 (0.32, 1.61)	0.72 (0.30, 1.74)	0.63 (0.32, 1.24)
Long-term population	21 (0.49)	17 (0.71)	0.79 (0.41, 1.54)	0.80 (0.39, 1.64)	0.71 (0.39, 1.30)
Placebo comparator	N=4257	N=907			
Broad MACE					
Short-term population	51 (1.20)	9 (0.99)	1.04 (0.50, 2.16)	1.04 (0.48, 2.17)	0.86 (0.45, 1.65)
Long-term population	69 (1.62)	13 (1.43)	1.02 (0.54, 1.92)	1.10 (0.56, 2.31)	0.89 (0.50, 1.60)
Custom MACE					
Short-term population	13 (0.31)	3 (0.33)	0.80 (0.23, 2.83)	0.78 (0.19, 4.76)	0.52 (0.21, 1.25)
Long-term population	21 (0.49)	4 (0.44)	0.92 (0.30, 2.83)	0.92 (0.28, 3.97)	0.60 (0.26, 1.39)
Active comparator	N=4257	N=1474			
Broad MACE					
Short-term population	51 (1.20)	26 (1.76)	0.82 (0.51, 1.32)	0.82 (0.48, 1.33)	0.79 (0.49, 1.28)
Long-term population	69 (1.62)	32 (2.17)	0.85 (0.55, 1.29)	0.84 (0.53, 1.35)	0.83 (0.54, 1.27)
Custom MACE					
Short-term population	13 (0.31)	10 (0.68)	0.68 (0.28, 1.66)	0.68 (0.26, 1.83)	0.60 (0.27, 1.31)
Long-term population	21 (0.49)	13 (0.88)	0.76 (0.36, 1.61)	0.76 (0.35, 1.72)	0.68 (0.34, 1.37)
Short-term population = randomized, controlled portions of all phase 2/3 trials up to the primary efficacy timepoint					
Long-term population = short-term population plus controlled, open-label, voluntary extensions					
¹ stratified, asymptotic Mantel-Haenszel					
² stratified, exact					
³ stratified, fixed-effects Mantel-Haenszel meta-analysis with continuity correction of 0.5 for arms with zero MACE					

Thyroid tumors:

1. Papillary thyroid carcinoma

Through database lock for the 120-day safety update, there have been six reports of papillary thyroid carcinoma in the liraglutide program, 5 (0.1%) with liraglutide (corresponding to 1.6 events per 1000 patient-years) and 1 (<0.1%) with comparator (corresponding to 0.6 events per 1000 patient-years). Subsequently, a sixth case of papillary thyroid cancer in a liraglutide-treated patient has been reported during the ongoing extension of the add-on to metformin trial. One of the patients diagnosed with papillary thyroid cancer had a dominant thyroid

nodule on ultrasound at screening with inconsistent results on repeat fine needle aspiration prompting surgery after approximately 100 days of treatment with liraglutide 0.6 mg. The other 6 cases of papillary thyroid cancer were incidental microcarcinomas detected upon thyroidectomy prompted by abnormal results on routine protocol-specified measurements of serum calcitonin or calcium stimulation testing. As noted by Dr. Mahoney, all liraglutide cases occurred with <1 year exposure to study medication (range 26-364 days for the liraglutide cases). These tumors are derived from thyroid follicular cells and are not related to the thyroid C-cell.

Dr. Mahoney notes that patients in all treatment arms underwent routine calcitonin measurements and, therefore, questions why there is an excess of papillary thyroid cancer cases with liraglutide relative to comparator. There are at least two potential explanations for this apparent imbalance. First, event rates were low resulting in unstable estimates. For example, two more papillary thyroid cancers in the comparator group or one less event with liraglutide and one more event with comparator would eradicate the apparent imbalance. Second, as discussed by Dr. Mahoney, there was a differential rate of thyroidectomy in the clinical program. Including the data from the advisory committee briefing document, there were 14 thyroidectomies among liraglutide-treated patients and 3 thyroidectomies among comparator-treated patients. Of note, 8 of the 14 thyroidectomies with liraglutide (1 patient with a thyroid nodule, 6 patients with elevated serum calcitonin, the highest of which was 23 ng/L, and 1 patient with an abnormal calcitonin stimulation test) and one of the 3 thyroidectomies with comparator (elevated serum calcitonin of 19.4 ng/L) occurred prior to release of the randomization codes. Therefore, the thyroidectomy imbalance is driven by surgeries that do not appear to have been influenced by knowledge of treatment assignment. One caveat is that three of these liraglutide-treated patients reported gastrointestinal symptoms prior to thyroidectomy. Investigators classified the causality of these adverse events as possibly or probably related to study medication; therefore, it is possible that these events may have effectively unblinded investigators.

At the advisory committee meeting, the panel was asked whether the available data on papillary thyroid cancer permit marketing of liraglutide. The vote was 12 “yes” to zero “no”. In general, the advisory panel stated that papillary microcarcinoma is common in the general population and that these were likely incidental findings at surgery that was prompted by routine calcitonin screening in the development program.

2. Medullary thyroid carcinoma

As discussed by Dr. Mahoney, there has been one reported case of medullary thyroid cancer in the liraglutide development program, but this case occurred in a comparator-treated patient and was presumably present pre-treatment because the baseline calcitonin exceeded 1000 ng/L. As noted by Dr. Mahoney, medullary thyroid cancer is typically indolent; therefore, large tumors are not expected in clinical trials, even if drug-induced.

3. C-cell hyperplasia

Dr. Mahoney notes a total of 6 cases of thyroid C-cell hyperplasia in the liraglutide program as of June 26, 2009, with 5 cases among liraglutide-treated patients (one with 0.6 mg, two with 1.2 mg, and two with 1.8 mg) and 1 case in a comparator-treated patient. Two of these 6 cases (1 with liraglutide and 1 with comparator) were classified as medullary thyroid carcinoma *in situ*. Of the remaining 4 cases (all with liraglutide), three were classified as diffuse C-cell hyperplasia and one was classified as focal C-cell hyperplasia. As discussed by Dr. Mahoney, in a patient without familial medullary thyroid cancer, the predictive value of C-cell hyperplasia for the future development of medullary thyroid cancer is controversial. All cases of C-cell hyperplasia were diagnosed after thyroidectomy, which was prompted by abnormal results on routine protocol-specified measurements of unstimulated serum calcitonin (n=5) or calcium stimulation testing (n=1). Exposure to liraglutide ranged from 28-484 days. The pre-operative calcitonin values in the 5 liraglutide-treated patients were only 3-7 ng/L above baseline calcitonin values and the 4 liraglutide-treated patients with abnormal pre-operative unstimulated calcitonin values already had abnormal unstimulated calcitonin values at baseline. The highest unstimulated serum calcium value among these 6 cases was approximately 30 ng/L. The liraglutide-treated patient who underwent thyroidectomy based on results of the calcium stimulation test had a pre-operative unstimulated serum calcium of 4.6 ng/L, a stimulated calcitonin at Week 0 of 21.2 ng/L and a stimulated calcitonin at Week 52 of 94.0 ng/L. This patient was found to have diffuse C-cell hyperplasia on pathology. As discussed by Dr. Mahoney, C-cell hyperplasia has been reported in a variety of conditions, such as aging, Hashimoto's thyroiditis, and hyperparathyroidism. In a small autopsy study, 2 of 13 adult women (15%) and 12 of 29 adult men (40%) with no evidence of co-existing thyroid disease met criteria for having C-cell hyperplasia.² Based on all the above considerations, there is no convincing evidence that liraglutide is associated with C-cell hyperplasia in the development program to date.

4. Calcitonin

Please see Dr. Mahoney's review for an excellent overview of medullary thyroid cancer and serum calcitonin. In the 52-week monotherapy trial, the 6-month serum calcitonin was measured at Week 28, whereas the 6-month serum calcitonin data for the four 26-week phase 3 trials were measured at Week 26. Therefore, when calcitonin data are pooled across phase 3 trials, the Week 28 data from the monotherapy trial are pooled with the Week 26 data from the other phase 3 trials. A similar approach was used for the 18-month calcitonin data, which was measured at Week 76 in one extension trial and Week 78 in the other extension trial.

Dr. Mahoney summarizes the calcitonin shift data included in the original NDA submission for the 5 phase 3 diabetes trials from baseline to Week 26/28, Week 52, and Week 76/78. After the advisory committee meeting, the sponsor submitted additional calcitonin analyses, including data from the obesity trial, two Japanese phase 3 trials, and extension data for the monotherapy trial and add-on to metformin trial through Week 104.

Dr. Mahoney places less emphasis on data beyond Week 26/28 because there are fewer data beyond this timepoint and she raises concerns about confounding due to the open-label,

² Guyétant S, et al. Sex-related C cell hyperplasia in the normal human thyroid: a quantitative autopsy study. *J Clin Endocrinol Metab.* 1997; 82: 42-47.

voluntary extension periods with high and somewhat differential dropout rates between treatment groups. Reasons for the considerably fewer patients with data beyond Week 26/28 include (1) no extensions for several of the 26-week phase 3 trials, (2) voluntary extensions with many patients choosing not to continue, and (3) continued dropout over time due to adverse events or other reasons. Based on the sponsor’s most recent analysis, there are approximately 600 liraglutide-treated patients with calcitonin data after 18 months and after 2 years of treatment (Table 13). Unblinding would not be expected to impact the actual objective calcitonin measurements, which were obtained at the same timepoints in the liraglutide and comparator treatment groups. In addition, other techniques such as patient-year exposures can be used to analyze data with differential dropout rates, when appropriate. Of note, few patients discontinued the trial as a result of calcitonin-related findings and very few completers were missing calcitonin data (2% at Week 52 and 3-5% at Week 104), which is more reassuring than having a large proportion of completers without calcitonin data. Despite the above-described limitations, the available calcitonin data at Weeks 52 and 104 can provide some insight into the likelihood of having elevations of serum calcitonin into potentially clinically important ranges at these timepoints.

Week	Liraglutide	Placebo	Active comparator
20/24/26/28	2972	519	1164
52	1442 (98%)	173 (98%)	475 (98%)
76/78	637	35	238
104	578 (95%)	30 (97%)	200 (95%)

Percentages represent the proportion of completers with available calcitonin data

Dr. Mahoney has noted differences between liraglutide and comparators for some calcitonin analyses. Some of her main findings are summarized below.

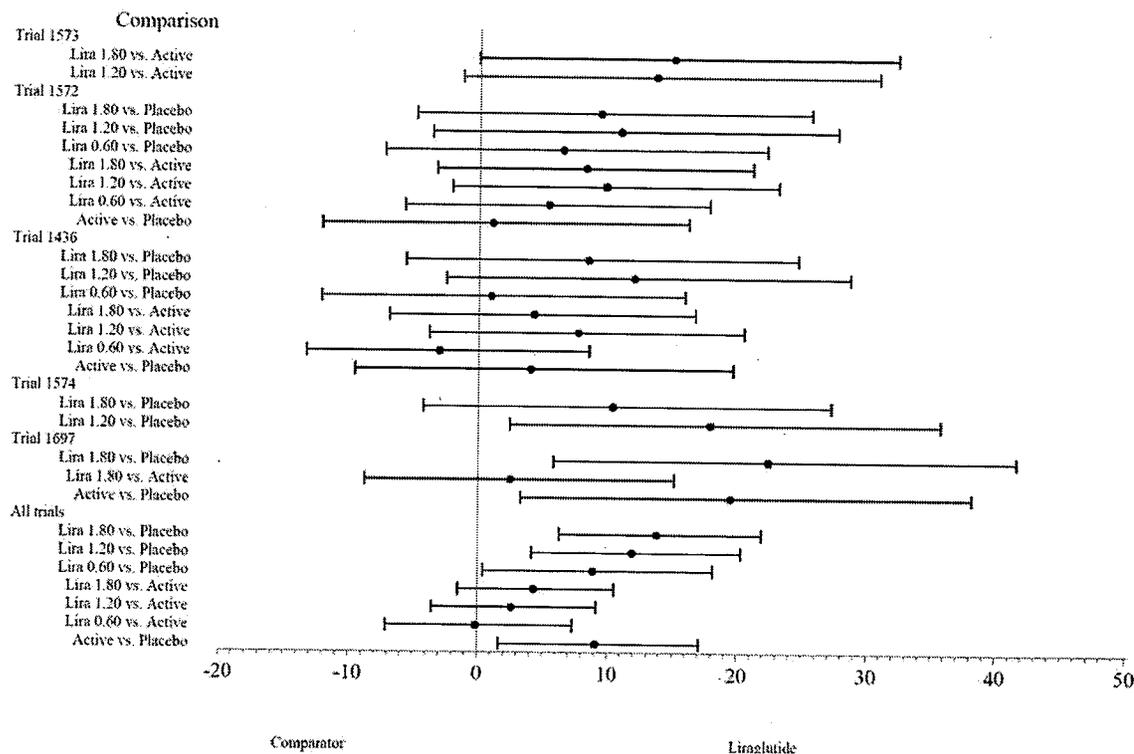
- Using the combined data from the 5 phase 3 trials, there was a dose-related trend for shift in calcitonin among women from below the limit of quantitation to within the limit of quantitation at Week 26/28 using LOCF (15.6% with 0.6 mg, 16.8% with 1.2 mg, and 19.2% with 1.8 mg vs. 14.5% with active comparator and 14.8% with placebo). There was no such trend for men.
- Using the combined data from the 5 phase 3 trials, the percentage of patients with any upward shift in serum calcitonin from baseline to Week 26/28 was numerically highest for the 1.8 mg dose (20%) and similar for the other treatment arms (17.3% with 0.6 mg, 16.2% with 1.2 mg, 16.0% with placebo, and 17.2% with active comparator). Note that “any upward shift” was defined as an increase across somewhat arbitrary categories of serum calcitonin. For example, this analysis includes patients who shifted from below the lower limit of quantification to within the reference range but also includes patients who shifted from $\leq 2x$ ULN to $>2x$ ULN. Dr. Mahoney did not note clear patterns of upward shifts in calcitonin that distinguished liraglutide from comparators at Week 52 or at Week 76/78.

- Using the combined data from the 5 phase 3 trials, the sponsor performed repeated measures analysis for calcitonin over time with the findings at Weeks 12 and 26/28 shown in Table 14. From these data, the sponsor compared each dose of liraglutide to placebo and to active comparator by calculating relative percent differences with corresponding 95% confidence intervals, as shown for Week 26/28 in Figure 1. Based on the lower plot, there appears to be a relationship between liraglutide dose and relative percent difference from placebo in serum calcitonin values at this timepoint. However, as shown in Table 14, the mean calcitonin value in all treatment groups was approximately 1.0 ng/L or lower. Note that the calcitonin assay in the phase 3 trials had a lower limit of quantification of 0.7 ng/L (values less than assay were imputed as 0.35 ng/L) and an upper limit of the normal range of 5.0 ng/L for women and 8.4 ng/L for men. The relative percent differences shown in the forest plot are based on LS mean differences between treatment groups of approximately 0.1 ng/L or less. In addition, the raw calcitonin data were reported by the laboratory to only one decimal place. Therefore, even though the calcitonin analyses in Table 14 and Figure 1 are reported to two decimal places, the data are only precise to the first decimal place. With the calcitonin analyses rounded to one decimal place, there is no difference between liraglutide and active comparator at Week 26/28, with a rounded LS mean of 1.0 ng/L for all three liraglutide doses and for active comparator.

Table 14. Repeated measures analysis for calcitonin for the five major phase 3 trials

	Week 12 calcitonin (ng/L) LS mean (95% CI)	Week 26/28 (ng/L) LS mean (95% CI)
Liraglutide 0.6 mg	0.78 (0.72, 0.84)	0.96 (0.90, 1.04)
Liraglutide 1.2 mg	0.78 (0.73, 0.83)	0.99 (0.94, 1.05)
Liraglutide 1.8 mg	0.76 (0.72, 0.81)	1.01 (0.95, 1.06)
Active comparator	0.70 (0.66, 0.74)	0.97 (0.91, 1.02)
Placebo	0.67 (0.63, 0.73)	0.89 (0.83, 0.95)

Figure 1. Relative percent difference in mean calcitonin values between treatment arms at Weeks 26/28 for the five major phase 3 trials.



- Calcium stimulation testing was performed in a subset of patients in the monotherapy trial and in the add-on to metformin+rosiglitazone trial at baseline and at study end. Mean calcitonin values were highest in the liraglutide 1.2 mg group, intermediate in the 1.8 mg group, and lowest in the comparator group. None of the comparisons for peak calcitonin values were statistically significant ($p=0.66$ for liraglutide 1.8 mg vs. comparator; $p=0.26$ for liraglutide 1.2 mg vs. comparator).

Based on population pharmacokinetic data, the clinical pharmacology reviewers concluded that there was no relationship between steady-state liraglutide exposure and the change from baseline in calcitonin at Week 28 in the monotherapy trial.

Figures 2-4 below show mean serum calcitonin values over time for several controlled trials with treatment durations of longer than 6 months. Across these trials, there is no consistent or meaningfully apparent difference in mean calcitonin values with liraglutide vs. comparator with mean values for all treatment groups near the lower limit of quantification. Limitations of the extension portions of the trials are summarized above.

Figure 2. Geometric mean calcitonin values over 2 years in the monotherapy trial (Week 0-52 is blinded; Week 52-104 is the open-label, voluntary extension) – n=228-245 at Week 0 and n=118-128 at Week 104 for liraglutide and active comparator

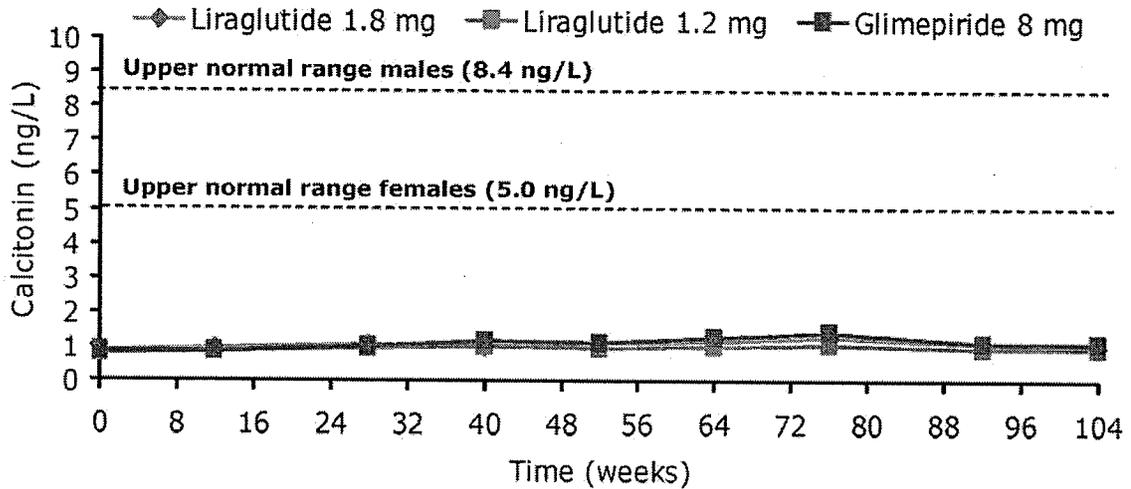


Figure 3. Geometric mean calcitonin values over 2 years in the add-on to metformin trial (Week 0-26 is blinded; Week 26-104 is the open-label, voluntary extension) – n=216-227 at Week 0 and n=117-129 at Week 104 for liraglutide and active comparator; n=110 at Week 0 and n=32 at Week 104 for placebo

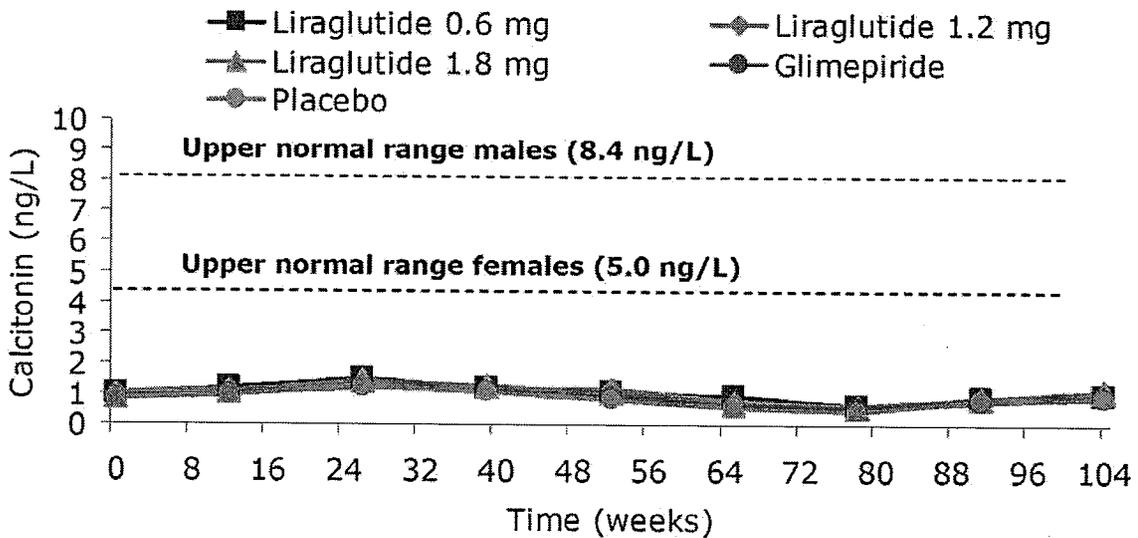


Figure 4. Geometric mean calcitonin values over 1 year in the obesity trial (at Week 52, patients on liraglutide and placebo were switched to liraglutide 2.4 mg and subsequently uptitrated to 3.0 mg) – n=90-98 at Week 0 and n=38-47 at Week 104

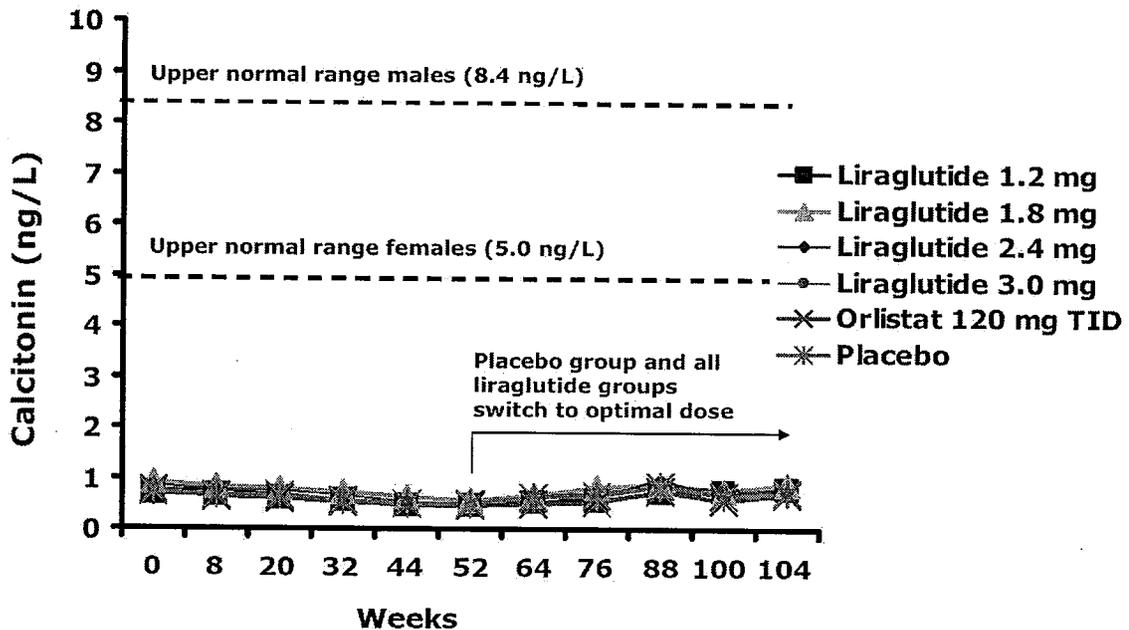


Table 15 summarizes the shift data for serum calcitonin (note that this table incorporates the corrected calcitonin data after the sponsor discovered a programming error, which is the reason for the slightly different numbers than those reported in Dr. Mahoney’s review). Data are presented as incidences and also by patient-year exposures to account for differential dropout rates between treatment groups. The proportion of liraglutide- and comparator-treated patients meeting the various shift criteria was low. For total liraglutide vs. total comparator, there are minimal, if any differences in the various shift analyses, although there are minor numerical imbalances against liraglutide in some analyses when evaluated by dose, particularly for 1.8 mg. A total of 11 liraglutide-treated patients (two with 0.6 mg, one with 1.2 mg, and eight with 1.8 mg), five active comparator-treated patients, and one placebo-treated patient developed at least one treatment-emergent serum calcitonin ≥ 20 ng/L. One of the liraglutide-treated patients had an increase in serum calcitonin from _____ at baseline to _____ at Week 12. There are no additional calcitonin data because the patient was discontinued prematurely due to nausea and diarrhea. For the remaining 10 liraglutide-treated patients, four had serum calcitonin values < 20 ng/L at the last clinic visit despite continued treatment with liraglutide and the other six had increases in serum calcitonin from baseline to endpoint of only _____ ng/L with serum calcitonin at endpoint ranging from _____, (the patient with the 7.1 ng/L increase to _____ at Week 26 was diagnosed with Hashimoto’s thyroiditis based on positive anti-TPO antibodies but had a normal thyroid ultrasound). For the six comparator-treated patients, four had serum calcitonin ≥ 20 ng/L at the last clinic visit, with endpoint values ranging from _____. In summary, seven liraglutide-treated patients (one on 0.6 mg, one on 1.2 mg, and five on 1.8 mg) and four comparator-treated patients had treatment-

emergent serum calcitonin values ≥ 20 ng/dL at the last clinic visit, which is consistent with the overall randomization scheme.

One patient had a treatment-emergent increase in serum calcitonin to >50 ng/L. This 48 year-old man was treated with liraglutide 1.8 mg as add-on to glimepiride and had serum calcitonin values of \sim g/L at Week 0, \sim ng/L at Week 12 and \sim g/L at Week 26. The patient did not report any thyroid-related adverse events. The sponsor is in the process of obtaining follow-up information on this patient.

b(4)

Table 15. Calcitonin shift analyses using last observation carried forward

Shift from baseline	Liraglutide				Comparator		
	0.6 mg	1.2 mg	1.8 mg	Total ¹	Placebo	Active	Total
N (safety dataset)							
Week 20/24/26/28	563	991	1455	3551	710	1412	2122
Week 52	272	497	479	1741	216	630	846
Week 104	184	327	328	839	61	320	381
<ULN to persistently \geqULN²							
Week 20/24/26/28, n (%)	6 (1.1)	10 (1.0)	27 (1.9)	46 (1.3)	6 (0.8)	15 (1.1)	21 (1.0)
Per 1,000 patient-years (PY)	23.2	22.9	41.8	29.4	20.7	23.7	22.7
Week 52, n (%)	0	3 (0.6)	6 (1.3)	9 (0.5)	0	6 (1.0)	6 (0.7)
Per 1,000 PY	0	6.9	14.1	5.7	0	10.9	8.1
Week 104, n (%)	0	1 (0.3)	2 (0.6)	3 (0.4)	0	2 (0.6)	2 (0.5)
Per 1,000 PY	0	1.7	3.4	2.0	0	3.5	3.0
From <ULN to $\geq 1.5x$ ULN							
Week 20/24/26/28, n (%)	1 (0.2)	2 (0.2)	7 (0.5)	10 (0.3)	3 (0.4)	5 (0.4)	8 (0.4)
Per 1,000 PY	3.9	4.6	10.8	6.4	10.3	7.9	8.7
Week 52, n (%)	0	4 (0.8)	1 (0.2)	5 (0.3)	0	2 (0.3)	2 (0.2)
Per 1,000 PY	0	9.2	2.4	3.2	0	3.6	2.7
Week 104, n (%)	0	1 (0.3)	2 (0.6)	3 (0.4)	0	2 (0.6)	2 (0.5)
Per 1,000 PY	0	1.7	3.4	2.0	0	3.5	3.0
From <20 ng/L to ≥ 20 ng/L							
Week 20/24/26/28, n (%)	1 (0.2)	1 (0.1)	8 (0.5)	10 (0.3)	1 (0.1)	3 (0.2)	4 (0.2)
Per 1,000 PY	3.9	2.3	12.4	6.4	3.4	4.7	4.3
Week 52, n (%)	1 (0.4)	0	3 (0.6)	4 (0.2)	0	2 (0.3)	2 (0.2)
Per 1,000 PY	3.8	0	7.1	2.5	0	3.6	2.7
Week 104, n (%)	1 (0.5)	0	0	1 (0.1)	0	1 (0.3)	1 (0.3)
Per 1,000 PY	3.1	0	0	0.7	0	1.8	1.5
From <50 ng/L to ≥ 50 ng/L							
Week 20/24/26/28, n (%)	0	0	1 (0.1)	1 (<0.1)	0	0	0
Per 1,000 PY	0	0	1.5	0.6	0	0	0
Weeks 52 and 104	0	0	0	0	0	0	0

¹includes liraglutide doses >0.6 to <1.2 mg and >1.8 mg (used in the two Japanese trials and in the obesity trial)

²all values (even if only one is available) after baseline \geq ULN

Week 20/24/26/28 – phase 3 diabetes trials, 20-week obesity trial, 24-week Japanese trials, 26-week exenatide trial

Week 52 – monotherapy trial and extensions for the add-on to metformin trial, Japanese trials and obesity trial

Week 104 – monotherapy and add-on to metformin extensions

Hypoglycemia: In the phase 3 trials, the sponsor defined hypoglycemia as “major” if the patient was unable to self-treat (i.e., required another person to administer food, glucagon, or intravenous glucose). For patients who were able to self-treat, hypoglycemia was defined as “minor” if the plasma glucose was less than 56 mg/dL and as “symptoms only” if the plasma glucose was ≥ 56 mg/dL or not available.

Minor hypoglycemia occurred less frequently with liraglutide than with active comparator, glimepiride, in both the monotherapy trial and add-on to metformin trial despite better glycemic control with liraglutide in the monotherapy trial and comparable glycemic control between liraglutide and glimepiride in the add-on to metformin trial (Table 16). Liraglutide and active comparator glargine had a comparable frequency of minor hypoglycemia in the add-on to metformin+sulfonylurea trial, although efficacy with liraglutide was slightly better (mean difference in HbA1c relative to glargine at Week 26 of -0.2%; $p < 0.01$), which may be related to inadequate titration of the glargine dose, as discussed under the Efficacy section of this memorandum. Liraglutide was associated with more frequent minor hypoglycemia than rosiglitazone 4 mg in the add-on to sulfonylurea trial, which may be explained by the better glycemic control with liraglutide relative to rosiglitazone in this trial (mean difference in HbA1c relative to rosiglitazone at Week 26 of -0.6 to -0.7%; $p < 0.0001$). In the four phase 3 trials that included both the 1.2 mg and 1.8 mg doses, there was no apparent relationship between liraglutide dose and the incidence of minor hypoglycemia. Liraglutide did not increase the frequency of minor hypoglycemia compared to placebo in the add-on to metformin trial but did so in the add-on to sulfonylurea, add-on to metformin+sulfonylurea, and add-on to metformin+rosiglitazone trials.

The incidence of major hypoglycemia was low (Table 16). However, all 9 patients reporting on-treatment major hypoglycemia were treated with liraglutide, 7 during the core phase 3 trials and two during the long-term extensions (based on data submitted up to, and including, the June 1 face-to-face meeting). A tenth patient who was participating in the add-on to metformin trial reported major hypoglycemia one day after discontinuation of liraglutide 0.6 mg. For the 9 patients with on-treatment major hypoglycemia, one patient was receiving liraglutide 1.8 mg as monotherapy, two patients were receiving liraglutide in combination with metformin, and a fourth patient was receiving liraglutide 1.8 mg as add-on to sulfonylurea. The remaining 5 patients were receiving liraglutide 1.8 mg in combination with metformin+sulfonylurea (one of these 5 patients reported 2 episodes of major hypoglycemia).

The sponsor reported that the major hypoglycemia event in the monotherapy patient occurred after insulin administration during a frequently-sampled intravenous glucose tolerance test, which was conducted as part of a substudy in this trial. The two patients with major hypoglycemia in the add-on to metformin trial had extenuating circumstances – one was reported to have a blood glucose of 65 mg/dL after insulin infusion after a recent diagnosis of osteomyelitis and the other patient had a blood glucose of 57 mg/dL one day after being hospitalized with an intracranial hemorrhage with uncertain food intake preceding the hypoglycemic event. In contrast, the 6 patients with hypoglycemia in the setting of concomitant sulfonylurea use had no reported contributory factors. The time course of the events in these 6 patients occurred 2 days to 10 months after initiation of study medication with 4 of the 6 patients experiencing major hypoglycemia within approximately the first 2

weeks of receiving study medication. Most of these events were not classified as serious adverse events, limiting available information.

In summary, the available evidence to date suggests that major hypoglycemia can occur with liraglutide, but this event is infrequent and most likely to occur with concomitant sulfonylurea use – a similar finding noted with other incretin-based therapies. The extenuating circumstances associated with isolated events of major hypoglycemia in the other treatment settings should be included in labeling.

Table 16. Hypoglycemic episodes in the phase 3 trials up until the primary efficacy timepoint*								
	Liraglutide 1.2 mg		Liraglutide 1.8 mg		Placebo		Active comparator	
	n/N (%)	Rate per 1000 PY	n/N (%)	Rate per 1000 PY	n/N (%)	Rate per 1000 PY	n/N (%)	Rate per 1000 PY
Monotherapy (52 weeks)					Glimepiride 8 mg			
N (PY)	251 (269)		246 (269)		-		248 (251)	
Minor	29 (12)	242	19 (7.7)	230	-	-	62 (25)	1659
Major	0	0	0	0	-	-	0	0
Add-on to metformin (26 weeks)					Glimepiride 4 mg			
N	240 (271)		242 (264)		121 (93)		242 (271)	
Minor	8 (3.3)	44	8 (3.3)	45	3 (2.5)	64	54 (22)	874
Major	1 (0.4)	3.7	0	0	0	0	0	0
Add-on to sulfonylurea (26 weeks)					Rosiglitazone 4 mg			
N	228 (103)		234 (110)		114 (47)		231 (105)	
Minor	21 (9.2)	506	19 (8.1)	472	3 (2.6)	170	10 (4.3)	124
Major	0	0	1 (0.4)	9.1	0	0	0	0
Add-on to metformin+rosiglitazone (26 weeks)								
N	177 (81)		178 (73)		175 (72)		-	
Minor	16 (9.0)	370	12 (6.7)	614	8 (4.6)	153	-	-
Major	0	0	0	0	0	0	-	-
Add-on to metformin+sulfonylurea (26 weeks)					Insulin glargine			
N	-		230 (107)		114 (53)		232 (112)	
Minor	-	-	63 (27)	1156	19 (17)	946	67 (29)	1287
Major	-	-	5 (2.2)	56	0	0	0	0

*does not include 3 events of major hypoglycemia that either occurred during the extensions (n=2) or after the last dose of study medication (n=1). These 3 events are discussed in the text.
PY = patient-years

Hypersensitivity reactions: The sponsor searched for adverse events related to immunogenicity across all liraglutide trials included in the original NDA and performed an updated analysis in the 120-day safety update. The search strategy used the SMQs for anaphylactic reactions, angioedema, and severe cutaneous reactions.

Table 17 shows the events identified by the above search strategy for all completed trials at the time of NDA submission. Dr. Mahoney notes that there did not appear to be an association between the occurrence of these events and the presence of anti-liraglutide antibodies.

Virtually all the preferred terms were reported in ≤ 1 liraglutide-treated patient except for urticaria (n=11), angioedema (n=2), and pharyngeal edema (n=2). There was only one serious adverse event related to immunogenicity and four patients who discontinued due to adverse events of immunogenicity (lip swelling, urticaria, pharyngeal edema, and periorbital edema). The lip swelling and urticaria leading to study drug discontinuation each occurred within 1 week of starting liraglutide. The event of pharyngeal edema resulting in study drug discontinuation occurred approximately 2.5 months after starting liraglutide in a patient with hypertension – there was no mention of whether the patient was concomitantly using an ACE inhibitor or angiotensin receptor blocker. The event of periorbital edema occurred approximately 3 months after starting liraglutide and resulted in premature discontinuation of study medication approximately 2.5 months later due to ongoing symptoms, which subsequently resolved.

The serious adverse event occurred overseas and was reported as angioneurotic edema, occurring 5 days after starting Bioparox (fusafungine, a non-FDA approved nasal or oral antibiotic spray) for treatment of acute laryngopharyngitis and 211 days after starting liraglutide. The patient was hospitalized with difficulty swallowing, facial edema and a sense of suffocation. The Bioparox was discontinued and glucocorticoids were administered. The patient recovered without interruption or discontinuation of liraglutide. She was taking an angiotensin receptor blocker started in the prior calendar year (date of initiation not specified but at least 4 months prior to the event) that was not discontinued either. Of note, there are rare reports of anaphylactic shock, bronchospasm, laryngeal spasm and laryngeal edema with fusafungine.³

The sponsor provided narratives for all immunogenicity events reported in Table 17, including those occurring in the 120-day safety update. The events have limited information because only one event met the regulatory definition for “serious”. Potentially important adverse events that occurred only in liraglutide-treated patients include angioedema, pharyngeal edema, eye edema, eye swelling, face edema, lip swelling, edema mouth, periorbital edema, and anaphylactic reaction. For these events, one occurred 6 days after the last dose of study medication (eye swelling), one was serious (angioedema case described above), two resulted in study drug discontinuation (pharyngeal edema and periorbital edema described above), and the remaining events resolved despite continued treatment with liraglutide.

Of note, the preferred term “hypersensitivity” was not included in the sponsor’s SMQ search for immunogenicity events. The sponsor provided narratives for events occurring during the phase 3 trials included in the original NDA that were coded to the preferred term of “hypersensitivity”, “drug hypersensitivity”, or “delayed hypersensitivity reaction”. Thirteen patients had adverse events that coded to one of these preferred terms and all of these patients received liraglutide. None of the events were considered serious based on the regulatory definition. In some cases, the event was attributed to concomitant antibiotic administration. Eleven of the thirteen patients had resolution of the adverse event despite continued treatment with liraglutide and two of the thirteen patients had anti-liraglutide antibodies. One patient discontinued due to “delayed hypersensitivity reaction” that occurred approximately one

³ http://www.medicines.ie/medicine/2582/SPC/Locabital/#CLINICAL_PRECAUTIONS (accessed September 21, 2009)

month after starting liraglutide. Study drug was discontinued on that same day and the event resolved 6 days later. The other patient who discontinued because of a hypersensitivity event was diagnosed with “drug hypersensitivity” approximately one month after starting liraglutide. Study drug was discontinued 3 days later and the adverse event subsequently resolved. The sponsor notes that none of the hypersensitivity reactions were associated with respiratory compromise, reduced blood pressure or symptoms of end-organ dysfunction, although lack of detailed information for most events limits definitive conclusions. The imbalance in hypersensitivity reactions should be included under Adverse Reactions in the package insert. Hypersensitivity reactions should be further evaluated in the cardiovascular trial and in a postmarketing epidemiological study.

Table 17. Immunogenicity events identified by the sponsor’s SMQ search (all completed trials at the time of NDA submission)		
	Liraglutide N=4211 n (%)	Non-liraglutide N=2272 n (%)
All immunogenicity events	24 (0.6)	5 (0.2)
Angioedema Standardized MedDRA Query (SMQ)	22 (0.5)	3 (0.1)
Urticaria	11 (0.3)	2 (0.1)
Angioedema	2 (<0.1)	0
Pharyngeal edema	2 (<0.1)	0
Eye edema	1 (<0.1)	0
Eye swelling	1 (<0.1)	0
Eyelid edema	1 (<0.1)	1 (<0.1)
Face edema	1 (<0.1)	0
Lip swelling	1 (<0.1)	0
Edema mouth	1 (<0.1)	0
Periorbital edema	1 (<0.1)	0
Anaphylactic reaction SMQ	1 (<0.1)	1 (<0.1)
Anaphylactic reaction	1 (<0.1)	0
Circulatory collapse	0	1 (<0.1)
Severe cutaneous reactions SMQ	1 (<0.1)	1 (<0.1)
Dermatitis bullous	1 (<0.1)	1 (<0.1)

Anti-liraglutide antibodies: In the four 26-week phase 3 trials, the sponsor measured anti-liraglutide antibodies at Weeks 0, 12, 26, and 27. In the 52-week monotherapy trial, the sponsor measured antibodies at Weeks 0, 12, 28, 40, and 53. At the last measurement, patients were to be off study drug for at least 5 days to limit potential interference of liraglutide with the assay (which otherwise may result in false negative results due to persistent unlabeled liraglutide in plasma sample competing with radiolabeled liraglutide in the assay). Therefore, patients continuing in the ongoing extensions for the monotherapy and add-on to metformin trials were not included in this analysis, because treatment was not interrupted. Please see Dr. Mahoney’s review for a discussion of the antibody assay and methodology.

Approximately 8-9% of liraglutide-treated patients in the five phase 3 trials had positive anti-liraglutide antibodies at the end of treatment (Table 18). There was no relationship to liraglutide dose and there was no relationship to treatment duration, as assessed by comparing the findings in the four pooled 26-week trials to the findings in the 52-week monotherapy trial. The incidence of neutralizing antibodies against liraglutide, as assessed by an *in vitro* cell-based assay, was not clearly related to liraglutide dose but appeared to be higher among liraglutide-treated patients in the 52-week monotherapy trial (2.3%) than in the 26-week trials (1.0%). Cross-reacting antibodies to native GLP-1 also appeared to be higher among liraglutide-treated patients in the 52-week trial (6.9%) compared to the 26-week trials (4.8%). The sponsor did not develop an assay to test whether any of the cross-reacting antibodies to native GLP-1 were neutralizing. One important limitation of the analyses is the large number of patients with missing data for antibody status.

Table 18. Patients with liraglutide antibodies at end of treatment in the five phase 3 trials (off study drug ≥5 days)

	Liraglutide				Comparator	
	0.6 mg n (%)	1.2 mg n (%)	1.8 mg n (%)	Total n (%)	Placebo n (%)	Active n (%)
Pool of the four 26-week trials	N=475	N=645	N=884	N=2004	N=524	N=705
Patients with a blood sample	239 (50)	377 (58)	593 (67)	1209 (60)	324 (62)	649 (92)
Positive liraglutide antibodies	22 (9.2)	33 (8.8)	50 (8.4)	105 (8.7)	1 (0.3)	1 (0.2)
Neutralizing antibodies to liraglutide	3 (1.3)	4 (1.1)	5 (0.8)	12 (1.0)	0	0
Cross-reacting antibodies to native GLP-1	14 (5.9)	19 (5.0)	25 (4.2)	58 (4.8)	0	0
52-week monotherapy trial	-	N=251	N=246	N=497	-	N=248
Patients with a blood sample	-	48 (20)	39 (16)	87 (18)	-	45 (18)
Positive liraglutide antibodies	-	4 (8.3)	3 (7.7)	7 (8.0)	-	0
Neutralizing liraglutide antibodies	-	1 (2.1)	1 (2.6)	2 (2.3)	-	-
Cross-reacting antibodies to native GLP-1	-	4 (8.3)	2 (5.1)	6 (6.9)	-	-

Dr. Mahoney discusses adverse events that appear to occur more frequently among liraglutide-treated patients who developed anti-liraglutide antibodies compared to those who remained antibody negative. She notes an overall imbalance (against antibody-positive patients) in the Infections and Infestations System Organ Class (40% vs. 36%) driven predominantly by differences in the incidence of infections of the nasopharynx and upper respiratory system. She also mentions an imbalance in adverse events of musculoskeletal pain. Limitations of this analysis include the low event rates (there are fewer than 10 occurrences for most adverse events occurring in liraglutide antibody-positive patients) and the large number of patients with missing data for antibody status.

As shown in Dr. Mahoney’s review, using the pooled data from the four 26-week phase 3 trials, there was no interaction (p-value >0.1) between reduction in HbA1c and presence of anti-liraglutide antibodies, regardless of whether the antibodies were neutralizing or cross-reacting with native GLP-1. However, as discussed by Dr. Mahoney, the three patients with the highest titers of anti-liraglutide antibodies had little change from baseline in HbA1c (change of 0 to -0.2%) that was not associated with anti-liraglutide neutralizing effect. I agree with Dr. Mahoney’s conclusion that these cases are too few to reach definitive conclusions,

but that it is possible that patients with higher titers of anti-liraglutide antibodies may have diminution in efficacy.

Injection site reactions: In the double-blind phase 3 trials, patients injected liraglutide or liraglutide placebo. For the five major phase 3 trials included in the original NDA submission, the incidence of injection site reactions was 2.0% with liraglutide (1.5% with 0.6 mg, 1.8% with 1.2 mg, and 2.4% with 1.8 mg) compared to 1.5% with placebo and 1.2% with active comparator. These differences were principally driven by the preferred terms of injection site rash (0.3% with liraglutide vs. no cases with comparator), injection site erythema (0.2% with liraglutide vs. no cases with comparator), and injection site reaction (0.2% with liraglutide vs. no cases with comparator). Dr. Mahoney did not identify an association between anti-liraglutide antibody status and local injection site reactions. However, conclusions are limited by low event rates (most preferred terms related to injection site reactions occurred in 1-5 liraglutide-treated patients).

There were four withdrawals due to injection site reactions in the major phase 3 trials included in the original NDA submission. All 4 events occurred among the 2501 liraglutide-treated patients – injection site erythema (1.8 mg), injection site nodule (1.8 mg), injection site bruising (0.6 mg), and injection site rash (0.6 mg). None of these events were reported as serious.

Pancreatitis: There are postmarketing reports of pancreatitis associated with Byetta, including more severe hemorrhagic and necrotizing forms, sometimes with death. In the 120-day safety, update, the sponsor searched preferred terms across all clinical trials and identified 7 reports of pancreatitis among liraglutide-treated patients and 1 report among a comparator (metformin+glimepiride)-treated patient, corresponding to incidence rates of 2.2 per 1000 patient-years and 0.6 per 1000 patient-years, respectively. Dr. Mahoney identified an additional liraglutide-treated patient with idiopathic pancreatitis confirmed by elevated lipase and CT imaging who was mentioned in the advisory committee briefing document but, for unclear reasons, was not included in the sponsor's tallies above.

There are risk factors for pancreatitis (e.g., cholelithiasis or alcohol use) in four of the liraglutide-treated patients and possibly also for the comparator-treated patient (dyslipidemia), but the imbalance against liraglutide persists even after excluding these patients.

The narrative for one of the liraglutide-treated patients reported to have pancreatitis does not contain sufficient information to definitively conclude that pancreatitis occurred. This patient was reportedly diagnosed with chronic pancreatitis on Day 88 but there is no mention of symptoms and no serum amylase or lipase results were reported.

The onset of pancreatitis occurred 50-669 days after initiation of liraglutide. One case occurred with 0.6 mg, two occurred with 1.2 mg, four occurred with 1.8 mg, and one occurred with 3.0 mg. One liraglutide-treated patient died (details are discussed under Deaths) and three other liraglutide-treated patients permanently discontinued study medication. The patients who continued treatment were not reported to have recurrent pancreatitis during the trial.

Of note, in the 20-week trial testing liraglutide doses up to 3.0 mg in healthy, obese patients, there was a serious adverse event of hospitalization for sudden-onset epigastric pain radiating to the back associated with vomiting 12 days after starting liraglutide 2.4 mg. The narrative mentions marked epigastric tenderness, normal abdominal ultrasound, and no available serum amylase measurement due to hemolyzed blood. The patient was treated with 10 mg of morphine and discharged pain-free after an overnight hospital stay. The clinical signs and symptoms suggest pancreatitis. This patient was not identified by the sponsor's preferred term search for pancreatitis discussed above. Therefore, the sponsor was asked to conduct a more general search for pancreatitis in their development program using the SMQ for acute pancreatitis. This approach did not identify any other potential cases of pancreatitis in liraglutide-treated patients (120-day safety update database).

In comparison, there is no imbalance in cases of pancreatitis (cut-off date August 31, 2008) based on premarketing and postmarketing controlled clinical trials of Byetta (2.3 events per 1000 patient-years with Byetta vs. 2.7 events per 1000 patient-years for placebo and 2.5 events per 1000 patient-years for insulin). The patient-year exposures to Byetta through August 31, 2008 (3065 patient-years) exceeds the liraglutide patient-year exposures in the 120-day safety-update database (2434 patient-years).

Laboratory data: Standard hematology, chemistry (including creatine phosphokinase), and urinalysis data were obtained in the five phase 3 trials. Serum calcitonin is discussed under the section on Adverse Events of Interest.

Dr. Mahoney noted no meaningful differences between treatment groups over time for mean and median values of hematology, chemistry, and urinalysis parameters. She notes that the sponsor did not adequately conduct outlier analyses in the original submission because laboratory values were reported as "clinically significant" or "not clinically significant" based on investigator assessment, which is somewhat subjective. Therefore, Dr. Mahoney requested objective outlier analyses (based on cutpoints, above which, a laboratory value would be considered an outlier) for key laboratory parameters. Dr. Mahoney identified an imbalance for serum bilirubin, as summarized below. This section also focuses on outliers for serum creatinine and serum transaminases (Table 19).

Of note, there is no imbalance in the proportion of patients with outlier serum ALT values in the controlled phase 3 trials. In addition, the sponsor reports no cases of Hy's Law (ALT >3x ULN plus total bilirubin \geq 2x ULN plus alkaline phosphatase <2x ULN) in the entire liraglutide development program (120-day safety update database).

A numerically greater proportion of liraglutide-treated patients (without a clear relationship to liraglutide dose) developed serum creatinine >ULN compared to placebo (8.3% vs. 4.8%), although the incidence of this finding with liraglutide was comparable to the incidence with active comparator (8.2%). A comparable proportion of liraglutide-, placebo-, and active comparator-treated patients developed serum creatinine >1.5x ULN, although only liraglutide-treated patients developed serum creatinine >2x ULN (n=4 or 0.2%). Two of these four liraglutide-treated patients had serum creatinine >2x ULN on the day of study drug initiation and serum creatinine normalized despite continued treatment with liraglutide. The third patient

had normal serum creatinine during 10 months of treatment with liraglutide then had an elevated serum creatinine of 2.4 mg/dL on the last study visit that occurred 1 week after a diagnosis of a urinary tract infection. The remaining liraglutide-treated patient had abnormal serum creatinine at baseline (1.9 mg/dL) that ranged from 2.1 to 2.8 during 1-year of treatment with liraglutide. The patient had a history of hypertension treated with quinapril. No additional data are available. Based on these four narratives, there is no convincing evidence of an association between liraglutide and renal dysfunction. Of note, the Byetta label is being updated to reflect postmarketing reports of altered renal function associated with the use of Byetta and to include cautionary language when Byetta is initiated or the dose is increased in patients with more advanced renal impairment. Byetta can cause nausea and vomiting, which may result in transient hypovolemia, resulting in worsening renal function, particularly in patients with tenuous renal function or those using concomitant medications known to affect renal function or hydration status. Because liraglutide can also cause nausea and vomiting, similar cautionary language should be included in the liraglutide label. In addition, renal safety should be included as an Adverse Event of Interest in the cardiovascular trial.

As noted by Dr. Mahoney, a numerically larger proportion of liraglutide-treated patients (4.0%) relative to comparator-treated patients (3.0%) developed mildly elevated serum bilirubin concentrations (>ULN but ≤2x ULN) with no relationship to liraglutide dose. This finding is not accompanied by an imbalance in serum ALT and there were no cases of Hy's Law, suggesting that hepatic injury is not likely. The significance of this isolated finding is unknown.

Table 19. Select laboratory outlier analyses for the five phase 3 trials occurring any time up to the primary efficacy timepoint							
	Liraglutide				Comparator		
	0.6 mg N=475 n (%)	1.2 mg N=896 n (%)	1.8 mg N=1130 n (%)	All N=2501 n (%)	Placebo N=524 n (%)	Active N=953 n (%)	Total N=1477 n (%)
Alanine aminotransferase (ALT)							
>ULN	101 (21.3)	168 (18.8)	229 (20.3)	498 (19.9)	98 (18.7)	206 (21.6)	304 (20.6)
>3x ULN	1 (0.2)	1 (0.1)	3 (0.3)	5 (0.2)	4 (0.8)	3 (0.3)	7 (0.5)
>5x ULN	0	0	2 (0.2)	2 (0.1)	1 (0.2)	1 (0.1)	2 (0.1)
>10x ULN	0	0	0	0	0	0	0
Serum creatinine							
>ULN	33 (6.9)	90 (10.0)	84 (7.4)	207 (8.3)	25 (4.8)	78 (8.2)	103 (7.0)
>1.5x ULN	1 (0.2)	3 (0.3)	4 (0.4)	8 (0.3)	2 (0.4)	4 (0.4)	6 (0.4)
>2x ULN	1 (0.2)	1 (0.1)	2 (0.2)	4 (0.2)	0	0	0
Total bilirubin							
>ULN	24 (5.0)	26 (2.9)	50 (4.4)	100 (4.0)	11 (2.1)	33 (3.5)	44 (3.0)
>2x ULN	0	0	1 (0.1)	1 (<0.1)	0	1 (0.1)	1 (0.1)
>5x ULN	0	0	1 (0.1)	1 (<0.1)	0	1 (0.1)	1 (0.1)
>10x ULN	0	0	0	0	0	0	0

Vital signs: As discussed by Dr. Yanoff, liraglutide did not have a consistent effect on systolic or diastolic blood pressure in the phase 3 trials. For example, point estimates for the adjusted mean change in systolic blood pressure from baseline with liraglutide vs. placebo typically ranged from -1 mmHg (in favor of liraglutide) to +1 mmHg (in favor of placebo) with no statistical significance ($p>0.64$) except in the add-on to metformin+rosiglitazone trial, where the reduction was -5 mmHg relative to placebo ($p<0.001$).

As discussed by Dr. Mahoney, liraglutide was associated with a 2-3 beat/min mean increase in heart rate relative to placebo and 1-2 beat/min mean increase relative to active comparator in an exploratory repeated-measures analysis using pooled data from the phase 3 trials. This finding is not expected to be clinically meaningful. Dr. Mahoney notes that 2 patients withdrew from the phase 3 trials for increased heart rate, both treated with liraglutide. She also notes a numerically higher incidence of adverse events related to heart rate with liraglutide compared to placebo and active comparator in the phase 3 trials. Table 20 below shows these data for all clinical trials included in the NDA submission. Note that event rates are very low (0.1-0.6%) and any numerical differences between total liraglutide and total comparator are small ($\leq 0.2\%$). More definitive cardiovascular data will come from the required cardiovascular safety trial.

Table 20. Adverse events associated with increased heart rate in the liraglutide clinical development program at the time of NDA submission

	Total liraglutide		Total comparator	
	N=4211 n (%)	PY=2241 Per 1000 PY	N=2272 n (%)	PY=1139 Per 1000 PY
Palpitations	27 (0.6)	12.0	9 (0.4)	7.9
Tachycardia	13 (0.3)	5.8	5 (0.2)	4.4
Atrial fibrillation	5 (0.1)	2.2	3 (0.1)	2.6
Sinus tachycardia	4 (0.1)	1.8	0	0
Supraventricular tachycardia	3 (0.1)	1.3	0	0
Ventricular tachycardia	1 (<0.1)	0.4	1 (<0.1)	0.9
Tachycardia paroxysmal	2 (<0.1)	0.9	0	0
Heart rate increased	5 (0.1)	2.2	1 (<0.1)	0.9

Drs. Derr and Yanoff have reviewed the body weight data in detail. Table 21 summarizes those data for change from baseline to the primary efficacy timepoint for each of the phase 3 trials.

Liraglutide 1.2 mg and 1.8 mg appear weight neutral when used in combination with glimepiride. However, liraglutide 1.2 mg and 1.8 mg reduce mean body weight by 1-3 kg relative to placebo when used as add on combination therapy with metformin, metformin+rosiglitazone, and metformin+glimepiride. The reduction in body weight with liraglutide relative to the active comparators appears larger than the reduction relative to placebo, which is expected because the tested active comparators (glimepiride, rosiglitazone, glargine) are all known to cause weight gain. This advantage with regard to body weight occurs in the setting of comparable or better glycemic efficacy with liraglutide relative to the

tested doses of these comparators. For the comparisons to rosiglitazone and insulin glargine, the body weight changes with liraglutide may have been even more favorable if optimal doses of these comparators had been used for glycemic efficacy.

Electrocardiograms: As discussed by Dr. Mahoney, the NDA included limited electrocardiogram analyses from the phase 3 trials. However, reassuring findings were noted in the Thorough QT study testing liraglutide doses up to the maximum recommended clinical dose of 1.8 mg. In addition, Dr. Mahoney notes no imbalances in the incidence of adverse events related to electrocardiograms in the pooled clinical development program.

Table 21. Change from baseline in body weight (kg) (intent-to-treat population with last-observation-carried-forward)							
	N	Baseline±SD	Adjusted mean change±SE	Change with lira relative to change with placebo		Change with lira relative to change with comparator	
				Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Monotherapy (Study 1573) – 52 weeks							
Lira 1.2 mg	251	92.1±19.0	-2.1±0.3	N/A		-3.2 (-3.9, -2.5)	<0.0001
Lira 1.8 mg	246	92.6±20.8	-2.5±0.3			-3.6 (-4.3, -2.9)	<0.0001
Glimep 8 mg	248	93.3±19.0	1.1±0.3				
Add-on to metformin (Study 1572) – 26 weeks							
Lira 0.6 mg	242	87.8±17.1	-1.8±0.2	-0.3 (-1.2, 0.6)	0.82	-2.7 (-3.5, -2.0)	<0.0001
Lira 1.2 mg	240	88.5±19.1	-2.6±0.2	-1.1 (-1.9, -0.2)	0.01	-3.5 (-4.3, -2.8)	<0.0001
Lira 1.8 mg	242	88.0±16.3	-2.8±0.2	-1.3 (-2.2, -0.4)	<0.01	-3.8 (-4.5, -3.0)	<0.0001
Placebo	121	91.0±17.0	-1.5±0.3				
Glimep 4 mg	242	89.0±16.8	1.0±0.2				
Add-on to glimepiride (Study 1436) – 26 weeks							
Lira 0.6 mg	233	82.6±17.7	0.7±0.2	0.8 (0.04, 1.6)	0.04	-1.4 (-2.0, -0.7)	<0.0001
Lira 1.2 mg	228	80.0±17.1	0.3±0.2	0.4 (-0.4, 1.2)	0.45	-1.8 (-2.4, -1.1)	<0.0001
Lira 1.8 mg	234	83.0±18.1	-0.2±0.2	-0.1 (-0.9, 0.6)	0.97	-2.3 (-3.0, -1.7)	<0.0001
Placebo	114	81.9±17.1	-0.1±0.3				
Rosi 4 mg	231	80.6±17.0	2.1±0.2				
Add-on to metformin+rosiglitazone (Study 1574) – 26 weeks							
Lira 1.2 mg	177	95.3±18.3	-1.0±0.3	-1.6 (-2.4, -0.9)	<0.0001	N/A	
Lira 1.8 mg	178	94.9±19.2	-2.0±0.3	-2.6 (-3.4, -1.8)	<0.0001		
Placebo	175	98.5±18.2	0.6±0.3				
Add-on to metformin+glimepiride (Study 1697) – 26 weeks							
Lira 1.8 mg	230	85.8±19.3	-1.8±0.3	-1.4 (-2.1, -0.7)	0.0001	-3.4 (-4.0, -2.9)	<0.0001
Placebo	114	85.4±16.3	-0.4±0.4				
Glargine	232	85.2±17.9	1.6±0.3				

Findings with higher liraglutide doses: The sponsor has completed a 20-week trial testing liraglutide doses of 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg vs. Orlistat in 564 healthy, obese patients (n=90-95 per treatment group). There were no deaths in this trial. Three serious adverse events occurred in patients receiving liraglutide doses >1.8 mg. One of these patients

developed sudden-onset epigastric pain radiating to the back associated with vomiting 12 days after starting liraglutide 2.4 mg (this patient is discussed in the Pancreatitis subsection of this memorandum under Adverse Events of Interest). The two other patients who reported serious adverse events with liraglutide >1.8 mg had appendicitis and transient ischemic attack.

Dr. Mahoney discusses the case of an accidental overdose of 17.4 mg liraglutide resulting in diaphoresis, vomiting, abdominal discomfort, and memory disturbances. The patient was hospitalized for 3 days, treated with ondansetron, ranitidine, dextrose, and saline, and recovered. There are no available serum amylase or lipase values. No reason was provided for the overdose. The device could administer at most 3.6 mg per injection. Therefore, a minimum of 5 separate injections were used.

Head-to-head data with exenatide: As mentioned under Efficacy, the sponsor has conducted a 26-week randomized head-to-head comparison of liraglutide to Byetta. In the 120-day safety update, the sponsor reported a lower incidence of nausea with liraglutide compared to Byetta over time. In addition, in the briefing package for the June face-to-face meeting, the sponsor reported a lower incidence of anti-liraglutide antibodies among the liraglutide-treated patients compared to the incidence of anti-exenatide antibodies among the Byetta-treated patients. However, the full study report has not been submitted to FDA. Therefore, these findings are considered preliminary and labeling of this information should not be entertained until after the study has been submitted and has undergone full FDA review.

9. Advisory Committee Meeting

The April 2, 2009, advisory committee meeting focused on liraglutide's cardiovascular safety and the thyroid C-cell tumor data. The advisory committee was asked to vote on the following four questions:

1. Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that liraglutide rules out unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?
2. Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?
3. Assuming the remainder of the risk:benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of liraglutide?
4. Assuming the remainder of the risk:benefit data are acceptable, do the available data on papillary thyroid cancer permit marketing of liraglutide?

This section of the memo will focus on Question 3 (Questions 1 and 4 are discussed in the Clinical Safety Section and Question 2 is discussed in the Non-Clinical Pharmacology Toxicology section). With regard to Question 3, six panel members voted "yes", six voted "no" and one abstained. The two thyroidologists on the panel voted differently with one favoring approval and the other voting against approval based on the current data. The thyroidologist voting for approval stated that there are no additional data that could be obtained in the premarketing setting that, in his mind, would resolve the uncertainty of the

relevance of the rodent C-cell tumor findings to humans. Instead, he stated that the relevance to humans will only become apparent after exposing a large part of the population to liraglutide for at least a decade. This viewpoint takes into account the overall rarity of medullary thyroid carcinoma and the typically indolent course of the disease. Others voting "yes" stated that the risk to humans is likely low and that liraglutide appears to be a promising treatment for type 2 diabetes.

Those voting "no" stated that the human risk of medullary thyroid carcinoma with liraglutide is unknown, that there are alternative anti-diabetic medications available, and that it was unclear whether liraglutide offers unique benefits in the treatment armamentarium for type 2 diabetes. The sponsor presented up to 2-years of calcitonin data at the advisory committee meeting. The thyroidologist voting against approval recommended additional long-term data—perhaps 6-12 months of longer observation with monitoring of calcitonin and other biomarkers for medullary thyroid carcinoma, such as procalcitonin and carcinoembryonic antigen. Please see Dr. Mahoney's review and the transcript from the advisory committee meeting for further details.

5. Pediatrics

The sponsor has requested a deferral for children ≥ 10 years old and a waiver for children < 10 years old. The Division and the Pediatric Review Committee (PeRC) agree with this proposal, which is consistent with our approach to other non-insulin treatments for type 2 diabetes (there are too few children less than 10 years of age with type 2 diabetes; therefore, studies in this population are highly impractical).

The sponsor's proposed pediatric plan consists of a randomized, double-blind, placebo-controlled, 2-part pharmacokinetic and pharmacodynamic study.

b(4)

A one-year, controlled treatment period is appropriate for the phase 3 pediatric trial but a 24-week primary efficacy timepoint is preferable and the extension should remain blinded to optimize interpretability of the data. In addition, the Division and PeRC have interest in obtaining controlled pediatric data for patients who are treatment-naïve and for patients who are on existing metformin therapy. For comparison, the Written Request for Byetta is evaluating efficacy and safety as monotherapy and as add-on to metformin and/or sulfonylurea.

Because of the thyroid C-cell tumor findings in rodents, the Division expressed concern with long-term exposure to liraglutide in children until more data are available. The carcinogenicity issue is less of a concern in the short-term pharmacokinetic/pharmacodynamic studies. Therefore, the Division and PeRC found it acceptable for the sponsor to proceed with the pharmacokinetic/pharmacodynamic study based on the current state-of-knowledge for liraglutide but agree that the action letter should specify the necessary needed data before the Division agrees with the conduct of longer-term studies in children. Lastly _____ . Therefore, PeRC recommended that the Division confirm whether the adult pen device can accurately deliver these smaller doses.

b(4)

The sponsor has proposed the following timelines for the pediatric trials:

b(4)

6. Other Relevant Regulatory Issues

Regulatory briefing: A regulatory briefing was held after the advisory committee meeting and after the face-to-face meeting with the sponsor. The main focus of this meeting was to solicit input from senior FDA officials regarding the impact of the non-clinical thyroid C-cell tumor findings on the approvability of liraglutide. Dr. Robert Temple noted that the clinical data are “moderately reassuring” and suggested that monitoring for serum calcitonin may be useful, provided that the monitoring is appropriately used (e.g., further workup if the calcitonin is elevated into the range that is more likely to be associated with medullary thyroid carcinoma as opposed to a workup being prompted by mild non-specific elevations). Other suggestions included limiting liraglutide to certain treatment settings (e.g., second-line therapy for those intolerant to Byetta). As discussed by Dr. Mahoney, a formal vote regarding approvability did not occur. The panel was also asked to comment on whether additional non-clinical studies, as proposed by the pharmacology-toxicology reviewers (e.g., animal studies with GLP-1 receptor antagonists or studies evaluating whether RET activation is involved in liraglutide-induced tumorigenicity) should be conducted pre-approval. Dr. Jenkins stated that there is interest in such studies but stated they are unlikely to provide pivotal information to support a decision on approvability.

Tradename: The Division of Medication Error Prevention and Analysis (DMEPA) has found the proposed tradename “Victoza” to be acceptable. Please see the reviews of Mr. Walter Fava

for details. The Tradename review was completed on July 21, 2009, with a re-review pending that will be completed within 90 days of the action date.

Financial disclosures: Dr. Yanoff reviewed the financial disclosure information and noted that — investigators with a potential financial conflict of interest enrolled a total of — patients across the liraglutide phase 3 trials. I concur with Dr. Yanoff that there is minimal, if any, potential bias from these data given the small number of affected patients, the double-blind trial designs, and the objective primary efficacy endpoint. As noted below and by Dr. Yanoff, the study site for one of these investigators was inspected and no regulatory violations were noted.

b(6)

Division of Scientific Investigations: The Division of Scientific Investigations (DSI) inspected phase 3 data at — clinical sites (screened a total of — patients, — of whom completed the trials) and some of the sponsor's records. The — sites were chosen based on enrollment of a sizeable number of patients. In addition, the principal investigator at 1 of the — sites had shares in Novo Nordisk totaling over \$50,000. One of the inspected sites had a few regulatory violations (e.g., delay in reporting of a serious adverse event to the institutional review board, some inadequate records concerning drug disposition). However, DSI concluded that the inspected portions of the trials appear to have been conducted adequately and that the data generated by the inspected sites can be used in support of the proposed indication. Please see the review of Dr. Susan Leibenhaut for details.

b(6)

DSI also inspected the clinical and analytical portions of the pivotal bioequivalence trial. Please see Section 5 of this memorandum for details.

As discussed by Dr. Mahoney, there were programming errors for some of the bilirubin, serum creatinine, biochemistry, hematology, and calcitonin analyses. The sponsor was asked to explain why these errors occurred and to provide an overview of their quality control measures pertaining to computer programming. The response was acceptable.

7. Labeling

Labeling discussions are ongoing at the time of this review. Key issues are summarized below. Please see the final label for further details.

- The recommended treatment doses should be 1.2 mg and 1.8 mg, as some patients are expected to obtain additional glycemic efficacy with 1.8 mg over 1.2 mg. The 0.6 mg dose has minimal efficacy and should, therefore, not be recommended for treatment but should be used during titration to minimize gastrointestinal side effects.
- Liraglutide should be contraindicated in patients with a history of, or predisposition to, medullary thyroid carcinoma and the thyroid C-cell tumor findings should be boxed.
- Information should be included on pancreatitis (language and placement should be similar to what is being proposed for Byetta), hypoglycemia (including the risk of major hypoglycemia, particularly when liraglutide is used with an insulin secretagogue), neoplasms, hypersensitivity reactions, antibody formation, and injection site reactions.

- There should be no statement about cardiovascular safety because of limitations of the cardiovascular data (e.g., post-hoc, non-adjudicated nature of the analyses, low event rates, low-risk patient population) and the potential for inappropriate promotion.
- Inappropriate promotional statements are being revised with input from the Division of Drug Marketing, Advertising and Communications (DDMAC) (see the review of Dr. Samuel Skariah for further details).
- The formatting will be reviewed by the Study Endpoints and Label Development (SEALD) group to ensure consistency with the Physician's Labeling Rule.
- The Medication Guide and Instructions for Use Leaflet will be reviewed by the Office of Surveillance and Epidemiology.

8. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

APPROVAL, pending agreement on labeling and a satisfactory response to the outstanding information request.

- Risk Benefit Assessment

Liraglutide causes thyroid C-cell tumors in rodents. The relevance of this finding to humans is unknown. As discussed by Dr. Mahoney, only 600 cases of medullary thyroid carcinoma are reported per year in the United States, which has a population of approximately 300 million persons. Approximately 20-25% of medullary thyroid carcinoma is inherited with the remaining 450-480 cases being sporadic. As of 2007, there are approximately 18 million people in the United States with diagnosed diabetes, with approximately 16-17 million having type 2 diabetes.⁴ Therefore, approximately 30 cases of non-familial medullary thyroid carcinoma are expected to be diagnosed each year among the entire population of patients with type 2 diabetes in the United States. For this reason, it is extremely unlikely to see even a single case of medullary thyroid carcinoma in a randomized, controlled clinical trial. For example, one would expect approximately 1 case of sporadic medullary thyroid carcinoma in a 12-year clinical trial consisting of 50,000 patients. Because the background rate for medullary thyroid carcinoma is very low, a clinical trial will not have meaningful power to rule out an increased risk for medullary thyroid carcinoma with liraglutide unless this risk is substantial (Table 22). By extension, a clinical trial is not expected to have meaningful power to detect patients with an increase in calcitonin that is caused by medullary thyroid carcinoma or by a preneoplastic lesion that is destined to become medullary thyroid carcinoma.

⁴ <http://diabetes.niddk.nih.gov/DM/PUBS/statistics/#allages> (accessed on September 18, 2009)

Table 22. Sample sizes needed for a single-arm trial to detect 2-fold to 100-fold increases over the background rate* in the risk for non-familial medullary thyroid carcinoma (from Drs. Derr and Sahlroot, FDA biostatisticians)

Power	Increase in risk for medullary thyroid carcinoma				
	2-fold	5-fold	10-fold	20-fold	100-fold
3-year treatment period					
80%	1,888,050	229,783	62,383	31,183	3,353
90%	2,578,783	278,383	110,850	40,517	4,793
5-year treatment period					
80%	1,132,830	137,870	37,430	18,710	2,012
90%	1,547,270	167,030	66,510	24,310	2,876
10-year treatment period					
80%	566,415	68,935	18,715	9,355	1,006
90%	773,635	83,515	33,255	12,155	1,438

Power calculations from StatXact, 1-sided alpha 0.05
 *450-480 sporadic cases of medullary thyroid carcinoma per year in the United States (the focus is on non-hereditary cases because liraglutide should be contraindicated in patients with inherited predisposition to medullary thyroid carcinoma)

Dr. Mahoney proposes first obtaining data on C-cell activation (e.g., calcitonin, procalcitonin, carcinoembryonic antigen) in approximately 4,500 liraglutide-treated patients followed for 3 years in the cardiovascular safety trial to rule out the potential for aggressive medullary thyroid carcinoma before considering approval of liraglutide. However, these additional data are unlikely to be informative to impact a regulatory decision. First, it is unknown whether drug-induced C-cell hyperplasia (if it is to occur with liraglutide) will undergo malignant transformation. Second, liraglutide did not induce aggressive medullary thyroid carcinoma in rodents. For example, liraglutide did not reduce survival in the lifetime rodent carcinogenicity studies despite causing thyroid C-cell tumors. In addition, there was a long latency for thyroid C-cell carcinomas, with the earliest appearance detected after ~60% of the mouse lifespan at 45-times clinical exposures and after ~70% of the rat lifespan at 8-times clinical exposures. As shown in Table 22, approximately 4,800 liraglutide-treated patients followed for 3 years has 90% power to detect only a very large (at least 100-fold) increase in the risk for medullary thyroid carcinoma. By extension, Dr. Mahoney’s proposal is not expected to have meaningful power to detect patients with an increase in calcitonin that is caused by medullary thyroid carcinoma or by a preneoplastic lesion that is destined to become medullary thyroid carcinoma.

The clinical data to date (with the limitations and caveats discussed throughout this memorandum) do not show a convincing signal of C-cell activation in 1,400 patients exposed to liraglutide for at least 1 year and 580 patients exposed to liraglutide for 2 years. The sponsor has been asked to obtain as much follow-up information as possible on the only liraglutide-treated patient who had a treatment-emergent increase in serum calcitonin from <50 ng/L at baseline to ≥50 ng/L. The response is pending. This patient had an increase in serum calcitonin during a 26-week trial from _____ at baseline to _____ at endpoint in January 2007. The largest increase in serum calcitonin in a comparator-treated patient was seen with **b(4)**

glimepiride in a patient whose serum calcitonin increased from --- ng/L at baseline to --- ng/L at Week 65 and --- ng/L at Week 104.

b(4)

Based on the clinical data to date and the rarity of medullary thyroid carcinoma in the general population, there are likely no additional clinical data that can be feasibly obtained premarketing to refine human risk. A non-clinical mechanism of action that excludes human risk would be ideal but the non-clinical reviewers and the sponsor have not been able to identify studies that would definitively determine the mechanism of action and the relevance to humans. If liraglutide is approved now, the cardiovascular trial will be conducted as a postmarketing requirement under the FDA Amendments Act. These authorities ensure that such trials are completed in a timely manner and that the trial designs adequately incorporate FDA comments. Because this trial has a low likelihood of having sufficient power to detect an increase in the risk of medullary thyroid carcinoma (or an elevation in a biomarker that is caused by medullary thyroid carcinoma or a preneoplastic lesion that is destined to become medullary thyroid carcinoma), my opinion is that it is not reasonable to hold up approval for many years on the small chance that a positive finding will emerge. In the unlikely event that there is a finding of concern in this trial regarding thyroid C-cell tumors (or another safety finding), changes to labeling and restrictions on use can be implemented, if needed.

Given the uncertainty regarding human risk for medullary thyroid cancer, one must consider why liraglutide should be approved at all. The clinical benefit of liraglutide in the treatment armamentarium for type 2 diabetes must also be considered and deemed worthwhile to balance the uncertainty of human risk for medullary thyroid carcinoma. As mentioned by Dr. Mahoney, there are 11 classes of medications currently approved for the treatment of type 2 diabetes. However, in 2003-2004, approximately 45% of adults with diabetes were not achieving the American Diabetes Association HbA1c target of $<7\%$.⁵ Therefore, there is an unmet need for new antidiabetic medications. Although there may be many reasons for the low proportion of patients meeting HbA1c goals, inadequacies with current therapies likely play a role. For example, although insulin is titratable, it is associated with weight gain and hypoglycemia. Metformin is recommended as the first-line treatment for type 2 diabetes but is contraindicated in patients with renal impairment and thiazolidinediones can cause or exacerbate heart failure in susceptible individuals.

Liraglutide results in a net improvement in HbA1c relative to placebo of approximately 1% or greater, has an overall low risk of hypoglycemia, causes weight loss, is dosed once-daily (albeit via injection), can be used in patients with some degree of renal impairment (unlike metformin) and is not expected to exacerbate or cause heart failure (unlike the thiazolidinediones). The weight loss effect is an important one because diabetes is often associated with obesity. Only three approved anti-diabetic medications cause weight loss (Symlin, metformin, and Byetta). Symlin is dosed three times daily by injection, has modest efficacy (net reduction in HbA1c of 0.3-0.4%), and is only indicated in combination with prandial insulin. Metformin is the recommended first-line treatment for type 2 diabetes but is contraindicated in patients with renal impairment, which is an important long-term complication of diabetes. Byetta has the same mechanism of action as liraglutide and it is

⁵ Ford ES, et al. Trends in A1c concentrations among U.S. adults with diagnosed diabetes from 1999 to 2004. *Diabetes Care*. 2008; 31: 102-4.

important to consider whether there is any incremental benefit to having liraglutide available given that it would be second-in-class. The sponsor submitted preliminary data from a 26-week, controlled, head-to-head trial of liraglutide and Byetta showing better glycemic control (net change in HbA1c of -0.3% favoring liraglutide), lower antibody formation, and lower incidence of nausea over time with liraglutide, but these data have not been submitted in their entirety for FDA review. Liraglutide is dosed once-daily, which is expected to result in better compliance than twice-daily administration with Byetta. Whether the risk for pancreatitis with liraglutide is greater than that with Byetta remains to be seen, although it is concerning that there is a numerical imbalance in the incidence of pancreatitis in the liraglutide development program but not in Byetta controlled trials. In my opinion, it is reasonable to make liraglutide available and leave it to the discretion of individual healthcare providers and their patients as to whether the uncertainty of risk for medullary thyroid carcinoma (as communicated via labeling and Risk Evaluation and Mitigation Strategies – see below), should be accepted in light of the benefits of liraglutide, while data on medullary thyroid carcinoma are accrued postmarketing (the probably only feasible approach to adequately refine human risk for medullary thyroid carcinoma).

An important consideration with approval is whether there should be active monitoring for medullary thyroid carcinoma in patients treated with liraglutide. The EMEA approved liraglutide without recommendations for routine screening for medullary thyroid carcinoma. Widely available screening options include neck physical exam, thyroid ultrasonography, and serum calcitonin measurements. Neck physical exams are part of good medical practice and should be encouraged for all patients, regardless of whether there is treatment with liraglutide. However, I recommend against routinely obtaining thyroid ultrasounds and serum calcitonin measurements in all patients treated with liraglutide. As discussed by Dr. Mahoney, thyroid nodules are common in the general population and the incidence increases with age with a prevalence as high as 50% based on ultrasonography or autopsy data.⁶ Most (95%) thyroid nodules are benign. However, fine needle aspiration is sometimes inconclusive even for benign nodules, requiring surgery for definitive diagnosis. Often nodules with benign pathology on fine needle aspiration still undergo repeat, periodic ultrasound to assess for interval change in nodule size in case the biopsy results were falsely negative. Routine ultrasonography is also expected to result in detection of incidental papillary microcarcinoma (<1 cm in diameter), given that autopsy studies have shown occult papillary thyroid carcinoma in up to one-third of patients who have died for unrelated reasons.⁷ Finding these incidental tumors will most likely prompt thyroidectomy because in the individual patient it will be impossible to know whether the discovered papillary microcarcinoma will remain clinically insignificant for the remainder of the patient's life or whether the tumor will have a more aggressive course. Therefore, routine thyroid ultrasonography has the potential for substantial negative public health implications.

⁶ American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical Guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract.* 2006; 12: 63-102.

⁷ Pearce EN and Braverman LE. Editorial: papillary thyroid microcarcinoma outcomes and implications for treatment. *J Clin Endocrinol Metab.* 2004; 89: 3710-2.

Serum calcitonin can be a biomarker for increased C-cell mass, but as discussed by Dr. Mahoney, modest elevations are non-specific (e.g., increased with renal impairment, proton pump inhibitor use, etc.) and do not reliably lead to diagnosis of C-cell hyperplasia or medullary thyroid carcinoma. For example, Costante et al.⁸ measured serum calcitonin in approximately 6,000 consecutive non-Multiple Endocrine Neoplasia type 2 patients with thyroid nodules and no renal failure. Approximately 95% of patients had calcitonin values <10 ng/L, 3.7% of patients had calcitonin values >10 and <20 ng/L, and 1.1% had calcitonin values \geq 20 ng/L. Fifteen patients were diagnosed with medullary thyroid carcinoma, none of whom had serum calcitonin values <20 ng/L. The positive predictive value for medullary thyroid carcinoma was 8% for patients with calcitonins of \geq 20 to <50 ng/L, 25% if the calcitonin was >50 to <100 ng/L, and 100% if the calcitonin was >100 ng/L. The positive predictive value for C-cell hyperplasia was 11% for patients with calcitonins of \geq 20 to <50 ng/L, 25% if the calcitonin was >50 to <100 ng/L, and 0% if the calcitonin was >100 ng/L. However, as discussed previously, it is controversial whether C-cell hyperplasia undergoes malignant transformation in patients with sporadic forms of C-cell hyperplasia. Of note, the positive predictive values in this study may not be representative of patients without known thyroid nodules who undergo measurement of calcitonin or those with renal impairment, a frequent complication of type 2 diabetes. Because renal impairment raises serum calcitonin values, it is possible that specificity for medullary thyroid carcinoma or C-cell hyperplasia will be lower for moderately elevated calcitonin values.

One reasonable approach could be to recommend periodic serum calcitonin measurements in liraglutide-treated patients with further workup for medullary thyroid carcinoma prompted when the serum calcitonin exceeds a chosen cutpoint (e.g., >50 ng/L or >100 ng/L). However, this will be difficult to institute uniformly in practice, where medical care is often nuanced and the physician is facing a patient with a serum calcitonin of, say 25 ng/L, which has a small but possible chance of reflecting medullary thyroid carcinoma (based on the Costante data above). Given the rarity of medullary thyroid carcinoma, it is much more likely that modest elevations in serum calcitonin will be false-positives. Therefore, routine screening with serum calcitonin will create frequent conundrums for the healthcare provider, lead to unnecessary further workup, and probably unnecessary surgeries (as occurred in the liraglutide development program). For this reason, serum calcitonin should not be routinely recommended for patients treated with liraglutide in clinical practice. Instead, my recommendation is that liraglutide-treated patients undergo a regular neck physical exam (which is standard medical practice) with further workup of detected abnormalities, as needed.

Please see my conclusions regarding cardiovascular safety under the Adverse Event section of this memorandum.

- Recommendation for Postmarketing Risk Management Activities

I recommend Risk Evaluation and Mitigation Strategies (REMS) that includes:

⁸ Costante G, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. *J Clin Endocrinol Metab.* 2007; 92: 450-5.

- A Medication Guide informing patients of the rodent thyroid C-cell tumor findings and the uncertainty of risk to humans. The sponsor has already agreed to the Medication Guide, the wording of which is under review.
- A Communication Plan that includes a Dear Health Care Provider letter, explaining the rodent thyroid C-cell tumor findings and the uncertain risk to humans as well as the pitfalls involved with screening for medullary thyroid carcinoma using thyroid ultrasound and serum calcitonin. I recommend exploring with Dr. Amy Egan (Deputy Director for Safety) and the Office of Surveillance and Epidemiology whether there are other components of REMS that could be worthwhile to implement, with a focus on activities that effectively communicate the uncertainty regarding risk for medullary thyroid carcinoma and activities that limit “collateral damage” from unnecessary further workup or surgeries due to pitfalls in screening with serum calcitonin or thyroid ultrasound.
 - Recommendation for other Postmarketing Study Commitments

The sponsor has submitted synopses of two proposed postmarketing studies and a protocol for a postmarketing cardiovascular trial. Please see the reviews of Drs. Mahoney and Diane Wysowski (Office of Surveillance and Epidemiology) for further details. Dr. Wysowski’s comments pertaining to the design of the epidemiological study and cancer registry study are in the process of being communicated to the sponsor. These studies should be postmarketing requirements under the FDA Amendments Act and the studies should be implemented only after FDA has agreed that the study designs are adequate to address our safety concerns.

- The cardiovascular safety trial must definitively rule out an unacceptable increase in cardiovascular risk (i.e., show that the upper bound of the 95% confidence interval for the risk ratio or hazard ratio comparing MACE events with liraglutide to MACE events with comparator is <1.3). Based on findings during the NDA review and known safety signals with other GLP-1 agonists, this trial must also evaluate the following adverse events of interest: medullary thyroid cancer and serum calcitonin elevations, pancreatitis, renal safety, serious hypoglycemia, hypersensitivity reactions, and neoplasms.
- Case series registry using North American cancer registry data akin to what has been instituted with Forteo for osteosarcoma. The sponsor is proposing that participating registries identify patients diagnosed with medullary thyroid cancer. These patients will be invited to participate in the study and pertinent information will be collected, including treatment with liraglutide. The sponsor proposes progress reports at _____ then _____ Given the typical latency of medullary thyroid carcinoma, I recommend that reports continue to occur through 20 years.
- A 3-5-year epidemiologic study using i3 Aperio claims database to compare initiators of liraglutide to matched initiators of exenatide and other diabetes drug classes. The proposed primary endpoint is thyroid cancer (there is no ICD code for medullary thyroid carcinoma). Other endpoints of interest should include pancreatic cancer (see below), serious hypoglycemia, and pancreatitis. The scope of this proposed trial (duration, sample size) is likely too small to adequately evaluate the primary endpoint of thyroid cancer. Instead, this

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trial (or another appropriately designed epidemiological study) will be better suited for assessing other safety signals of interest, such as hypersensitivity reactions and pancreatitis.

- Non-clinical studies as requested by Drs. Parola and Davis-Bruno that evaluate potential pathways by which liraglutide induces thyroid C-cell tumors in rodents and mechanistic studies, like those requested for Byetta, that help improve our understanding of the association between GLP-1-based therapies and pancreatitis. There is also interest in non-clinical studies pertaining to pancreatic cancer (see below).
- As discussed above, the sponsor will also be required to conduct pediatric studies under the Pediatric Research Equity Act (PREA).

I also recommend the following:

- An informational session (Safety First Pilot) with the major endocrine professional associations after approval, as was done for Onglyza and Cycloset.
- I concur with the sponsor's proposal to _____ **b(4)**
- There is emerging interest in also evaluating potential risk for pancreatic cancer with GLP-1 based therapies based on a recently published article showing pancreatic ductal hyperplasia and metaplasia with Januvia in a rat model of diabetes. Pancreatic cancer can be included as an adverse event of interest in the cardiovascular trial and in the epidemiological study. In addition, the non-clinical pharmacology/toxicology reviewers may wish to develop a postmarketing requirement that further evaluates this signal in animals.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

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10/14/2009

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10/15/2009