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APPLICATION NUMBER:

206321Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	10 November 2014
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	206321
Applicant	Novo Nordisk
Date of Submission	20 December 2013
PDUFA Goal Date	20 October 2014
Proprietary Name / Established (USAN) names	SAXENDA / liraglutide
Dosage forms / Strength	Injectable solution, 6 mg/mL, to be administered subcutaneously at a maintenance dose of 3 mg daily via a pre-filled PDS290 pen injector
Proposed Indication	Chronic weight management
Recommended:	Approval

Material Reviewed/Consulted & Primary Reviewer(s)		
Medical Officer Review	18 Oct 2014	Julie Golden, MD
Statistical Review (Efficacy)	15 Sep 2014	Bradley McEvoy, DrPH
Statistical Review Addendum (Efficacy)	16 Oct 2014	Bradley McEvoy, DrPH
Statistical Review (CV Safety)	12 Sep 2014	Rongmei Zhang, PhD
Clinical Pharmacology Review	19 Sep 2014	Jayabharathi Vaidyanathan, PhD
QT-IRT Consult	21 Oct 2011	Zhu Hao
Study Endpoints Review	03 Oct 2014	Sarrit Kovacs, PhD
Epidemiology: Review of Clinical Trials	18 Aug 2014	Christian Hampp, PhD
Epidemiology: Review of Interim Study Report	30 Jun 2014	Christian Hampp, PhD
Division of Oncology Drug Products 1 Consult	03 Jul 2014	Jonathan P. Jarow, MD
Division of Neurology Products Consult	21 Oct 2014	Ronald Farkas, MD, PhD
Pharmacovigilance Review	13 Aug 2014	Debra L. Ryan, PharmD, MBA & Carolyn J. Tabak, MD, MPH
Clinical Review of Post-marketing MTC Cases	26 Sep 2014	Marina Zemskova, MD
CMC Review	14 May 2014	Joseph Leginus, PhD
Microbiology Review	16 Jan 2014	Bryan S. Riley, PhD
Pharmacology/Toxicology Review	15 Sep 2014	Anthony L. Parola, PhD
REMS Modification Review #1	26 Sep 2014	Amarilys Vega, MD, MPH & Kate Oswell, MA
REMS Modification Review #2	16 Oct 2014	Amarilys Vega, MD, MPH & Kate Oswell, MA
Clinical Inspection Summary/OSI	02 Sep 2014	Cynthia F. Kleppinger, MD
CDRH Human Factors Review	22 Aug 2014	QuynhNhu Nguyen
CDRH Device Review	16 Apr 2014	Sajjad H. Syed
CDRH Office of Compliance	30 Apr 2014	LCDR John W. Diehl
OSE/DMEPA Human Factors & Labeling Rev.	22 Jul 2014	Sarah K. Vee, PharmD
OSE/DMEPA Proprietary Name Review	01 Apr 2014	Sarah K. Vee, PharmD
OPDP Labeling Consult	14 Aug 2014	Kendra Y. Jones
DMPP/OPDP Patient Labeling Review	15 Oct 2014	Sharon W. Williams, MSN, BSN, RN (DMPP) & Kendra Y. Jones (OPDP)

QT-IRT: QT Interdisciplinary Review Team; MTC: Medullary thyroid cancer; CMC: Chemistry, Manufacturing, and Controls; REMS: Risk Evaluation and Mitigation Strategy; OSI: Office of Scientific Investigations; CDRH: Center for Devices and Radiological Health; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; DMPP: Division of Medical Policy Programs

1. INTRODUCTION

In the present application, the applicant has proposed that "Saxenda is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea."

This review summarizes the conclusions and regulatory recommendations of the review disciplines assigned to review the safety and efficacy of Saxenda (liraglutide 3 mg for injection) for chronic weight management. I am not aware of any disagreements within or between the review disciplines regarding final regulatory recommendations; all disciplines have recommended approval.

2. BACKGROUND

During the past two decades, there has been a dramatic increase in obesity in the United States. More than one-third (nearly 79 million) of U.S. adults and approximately 17% of children and adolescents have obesity according to the Centers for Disease Control and Prevention (CDC). Obesity is associated with increased risk for all-cause and cardiovascular mortality, and having obesity raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes mellitus, cardiovascular disease, gallbladder disease, osteoarthritis, and sleep apnea. Although a comprehensive program of dietary strategies and lifestyle intervention/counseling is of paramount importance for affected individuals,[1] it is well recognized that these efforts are often insufficient to achieve health outcome goals.

Despite the extraordinarily adverse impact of overweight and obesity on patients and the healthcare system, there is a paucity of approved pharmacologic interventions to aid the treatment of obesity. The currently available FDA-approved medications for chronic weight management are Xenical (orlistat; approved in 1999), Belviq (lorcaserin HCl; 2012), Qsymia (phentermine/topiramate XR; 2012), and Contrave (naltrexone HCl/bupropion HCl; 2014).

Liraglutide is a human glucagon-like peptide 1 (GLP-1) analog that was approved 25 January 2010, under the tradename Victoza at a maximum dosage of 1.8 mg daily, for the treatment of type 2 diabetes mellitus (T2DM). During clinical trials designed to support approval for T2DM, it was noted that liraglutide appeared to reduce body weight, and the sponsor held a pre-IND/end-of-phase 2 meeting with the Division in March 2008 to discuss the development of liraglutide for weight management. It bears mention that the target population with overweight/obesity far surpasses the estimated 29 million people in the United States with diabetes.

Victoza was approved with a boxed warning to notify prescribers that the drug causes thyroid C-cell tumors at clinically relevant exposures in both rats and mice; the human relevance of this observation had not, and has still not, been determined by clinical or nonclinical studies. Given the strength of this nonclinical signal, however, it was determined that the benefit/risk of Victoza for the treatment of T2DM could only be favorable if approved with a Risk Evaluation and Mitigation Strategy (REMS), which comprises a communication plan and a timetable of assessments. The REMS also aimed to inform patients and providers about the risk of acute pancreatitis (including necrotizing pancreatitis).

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[1] Jensen MD, *et al.* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014 Jun 24; 129(25 Suppl 2):S102-38.

3. CMC / DEVICE

CMC

Dr. Leginus conducted the CMC review for Saxenda. The drug products of the current NDA (Saxenda) and the previously approved Victoza (liraglutide [rDNA] injection; NDA 22341) have the same drug substance, (b) (4). Both NDAs use an identical 3-mL glass cartridge as the primary container closure system, although the glass cartridge for Saxenda will be provided in a different pen injector (PDS290).

Dr. Leginus recommends approval from a CMC perspective. He has no recommendations for post-marketing commitments, agreements, or risk management steps. I concur with his assessment.

Microbiology

Dr. Riley noted that the proposed drug product is identical to an approved drug product from a product quality microbiology perspective and, therefore, no additional product quality microbiology assessment is necessary.

Facilities Review/Inspection

The facilities report from the Office of Compliance states that the overall recommendation is acceptable.

Device Review

The primary packaging for Saxenda is the same as that approved for Victoza under NDA 22341, i.e., a 3-mL cartridge, (b) (4) The secondary packaging is an assembled PDS290 pen injector, which is a pre-filled, multiple-dose, disposable, delivery device that contains the 3-mL cartridge. The PDS290 liraglutide 3 mg pen injector is based on the approved FlexTouch® pen injector.

Device-related requests for information were conveyed to the applicant in the filing communication dated 04 March 2014. The applicant's responses, received 21 March 2014, were reviewed by Sajjad Syed (Electrical Engineer, CDRH General Hospital Devices Branch) and LCDR John W. Diehl (Regulatory Operations Officer, CDRH Office of Compliance, Division of Manufacturing and Quality) and found to be adequate. Dr. Patricia Beaston, an endocrinologist with CDRH's General Hospital Devices Branch, reviewed dose accuracy for the device as well (referenced in S. Syed's memo). CDRH indicated that there were no additional questions regarding device biocompatibility, safety, or performance.

Human Factors

QuynhNhu Nguyen reviewed a 129-subject human factors validation study from the CDRH perspective and identified concerns regarding needle stick injury and use errors that could result in mis-dosing.

Dr. Vee also reviewed this study from the DMEPA perspective. She noted that although some untrained users encountered difficulties while administering this product, the same difficulties "have also been reported with the use of other prefilled injection pen devices and have been managed reasonably well through labeling." She states that failure to perform these tasks would result in underdoses in most instances and would not be expected to cause serious harm acutely. This same pen-injector platform (PDS290) has been approved for Novolog and Levemir. Recommendations to improve labeling were provided.

I do not believe that there are outstanding issues related to human factors that would preclude approval with appropriate labeling.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. Anthony Parola reviewed the nonclinical data supporting this application, which cross-referenced pivotal nonclinical studies that were previously reviewed (by Dr. Parola) under Victoza NDA 22341. See Dr. Parola's review for a thorough discussion of the nonclinical data.

The proposed dosage for Saxenda is 3 mg/day, compared with the recommended maximum dosage of 1.8 mg/day for Victoza for the treatment of type 2 diabetes mellitus (T2DM). Because systemic clearance of subcutaneously injected liraglutide increases with body weight in humans, however, systemic exposure at steady state in obese adults administered 3 mg/day was only slightly higher than that in healthy adults administered 1.8 mg/day ($AUC_{0\text{-}24h}$ 854 vs. 809 nM·h) despite the 1.7-fold higher dose. Thus, Dr. Parola notes that "human exposure multiples based on systemic exposure for findings in nonclinical safety studies of liraglutide, including carcinogenicity and reproductive and developmental toxicity studies, are similar for 3.0 mg/day liraglutide in obese adults and 1.8 mg/day liraglutide in healthy adults."

Safety and toxicity of liraglutide were evaluated in safety pharmacology studies, single- and repeat-dose toxicity studies, genetic toxicity studies, 2-year carcinogenicity studies in rats and mice, reproductive and developmental toxicity studies, local tolerance studies, and mechanistic studies of liraglutide-induced thyroid C-cell tumors in rodents. All pivotal nonclinical safety studies were reviewed under Victoza NDA 22341. Dr. Parola summarizes that liraglutide toxicity occurred in thyroid (mice and rats) and at injection sites (mice, pigs, and monkeys), and included a mild anemia (mice, rats, and monkeys).

Carcinogenicity

Two-year lifetime carcinogenicity studies in mice and rats showed that liraglutide causes thyroid C-cell tumors at clinically relevant exposures in male and female mice and rats, as well as fibrosarcomas on the dorsal skin and subcutis of male mice. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice and rats. The nonclinical data regarding thyroid C-cell tumors, as summarized in the FDA briefing document for the 11 September 2014 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), are presented below. Note that the no observed adverse effect level (NOAEL) for thyroid C-cell tumors in mice was 0.2 mg/kg/day liraglutide (1.8-times human exposure based on AUC comparison); a NOAEL was not established in the rat carcinogenicity study. These nonclinical data regarding thyroid C-cell tumors formed the basis for a boxed warning and Risk Evaluation and Mitigation Strategy (REMS) for Victoza. The approved labeling for Victoza and the proposed labeling for Saxenda state that it is unknown whether liraglutide will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies.

Table 1. Incidence (% affected) of Thyroid C-Cell Proliferative Lesions in a 104-week Carcinogenicity Study of Liraglutide in CD-1 Mice

	Sex	Male[1]					Female[1]				
	Liraglutide Dose (mg/kg/day)	0	0.03	0.2	1	3	0	0.03	0.2	1	3
	Human Exposure Multiple[2]	-	0.2	1.8	10	38	-	0.2	1.8	10	38
Thyroid C-cells	Focal Hyperplasia	0	0	1.5	16*	38*	0	0	10*	15*	29*
	Adenoma (benign)	0	0	0	13*	19*	0	0	0	6*	20*
	Carcinoma (malignant)	0	0	0	0	0	0	0	0	0	2.6
	Total Tumors	0	0	0	13*	19*	0	0	0	6*	22*

[1]N = 75 - 79 mice/sex examined in 0 and 3 mg/kg/day liraglutide groups, 65 – 67 mice/sex examined in 0.03, 0.2, and 1.0 mg/kg/day liraglutide groups

[2]Human exposure multiple based on plasma liraglutide AUC comparison at the maximum recommended human dose of 3.0 mg/day liraglutide yielding estimated steady state $AUC_{0\text{-}24h}$ 854 nM.hr in obese adults

*Statistically significantly different from controls by pairwise comparison ($p \leq 0.05$)

Underlined value exceeds historical control group maximum for thyroid C-cell adenomas or carcinomas (0% M, F) and focal hyperplasia (0% M, 0.9% F)

Source: FDA briefing document for 11 Sept 2014 EMDAC, p. 335.

Table 3. Incidence (% affected) of Thyroid C-Cell Proliferative Lesions in a 104-week Carcinogenicity Study of Liraglutide in Sprague Dawley Rats

	Sex	Male[1]				Female[1]			
	Liraglutide Dose (mg/kg/day)	0	0.075	0.25	0.75	0	0.075	0.25	0.75
	Human Exposure Multiple[2]	-	0.5	2.7	7.9	-	0.5	2.7	7.9
Thyroid C-cells	Focal Hyperplasia	22	29	40	48*	28	28	55*	48
	Adenoma (benign)	12	16	42*	46*	10	27*	33*	56*
	Carcinoma (malignant)	2	8	6	14*	0	0	4.1	6
	Total Tumors	14	22	42*	56*	10	27	37*	58*

[1]N = 49 – 50 rats/sex/dose examined

[2]Human exposure multiple based on plasma AUC comparison at the maximum recommended human dose of 3.0 mg/day liraglutide yielding $AUC_{0\text{-}24h}$ 854 nM.hr in obese adults

*Statistically significantly different from controls by pairwise comparison ($p < 0.05$)

Underlined value exceeds historical control background incidence maximum for thyroid C-cell adenomas (21.1% M, 16.0% F), carcinomas (2.1% M, 4.0%, F), and focal hyperplasia (14.3% M, 20.0% F)

Source: FDA briefing document for 11 Sept 2014 EMDAC, p. 336.

Approval of Victoza included 2 post-marketing requirements (PMRs) to evaluate the effects of liraglutide on proliferative C-cell lesions in mice. In the first study, intended to satisfy Victoza PMR 1583-3, liraglutide was subcutaneously administered to CD-1 mice for 26 weeks (25% of their total lifespan) followed by a 78-week recovery period to determine if transient exposure to liraglutide increases the lifetime risk of developing proliferative C-cell lesions. Dr. Parola notes that mice treated with 3.0 mg/kg/day appeared to be at an increased risk for developing proliferative thyroid C-cell lesions (preneoplastic focal C-cell hyperplasia in males and benign C-cell adenoma in females) for up to 78 weeks after treatment was stopped. However, as a result of a low incidence of proliferative C-cell lesions in concurrent control group male mice as well, a clear relationship to liraglutide treatment was not established. Thus, whether or not transient exposure to liraglutide increases the lifetime risk of proliferative C-cell lesions in mice was not adequately addressed by this study.

The second study, intended to satisfy Victoza PMR 1583-5, was a 13-week repeat-dose study of liraglutide in wild-type and GLP1R-deficient mice that demonstrated liraglutide-induced thyroid C-

cell hyperplasia and activation of ribosomal protein S6, in both normal and hyperplastic C-cells, are both GLP1R-dependent in mice. Liraglutide did not activate the rearranged during transfection (RET) proto-oncogene.

As stated in Victoza labeling, in the 2-year carcinogenicity study in mice, a treatment-related increase in fibrosarcomas occurred on the dorsal skin and subcutis in males in the 3 mg/kg/day group. Fibrosarcomas at or near the injection site were attributed to the high local concentration of drug; the concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration administered to mice (0.6 mg/mL).

Pancreatitis

Pancreatitis is a safety concern of special interest for liraglutide as well as other members of the GLP1-agonist class. Review of repeat-dose toxicity studies of liraglutide submitted to Victoza NDA 22341, including chronic toxicity studies in rats and monkeys and carcinogenicity studies in mice and rats, did not show any substantive evidence of pancreatitis (or pancreatic cancer). Dr. Parola reviewed additional nonclinical data (summarized on pp. 150-151 of his review) that did not support a causal role for GLP-1 agonists and pancreas injury. Approval of Victoza included a post-marketing requirement to determine the effects of liraglutide on the exocrine pancreas in a rodent model of insulin-resistant T2DM (NDA 22341; PMR 1583-4). In this study, up to 1.0 mg/kg/day liraglutide for 3 months had no adverse effects on the exocrine pancreas of male or female hyperglycemic Zucker Diabetic Fatty (ZDF) fa/fa rats.

Cholelithiasis and Cholecystitis

As described in the Clinical Safety portion of this memo, treatment with liraglutide was associated with an increased incidence of adverse events related to the gallbladder in clinical trials for weight management; this was not observed in clinical trials employing ≤1.8 mg/day for the treatment of T2DM. In repeat-dose toxicity studies, up to 5 mg/kg/day liraglutide had no effect on gallbladder in mice treated for up to 13 weeks or cynomolgus monkeys treated for up to 52 weeks. In the 2-year carcinogenicity study of liraglutide in mice, liraglutide increased the incidence of macroscopic pathology findings involving the gallbladder (i.e., abnormal contents, dilation/distension, enlargement) but these findings were not dose-related and did not correlate with microscopic pathology.

Reproductive and Developmental Toxicity

The approved Victoza labeling and the proposed Saxenda labeling note that liraglutide was teratogenic in rats and rabbits at clinically relevant exposures. No additional relevant data were submitted to the Saxenda NDA. Victoza is labeled as pregnancy category C based on these data, but Saxenda will be labeled as pregnancy category X, since weight loss offers no potential benefit to a pregnant woman and may result in fetal harm.

Nonclinical Recommendation

Dr. Parola concludes, "Based on prior approval of up to 1.8 mg/day liraglutide for the treatment of type 2 diabetes mellitus, the approval of other long-acting GLP-1 receptor agonists that are known or suspected to induce rodent thyroid C-cell tumors of unknown human relevance, similar steady state systemic exposure to liraglutide in obese adults administered 3.0 mg/day liraglutide compared to healthy adults administered 1.8 mg/day, and no new safety concerns from nonclinical studies for the proposed indication for weight management in obese adults or overweight adults with at least [one] weight-related comorbidity, I recommend approval of up to 3.0 mg/day liraglutide for the proposed

weight management indication" (p. 6). I agree that there are not any nonclinical deficiencies that would preclude approval.

5. CLINICAL PHARMACOLOGY

Dr. Jayabharathi Vaidyanathan reviewed this application from the clinical pharmacology and pharmacometrics perspective. The Office of Clinical Pharmacology recommends approval. I agree that there are no deficiencies related to clinical pharmacology that would preclude approval.

General pharmacology information for liraglutide was reviewed under Victoza NDA 22341 and appears in the Victoza package insert and Dr. Vaidyanathan's review.

Intrinsic Factors

Baseline body weight was the most significant covariate affecting the clearance (CL/F) of liraglutide as determined by the population PK analysis conducted for both programs, with an increase in liraglutide clearance as body weight increases. Using data from phase 3 trials 1839 (non-diabetics) and 1922 (type 2 diabetics), the effects of other covariates on the clearance of liraglutide were considered as well: age, sex, race, ethnicity, dose, and glycemic status at baseline (normoglycemia, pre-diabetes, and T2DM). Among these, sex was the other significant covariate, with males having 24% lower liraglutide exposure than females, after accounting for body weight differences. In addition, in trial 1922, obese diabetic subjects had ~16% lower exposure than obese normoglycemic or prediabetic subjects. Dr. Vaidyanathan concluded, however, that no dose adjustments are recommended based on sex or diabetic status. Furthermore, she determined that there does not appear to be a need for different dosing regimens for patients with lower body weight or patients who lose weight during treatment.

The following figures show the correlation of body weight to AUC for subjects receiving the 3 mg dose in the obesity trials (Figure 2) and the distribution of AUC in the Victoza and obesity programs (Figure 3). Dr. Vaidyanathan notes that although overlap in AUCs was observed in the two programs, the proportion of subjects in the obesity program having higher AUC was greater in the obesity program (3 mg dose) than in the Victoza program (1.8 mg dose). Approximately 16% of subjects in the obesity trials receiving liraglutide 3 mg/day had exposures higher than the maximum AUC observed with the 1.8 mg/day dose in the Victoza trials.

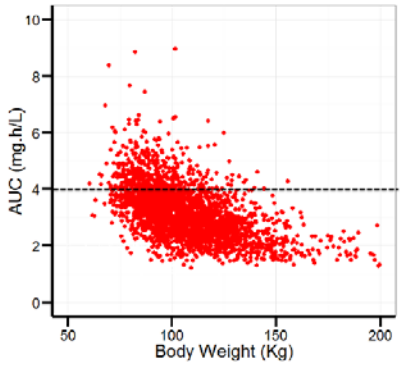


Figure 2: Correlation of liraglutide exposure to body weight in Obesity trials. Data for subjects receiving 3.0 mg dose is shown.
The horizontal line shows the maximum exposure level observed in the T2DM population receiving 1.8 mg dose.

Source: Dr. Vaidyanathan's review, p. 7.

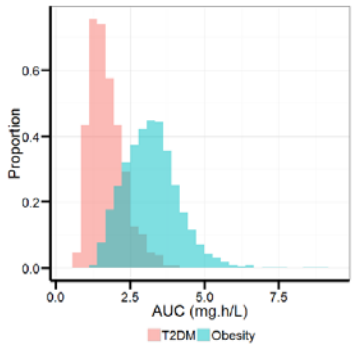


Figure 3: Distribution of liraglutide exposure obtained from population PK analysis following administration of 1.8 mg dose in T2DM program (Pink) and 3.0 mg dose in obesity program (Blue)

Source: Dr. Vaidyanathan's review, p. 7.

Regarding C_{max}, the sponsor compared the observed liraglutide C_{max} from the cardiac electrophysiology (TQTc) trial (i.e., NN211-1644; NDA 22341) and trials 1839, 1807 (a dose-ranging trial), and 3630. There was substantial overlap in the observed liraglutide C_{max} following administration of either the 1.8 mg or 3.0 mg dose. In part, this observation led the QT-IRT to agree that the thorough QTc study conducted for the Victoza development program was sufficient to support the current NDA as well.

Dose-Response/Exposure-Response for Efficacy

Trial 1807 evaluated daily doses of liraglutide 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg compared with placebo (and open-label orlistat). The results from this trial, which had a primary endpoint of change in body weight from baseline to Week 20, supported the choice of 3 mg/day for phase 3 trials. Consistent with the observed dose-response relationship, Dr. Vaidyanathan states that there was a clear relationship between liraglutide exposure (data from trials 1807, 1839, and 1922) and weight loss, with increasing exposure leading to greater weight loss. The weight loss appeared to reach plateau at the highest exposure.

6. CLINICAL/STATISTICAL- EFFICACY

Dr. Julie Golden and Dr. Brad McEvoy reviewed the efficacy of Saxenda for chronic weight management from a clinical and statistical standpoint, respectively. Both reviewers conclude that Saxenda is more effective than placebo with regard to weight loss, and Dr. Golden adds that the treatment difference is clinically meaningful.

The efficacy of Saxenda for a weight-related indication was evaluated in a single phase 2 dose-ranging trial (trial 1807) and four phase 3 trials: a 56-week trial in patients without T2DM (1839); a 56-week trial in patients with T2DM (1922); a 56-week trial in patients without T2DM who were able to lose ≥5% body weight during a 4-12-week run-in period by following a low-calorie diet (1923); and a 32-week trial in patients with moderate to severe obstructive sleep apnea (3970), in which the primary endpoint was the apnea-hypopnea index (AHI). All trials included a 4-week titration period at the onset of dosing. For details regarding the individual trial designs, see the thorough reviews of Dr. Golden and Dr. McEvoy.

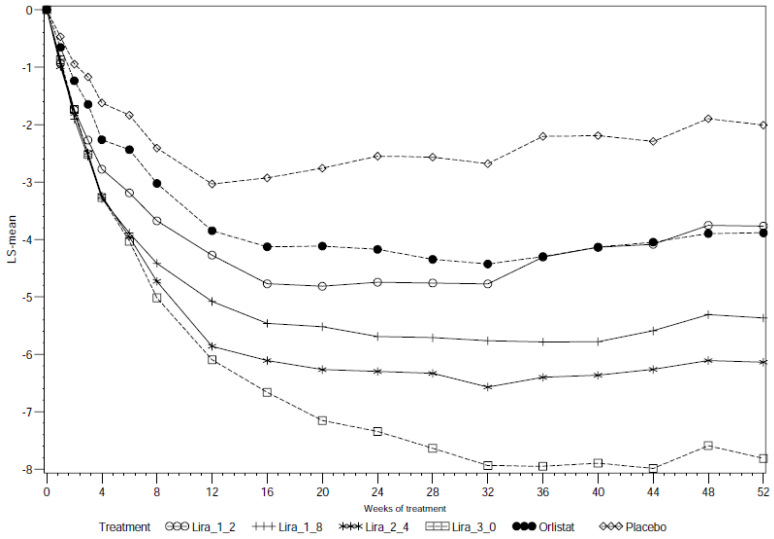
In the trials conducted in patients without T2DM or sleep apnea (i.e., 1839, 1923, and 1807), most participants (76-81%) were women; in the trial of patients with T2DM (1922), there was a similar proportion of men and women; and in the trial with patients with obstructive sleep apnea (3970), most participants (72%) were men. Across these trials, mean BMI ranged from 34 to 39 kg/m^2. The mean age

in most trials was approximately 46 years, except for trial 1922 where the mean age was 55 years. The majority of patients were white (85% overall). Regarding comorbidities, more patients in trial 1922 had hypertension (69%) or dyslipidemia (67%) than those in trial 1839 (35% and 29%, respectively), as one would expect in the diabetic and non-diabetic populations, respectively. Overall, 9% of patients had a history of cardiovascular disease as assessed by MedDRA queries of past medical history.

Effects on Body Weight

In **trial 1807**, 564 obese patients without T2DM were randomly assigned to receive liraglutide 1.2, 1.8, 2.4, or 3 mg once daily, liraglutide placebo once daily, or open-label orlistat 120 mg three times daily, with equal allocation. Patients could continue into an optional extension period for an additional 84 weeks, with the patients and investigators (but not the sponsor) remaining blind to treatment allocation from week 20 to 52. Beyond week 52, all liraglutide- or placebo-treated patients were switched to open-label liraglutide (initially 2.4 mg daily, later changed to 3 mg daily). As shown in the figure below, excerpted from Dr. Golden's review, this trial supported a dose-response relationship for liraglutide with weight loss, and guided the sponsor's decision to develop a dose of 3 mg daily for a weight management indication. Dr. McEvoy cautions that data beyond week 20 should be interpreted "extremely cautiously due to the likely bias resulting from a sizable number of subjects not consenting to the 84 week extension period."[2]

Figure 7. Change in Body Weight (kg), LOCF, Trial 1807 52-Week Interim Analysis



Source: NN8022-1807-ext Clinical Trial Report, Figure 11-1

In **trial 1839**, the largest phase 3 trial in this development program, 3,731 patients without T2DM but with obesity or overweight with at least one other weight-related comorbid condition were randomly assigned 2:1 to daily doses of liraglutide 3 mg or placebo. Patients with pre-diabetes at baseline (one of the stratification factors) were assigned to 160 weeks of treatment, but data after week 56 were not included in the submission. Patients without pre-diabetes were randomized to 56 weeks of treatment, which was followed by a 12-week placebo-controlled randomized withdrawal (1:1) for those initially

[2] Dr. McEvoy points out that 472 (84%) of the 564 randomized patients completed the 20-week main treatment period, with 74 (16%) of these 472 subjects not enrolling into the extension period. Furthermore, he notes that the decision not to continue follow-up appears to be associated with the degree of weight loss at week 20, with the patients that enrolled into the extension having more favorable average weight reductions than those that did not (p. 16 of statistical review).

assigned to liraglutide. The pre-specified primary efficacy endpoints included (1) % change in fasting body weight from baseline; (2) proportion of patients losing ≥5% of fasting baseline body weight; (3) proportion of subjects losing ≥10% of fasting baseline body weight; and (4) onset of T2DM in subjects with pre-diabetes at week 160 (not submitted with NDA). In this trial, the proportions of subjects who discontinued study drug prior to the primary endpoint assessment (at week 56) were 28% and 36% for liraglutide and placebo, respectively.

In **trial 1922**, 846 patients with T2DM and either obesity or overweight were randomly assigned 2:1:1 to daily doses of liraglutide 1.8 mg, 3 mg, or placebo for 56 weeks. Subjects treated with sulfonylureas were asked to reduce the dose of the sulfonylurea by 50% to reduce the risk for hypoglycemia. If fasting plasma glucose exceeded pre-specified limits, the investigator could provide glycemic rescue by adding an antidiabetic medication or increasing the dose of an existing medication. The co-primary endpoints were the same as the weight-related endpoints in trial 1839. In this trial, the proportions of subjects who discontinued study drug prior to the primary endpoint assessment were 22%, 23%, and 34% for liraglutide 1.8 mg, 3 mg, and placebo, respectively.

In **trial 1923**, 422 subjects without T2DM but with obesity or overweight with at least one other weight-related comorbid condition first entered a low-calorie-diet (1200-1400 kcal/day) run-in period. Those who successfully lost ≥5% of their body weight within 12 weeks of dietary/lifestyle intervention were then randomly assigned 1:1 to daily doses of liraglutide 3 mg or placebo for 56 weeks. The co-primary endpoints were (1) % change in fasting body weight from baseline; (2) proportion of subjects that maintained the ≥5% reduction in initial fasting body weight achieved during the low-calorie-diet run-in period; and (3) the proportion of subjects losing at least 5% of of fasting baseline body weight. In this trial, the proportions of subjects who discontinued study drug prior to the primary endpoint assessment were 25% and 30% for liraglutide and placebo, respectively. A similar proportion of randomized subjects discontinued because of adverse events (~9% in each group).

In **trial 3970**, 359 subjects with obesity and moderate or severe obstructive sleep apnea, but not T2DM, were randomly assigned 1:1 to daily doses of liraglutide 3 mg or placebo for 32 weeks. The primary endpoint was the change in AHI rate (events/hour). In this trial, the proportions of subjects who discontinued study drug prior to the primary endpoint assessment were 26% and 21% for liraglutide and placebo, respectively. Weight-related endpoints were secondary endpoints for this trial, so I have not described them in this summary review.

With the exception of the sleep apnea trial, the primary efficacy endpoints were designed to follow the 2007 FDA Draft Guidance for Industry, *Developing Products for Weight Management*. As outlined in this guidance, efficacy can be established by satisfying at least one of two criteria after one year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant; and
- The proportion of subjects who lose ≥5% of baseline weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

The guidance also suggests that the analysis should be applied to the last observation carried forward (LOCF) on treatment in the modified ITT population, defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Since the publication of this draft guidance in 2007, however, the Division's view on handling of missing data has evolved. The Division has reconsidered the use of LOCF following the 2010 publication of the

FDA-commissioned report on missing data by the National Academy of Sciences, the *Prevention and Treatment of Missing Data in Clinical Trials.*[3] Thus, during the review of this application, the statistical reviewers conducted a detailed review of the results with an emphasis on the impact of missing data.

Concentrating on trials 1839, 1922, and 1923, Dr. McEvoy noted that a sizable proportion of subjects did not have a weight assessment at week 56, with missing data occurring more frequently in the placebo groups (19% to 26%) than in the liraglutide 3 mg groups (17% to 20%). Because off-treatment values were excluded from the sponsor's primary analysis, even if measured, it is notable that the proportion of randomized subjects that lacked an on-treatment assessment at week 56 ranged from 31% to 45% for the placebo groups and 25% to 27% for the liraglutide 3 mg groups. (The majority of subjects that discontinued study drug prematurely did not return for a week 56 assessment.)

Dr. McEvoy assessed the assumptions made by carrying forward last-available observations on treatment (LAO-OT) and concluded that his results "provide empirical confirmation that the primary analysis cannot be used to describe the ITT effect." Furthermore, he found the sponsor's sensitivity analyses inadequate to assess the potential impact of missing data. He favored using all available data at week 56 (whether on-treatment or off-treatment) in the analysis, and additionally using information from retrieved dropouts to represent the missing week 56 values for non-retrieved dropouts. The preferred approach of the Division of Biometrics II was multiple imputation using retrieved dropouts (MI-RD) when possible; for trial 1923 and the liraglutide 1.8 mg arm of trial 1922, a retrieved dropout weighted analysis (RD-Weighted) was preferred because of the small number of retrieved dropouts in these analyses. See Dr. McEvoy's review for additional details, sensitivity analyses, and a discussion of the limitations of this approach. Although it is recognized that retrieved dropouts are not a random sample of the subjects who discontinued (i.e., unlikely to be statistically representative of the non-retrieved dropouts), the statistical review team believes that this group better reflects what happened to the non-retrieved dropouts at week 56 than using LAO-OT.

The following table presents the sponsor's primary analysis for % change in fasting body weight in trials 1839, 1922, and 1923 using the LAO-OT approach, excerpted from Dr. McEvoy's review (p. 33).

Table 15. Primary analysis results for change in fasting body weight (%) in Trials 1839, 1922, and 1923

Trial	Treatment Group	N	Adj. mean change from baseline	Diff. in adj. means Lira-Placebo (95% CI)
1839	Liraglutide 3.0 mg	2432	-8.0%	-5.4% (-5.8, -4.95)
	Placebo	1220	-2.6%	
1922	Liraglutide 3.0 mg	411	-5.9%	-4.0% (-4.8, -3.1)
	Liraglutide 1.8 mg	202	-4.6%	-2.6% (-3.6, -1.6)
	Placebo	210	-2.0%	
1923	Liraglutide 3.0 mg	194	-6.1%	-6.1% (-7.5, -4.6)
	Placebo	188	-0.1%	

Source: FDA statistical reviewer

In contrast, the following table from Dr. McEvoy's review (p. 33) presents sensitivity analyses conducted by the sponsor and FDA. I have highlighted the results that the Division of Biometrics II believes to best represent the magnitude of liraglutide's effect on weight.

[3] The sponsor was informed of this evolution of thinking in a 06 May 2013 advice letter.

Table 16. Sensitivity analysis results for change in body weight (%) in Trials 1839, 1922, and 1923

	1839	1922		1923
Sensitivity Analysis	**Lira 3.0 mg - Pla. (95% CI)**	**Lira 3.0 mg - Pla. (95% CI)**	**Lira 1.8 mg - Pla. (95% CI)**	**Lira 3.0 mg - Pla. (95% CI)**
Sponsor's				
Completers	-5.7% (-6.3, -5.1)	-4.1% (-5.3, -2.9)	-2.7% (-4.0, -1.3)	-
LAO (FAS)	-5.2% (-5.6, -4.7)	-4.0% (-4.8, -3.1)	-2.7% (-3.7, -1.7)	-
BOCF (ITT)	-5.3% (-5.7, -4.8)	-3.8% (-4.7, -3.0)	-2.4% (-3.4, -1.4)	-5.4% (-6.8, -3.9)
MMRM (FAS)	-5.8% (-6.3, -5.3)	-4.4% (-5.5, -3.3)	-2.9% (-4.2, -1.7)	-6.1% (-7.7, -4.6)
MI (FAS)	-5.5% (-6.0, -5.0)	-4.0% (-5.1, -2.9)	-2.7% (-4.0, -1.4)	-
FDA				
MI-RD (ITT)	-4.6% (-5.4, -3.9)	-3.4% (-4.5, -2.3)	-	-
RD-Weighted (ITT)	-4.8% (-5.3, -4.3)	-3.8% (-4.7, -2.9)	-2.5% (-3.5, -1.5)	-5.3% (-6.8, -3.8)
BOCF (ITT)	-4.5% (-5.0, -4.1)	-3.6% (-4.5, -2.8)	-2.4% (-3.4, -1.4)	-

Source: FDA statistical reviewer

Regarding the categorical analysis, whether one considers the sponsor's primary analysis, a sensitivity analysis in which patients with off-treatment or missing values are considered to be "non-responders," or the FDA statisticians' preferred approach, the proportions of patients who achieved ≥5% weight loss at one year exceed 35% and are more than double placebo for trials 1839, 1922, and 1923. The following table from Dr. McEvoy's review (p. 34) presents the primary categorical analyses.

Table 17. Primary analysis results for responder endpoints in Trials 1839, 1922, and 1923

Trial	Responder Endpoint	Treatment Group	N	n (%)	Difference* Lira-Placebo (95% CI)	Odds Ratio* Lira/Placebo (95% CI)
1839	5%	Lira 3.0 mg	2432	1536 (63%)	36.0% (32.9, 39.2)	4.8 (4.1, 5.6)
		Placebo	1220	331 (27%)		
	10%	Lira 3.0 mg	2432	805 (33%)	22.5% (20.0, 25.1)	4.3 (3.5, 5.3)
		Placebo	1220	129 (11%)		
1922	5%	Lira 3.0 mg	411	205 (50%)	36.1% (29.4, 42.8)	6.8 (4.3, 10.7)
		Lira 1.8 mg	202	72 (36%)	21.8% (13.7, 29.9)	3.7 (2.2, 6.1)
		Placebo	210	29 (14%)		
	10%	Lira 3.0 mg	411	96 (23%)	19.1% (14.1, 24.0)	7.1 (3.5, 14.5)
		Lira 1.8 mg	202	29 (14%)	10.1% (4.5, 15.6)	3.8 (1.8, 8.4)
		Placebo	210	9 (4%)		
1923	Maintain	Lira 3.0 mg	194	158 (82%)	32.5% (23.5, 41.5)	4.8 (3.0, 7.7)
		Placebo	188	92 (50%)		
	5%	Lira 3.0 mg	194	98 (51%)	28.7% (19.5, 37.9)	3.9 (2.4, 6.1)
		Placebo	188	41 (22%)		

Source: FDA statistical reviewer
* Odds ratio estimates are from an adjusted analysis while the estimated risk difference is unadjusted

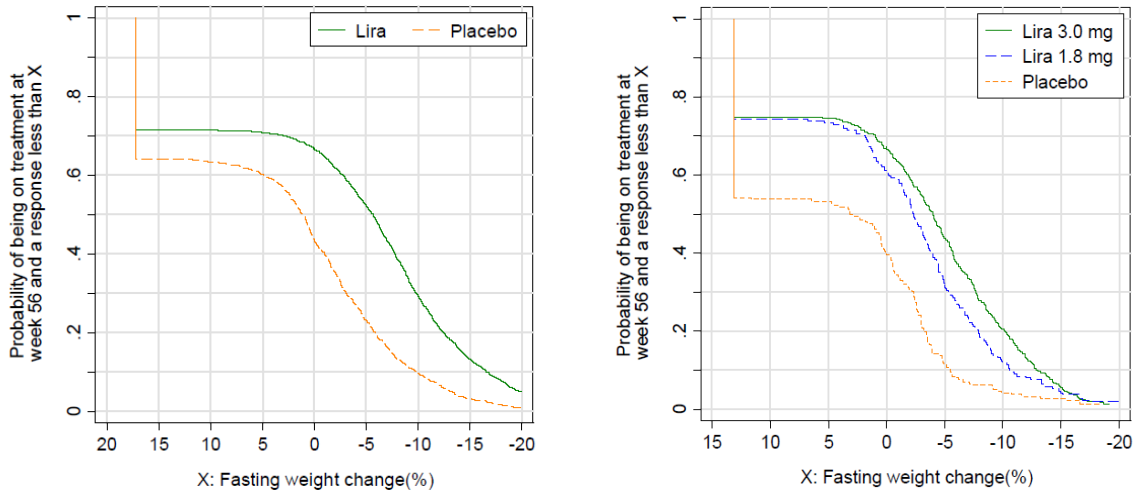
The following table (p. 35 of Dr. McEvoy's review) presents the applicant's sensitivity analyses as well as the analyses preferred by our statisticians. Once again, I have highlighted the values that the Division of Biometrics II recommends for labeling.

Table 18. Sensitivity analysis results for responder endpoints in Trials 1839, 1922, and 1923

	1839			1922			1923		
Endpoint/ Sensitivity Analysis	Lira 3.0mg n (%)	Placebo n (%)	Difference: Lira - Placebo (95% CI)	Lira 3.0mg n (%)	Placebo n (%)	Difference: Lira - Placebo (95% CI)	Lira 3.0mg n (%)	Placebo n (%)	Difference: Lira - Placebo (95% CI)
5% responder									
Completers	1317 (73%)	292 (36%)	37% (33, 39)	186 (59%)	24 (21%)	38% (29, 47)	83 (53%)	32 (22%)	31% (21, 41)
Fails (FAS)	1317 (54%)	292 (24%)	30% (27, 33)	186 (45%)	24 (11%)	34% (27, 40)	83 (43%)	32 (17%)	26% (17, 35)
MI-RD (ITT)	1542 (62%)	420 (34%)	28% (24, 32)	211 (50%)	40 (20%)	31% (22, 39)			
RD Weights (ITT)	1528 (62%)	381 (31%)	31% (28, 34)	215 (51%)	31 (15%)	36% (29, 42)	94 (44%)	44 (21%)	23% (14, 31)
10% responder									
Completers	739 (41%)	122 (15%)	26% (23, 29)	87 (27%)	9 (8%)	20% (13, 27)	-	-	-
Fails (FAS)	739 (30%)	122 (10%)	20% (18, 23)	87 (21%)	9 (4%)	17% (12, 22)	-	-	-
MI-RD (ITT)	841 (34%)	186 (15%)	19% (15, 22)	95 (23%)	14 (7%)	16% (9, 21)	-	-	-
RD Weights (ITT)	855 (34%)	174 (14%)	20% (18, 23)	98 (23%)	13 (6%)	17% (12, 22)	-	-	-
Maintain									
Completers	-	-	-	-	-	-	126 (81%)	69 (48%)	33% (23, 43)
Fails (FAS)	-	-	-	-	-	-	126 (65%)	69 (37%)	28% (19, 38)
MI-RD (ITT)	-	-	-	-	-	-	-	-	-
RD Weights (ITT)	-	-	-	-	-	-	152 (72%)	94 (45%)	27% (18, 36)

Source: FDA statistical reviewer

Although the FDA guidance concentrates on 5% weight loss, either as a mean difference between groups or as a measure of clinically significant weight loss for an individual patient, I find cumulative distribution functions helpful to describe the variation in changes in weight achieved in treatment groups. In his review, Dr. McEvoy presents empirical distribution plots that allow one to answer the question, "For a patient considering treatment with liraglutide for 56 weeks, how likely are they to stay on treatment for the intended duration and experience a change in fasting weight of at least a certain degree?" Below, I have included the relevant plots from trial 1839 (left) and trial 1922 (right).[4]



Empirical distribution plots of being on-treatment and having a fasting weight change of x% at week 56 for trial 1893 (left) and trial 1922 (right).
Source: Figures 10 and 11 from statistical review.

These plots show a clear rightward shift of liraglutide vs. placebo, across the range of observed changes in fasting weight, which supports the drug's efficacy with regard to weight loss.

[4] Trial 1923 only randomized subjects who were able to successfully lose ≥5% of fasting body weight during a 12-week run-in period; therefore, I do not believe that this trial population is generalizable to the majority of patients who will seek treatment with Saxenda. For this reason, I have not included an empirical distribution function from trial 1923 in this summary.

In general, change in body weight over time appeared to eventually reach a plateau around weeks 34-40 in each of the 56-week trials. Dr. Golden presents these results in her review for trials 1839 (Figure 12, p. 63), 1922 (Figure 15, p. 70), and 1923 (Figure 16, p. 75). Trial 1839 included a randomized withdrawal period, which confirmed the continued efficacy with liraglutide with long-term (i.e., one year) treatment.

Subgroups

Dr. McEvoy conducted subgroup analyses for % change in fasting weight using the sponsor's primary analysis (i.e., LOCF using LAO-OT) and considered intrinsic factors (sex, age, race, region, weight, and BMI) as well as trial-specific factors (i.e., stratification factors, as applicable). Across trial 1839, 1922, and 1923, two factors consistently favored one level over another: (1) women had more favorable reductions in weight than men, and (2) subjects that weighed less at baseline (≤ sample median) lost more weight than those that weighed more at baseline (> median). Since women tended to weigh less than men, on average, it is possible that the effect observed for sex could be described, in part, by differences in baseline weight. However, as noted previously (see Intrinsic Factors, p. 7), men had 24% lower liraglutide exposure than women, even after accounting for body weight differences. I have summarized the results of these subgroup analyses below:

Factor	Level	1839	1922	1923
		Lira 3mg – Pbo (95% CI)	Lira 3mg – Pbo (95% CI)	Lira 3mg – Pbo (95% CI)
Sex	Female	-5.9% (-6.4, -5.4)	-4.9% (-6.0, -3.8)	-6.8% (-8.5, -5.2)
	Male	-3.5% (-4.4, -2.6)	-3.0% (-4.3, -1.7)	-2.7% (-5.3, -0.2)
Weight	≤ median	-5.9% (-6.5, -5.3)	-4.5% (-5.7, -3.3)	-7.0% (-9.1, -5.0)
	> median	-4.8% (-5.4, -4.2)	-3.3% (-4.5, -2.1)	-5.0% (-7.0, -3.0)

Source: Excerpted from Table 21, statistical review, p. 40.

Effects on Secondary Endpoints

Dr. McEvoy and Dr. Golden both highlight that there was no pre-specified method for preserving study-wise type I error for the secondary endpoints in the individual weight management trials, including secondary endpoints related to body composition in trial 3970 and glycemic control in trial 1922. The following table presents the results for secondary endpoints related to anthropometric data, glycemic control, and lipids from trials 1839, 1922, and 1923, excerpted from Dr. McEvoy's review (p. 38). The observed effects on these secondary endpoints are reassuring in that they appear to be in the directions that one would expect to be beneficial, although the magnitudes of some of the described liraglutide-induced changes are of questionable clinical significance.

Figure 13. Analysis of secondary endpoints at week 56 (FAS, LOCF with LAO-OT)

Endpoint	1839 Diff. in mean change; Lira 3.0 mg - Placebo (95% CI)	1922 Diff. in mean change; Lira 1.8 mg - Placebo (95% CI)	1922 Diff. in mean change; Lira 3.0 mg - Placebo (95% CI)	1923 Diff. in mean change; Lira 3.0 mg - Placebo (95% CI)
Body Composition				
BMI (kg/m^2)	-2.0 (-2.2, -1.9)	-1.5 (-1.8, -1.2)	-0.9 (-1.3, -0.6)	-2.0 (-2.5, -1.6)
Fasting Body Weight (kg)	-5.6 (-6.0, -5.1)	-4.1 (-5.0, -3.2)	-2.7 (-3.7, -1.6)	-5.9 (-7.3, -4.4)
Waist Circumference (cm)	-4.2 (-4.7, -3.7)	-3.2 (-4.2, -2.2)	-2.1 (-3.2, -0.9)	-3.5 (-4.8, -2.2)
Glucose				
HbA1c (overall, %)	-0.2 (-0.2, -0.2)	-0.9 (-1.1, -0.8)	-0.7 (-0.9, -0.6)	-0.3 (-0.3, -0.2)
HbA1c (pre-diabetic, %)	-0.3 (-0.3, -0.2)	-	-	-
FPG (overall, mg/dL)	-6.9 (-7.5, -6.3)	-31.9 (-38.1, -25.6)	-23.0 (-30.3, -15.8)	-6.9 (-9.0, -4.7)
FPG (pre-diabetic, mg/dL)	-8.1 (-8.9, -7.3)	-	-	-
Lipids				
Triglycerides (mg/dL)	-16 (-20, -12)	-33.3 (-54.4, -12.1)	-21.9 (-46.2, 2.5)	-1.9 (-3.7, -0.2)
Total Cholesterol (mg/dL)	-4.6 (-6.6, -2.6)	-6.0 (-11.2, -0.8)	-6.4 (-12.4, -0.4)	-2.0 (-4.4, 0.4)
HDL Cholesterol (mg/dL)	0.9 (0.2, 1.5)	0.9 (-0.3, 2.1)	0.6 (-0.7, 2.0)	0.1 (-0.6, 0.8)
LDL Cholesterol (mg/dL)	-2.8 (-4.6, -1.1)	-2.1 (-6.3, 2.1)	-4.6 (-9.4, 0.2)	-1.7 (-3.7, 0.3)

FPG-Fasting Plasma Glucose

Regarding glycemic control, in trial 1922, the baseline mean HbA1c was 7.9-8.0% in all three arms. From baseline to week 56 (LOCF), the absolute change in HbA1c was -0.38%, -1.13%, and -1.32% in the placebo, liraglutide 1.8 mg, and liraglutide 3 mg arms, respectively. Changes in fasting plasma glucose (FPG) were qualitatively similar. In addition, these changes were observed despite a dose-related reduction in use of oral antidiabetic drugs: at week 56/LOCF, the percentages of subjects who increased antidiabetic medications (number of meds or dose) were approximately 27%, 9%, and 5% for the placebo, liraglutide 1.8 mg, and liraglutide 3 mg arms, respectively; conversely, the percentages who reduced use of antidiabetic medications were approximately 6%, 8%, and 13% for the same groups. The extent to which weight loss-dependent effects on glycemic control contributed to the known weight loss-independent effects of liraglutide was not determined.

Glycemic parameters were also assessed in trial 1839, which excluded patients with T2DM but enrolled patients with and without pre-diabetes (a stratification factor). As expected, patients with pre-diabetes had a higher baseline HbA1c (5.7% vs. 5.3%), and the effect of liraglutide 3 mg daily on HbA1c was larger in patients with pre-diabetes compared with those without (placebo-subtracted change: -0.25% vs. -0.19%; interaction P=0.0005). This is an expected effect given the mechanism of action of liraglutide and the fact that liraglutide-induced insulin secretion is glucose-dependent. Dr. Golden states that "[a]lthough the benefits of improving glycemic parameters in patients without type 2 diabetes is not entirely clear, the Diabetes Prevention Program demonstrated that intensive lifestyle intervention delayed or prevented type 2 diabetes in patients at high risk over an average follow-up of 2.8 years, and one could assume that improvements in glycemic parameters in those at risk for type 2 diabetes would be salutary."

(b) (4)

(b) (4)

Dr. Golden notes that treatment with liraglutide was also associated with reductions in systolic blood pressure of approximately 2.6 to 2.8 mmHg and reductions in diastolic blood pressure of 0.3 to 0.9 mmHg. In addition, as shown in the table above, liraglutide-induced changes in the lipid profile were directionally favorable although modest in magnitude.

Dr. Golden also describes results from patient report outcome (PRO) instruments administered in trial 1839, including the IWQoL-Lite, the SF-36, and TRIm-Weight. She notes that the PRO instrument endpoints were not pre-specified and were not adjusted for multiplicity. The sponsor did not justify or pre-specify "clinically meaningful" score changes for these instruments. In general, changes that may be consistent with clinical improvement were observed for liraglutide-treated patients, compared with placebo, in all domains of the IWQoL-Lite and SF-36, but the Study Endpoints and Labeling Team identified several limitations of these results.[5] Results of the TRIm-Weight questionnaire suggested possible improvements in the total, weight management, and treatment burden scores, but a worsening in the experience of side effects score, for liraglutide compared with placebo. In trial 1922, an improvement in the IWQoL-Lite total score was driven by a treatment difference in the physical function domain without any evidence of an effect from either of the liraglutide 1.8 mg or 3 mg doses on the other four domains (self-esteem, sexual life, public distress, and work), compared with placebo. I agree with Dr. Golden (b) (4) , these results do lend some support to the conclusion that the magnitude of weight loss observed with liraglutide likely improves how a patient feels or functions.

Obstructive Sleep Apnea

In trial 3970, which aimed to show an effect of liraglutide on the severity of obstructive sleep apnea, the observed between-group difference in AHI was 6 events/hour at the primary endpoint. Dr. Golden notes that a clinically significant difference in AHI has not been established (acknowledged by the sponsor in the clinical trial report[6]), the results of this single trial were not robust to all sensitivity

[5] Dr. Kovacs conducted a Study Endpoints review directed toward the applicant's presentation of results from the IWQoL-Lite and SF-36, for trial 1839, in their briefing document for the 11 Sept 2014 EMDAC meeting. (b) (4)

[6] "As the clinically relevant change in AHI has not been established yet, the difference to detect for this sample size calculation has been based on the expected difference in AHI when a weight loss difference of 6 kg was observed between liraglutide 3.0 mg and placebo (as observed in the NN8022-1923 and NN8022-1807 trials)" (p. 96 of NN8022-3970 Clinical Trial Report).

analyses, the trial was only 32-weeks' duration, and secondary endpoints that may help assess whether the primary result was clinically meaningful were not supportive. Taken together, I agree with Dr. Golden that this trial does not provide adequate evidence of a clinically meaningful effect of liraglutide on obstructive sleep apnea.

7. SAFETY

Dr. Golden conducted a comprehensive review of the Saxenda safety database; see her review for full details. The safety of Saxenda is informed by not only the clinical development program for its use in the treatment of overweight/obesity but also by the Victoza development program (liraglutide doses up to 1.8 mg daily for T2DM) and its post-marketing experience.[7,8] In this summary review, however, I will primarily focus on the safety data obtained from the Saxenda development program.

The sponsor pooled the single phase 2 trial (1807) and the four phase 3 trials (1839, 1922, 1923, 3970) into a "weight management pool." A total of 3872 individuals were exposed to at least one dose of liraglutide, with 3384 exposed to liraglutide 3 mg, and 2341 exposed to liraglutide 3 mg for ≥12 months. The total exposure was 3373 patient-years (PY) for any dose of liraglutide, 2974 PY for liraglutide 3 mg, and 1601 PY for placebo.

Deaths

In the weight management program, there have been 3 deaths in liraglutide-treated patients: 2 patients with histories including coronary artery disease died of sudden cardiac death (both liraglutide 3 mg), and 1 patient with T2DM, morbid obesity, CV disease, and hypoventilation syndrome died of pulmonary embolism and resulting complications during the off-treatment follow-up period of trial 1922 (liraglutide 1.8 mg). Dr. Golden concluded that given the patients' ages and comorbidities, she was unable to determine that liraglutide contributed to any of these deaths; I agree with her assessment. Three patients assigned to placebo also died (cardiac failure; pulmonary fibrosis; and cardiorespiratory arrest).

Non-Fatal Serious Adverse Events

Overall, in the main treatment periods of the weight management pool (i.e., excluding the ongoing portion of trial 1839), there were more patients in the liraglutide groups who experienced SAEs than those in the placebo groups: 213 (6.3%) of 3384 liraglutide 3 mg-treated patients (6.4% of any dose

[7] As one component of reviewing the post-marketing safety experience with Victoza, Dr. Christian Hampp reviewed the Year 3 interim report for PMR #1583-6, which was submitted with the Saxenda NDA. This PMR was a five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza and patients with type 2 diabetes not exposed to Victoza, as well as the incidence of serious hypoglycemia, pancreatitis, hypersensitivity, and overall malignant neoplasms. (b) (4)

[8] At the request of the Division, the Division of Pharmacovigilance I (DPVI) was consulted and conducted a review to provide a post-marketing overview of the safety profile of Victoza since approval including potential safety signals; to review the regulatory actions that have been taken in response to post-marketing reports; and to evaluate serious post-marketing reports and the published medical literature regarding events of special interest highlighted by the Division. In short, DPVI did not identify previously unknown safety signals for liraglutide in the FDA Adverse Event Reporting System (FAERS) database or the literature. The review did, however, identify nine cases of MTC that were identified via a FAERS search; additional post-marketing cases were identified after their review was finalized, which are discussed later in my review. See the review by Dr. Deb Ryan and Dr. Carolyn Tabak for full details of the DPVI evaluation.

liraglutide) vs. 89 (4.6%) of 1941 placebo-treated patients. Dr. Golden notes that this difference was primarily driven by SAEs in the *Hepatobiliary disorders* SOC (1.3% vs. 0.3% for liraglutide 3 mg and placebo, respectively), which was largely the result of gallbladder disorders, and in the *Neoplasms benign, malignant, and unspecified* SOC (0.8% vs. 0.4%). These, as well as other imbalances noted, will be explored further below. In the 120-day safety update, it was reported that a total of 85 (7.8%) liraglutide-treated patients and 34 (6.8%) placebo-treated patients had experienced at least one SAE in the ongoing phase of trial 1839.

Adverse Events Leading to Discontinuation

In the weight management pool, the percentage of patients who discontinued study drug as a result of AEs was higher in those randomized to liraglutide 3 mg than placebo (9.8% vs. 4.3%). The majority of discontinuations of liraglutide 3 mg as a result of AEs typically occurred during the initial ~8 weeks of treatment. The most common category of AEs leading to discontinuation was *Gastrointestinal disorders* (6.2% vs. 0.8% for liraglutide 3 mg and placebo, respectively), with the most common AEs being nausea (2.9%), vomiting (1.7%), and diarrhea (1.4%). Other AEs that more frequently led to discontinuation of liraglutide 3 mg than placebo were fatigue, asthenia, headache, dizziness, neoplasms, and increased lipase. Six patients treated with liraglutide 3 mg, and none treated with placebo, discontinued drug because of acute pancreatitis. One patient treated with liraglutide 3 mg and two treated with placebo discontinued as a result of psychiatric disorders. These safety concerns are discussed further below.

Common Adverse Events

The most common adverse events observed with liraglutide 3 mg in the weight management pool were nausea, diarrhea, constipation, vomiting, hypoglycemia, and decreased appetite. The majority of the gastrointestinal disorders were mild or moderate in severity, but the proportion of patients reporting severe gastrointestinal events was higher in patients treated with liraglutide 3 mg than placebo (4.8% vs. 1.4%). Discontinuation of study drug as a result of these disorders mainly occurred within the first 2-3 months of the treatment period. Among liraglutide-treated patients, nausea and vomiting occurred in 40% and 15%, respectively; among placebo-treated patients, 14% and 4%. In trials 1807 and 1922, in which more than one liraglutide dose was investigated, nausea/vomiting appeared dose-related. Dr. Golden points out that nausea and vomiting were reported with similar frequency in patients regardless of whether they achieved ≥5% weight loss, suggesting that weight loss was not entirely a result of these symptoms.

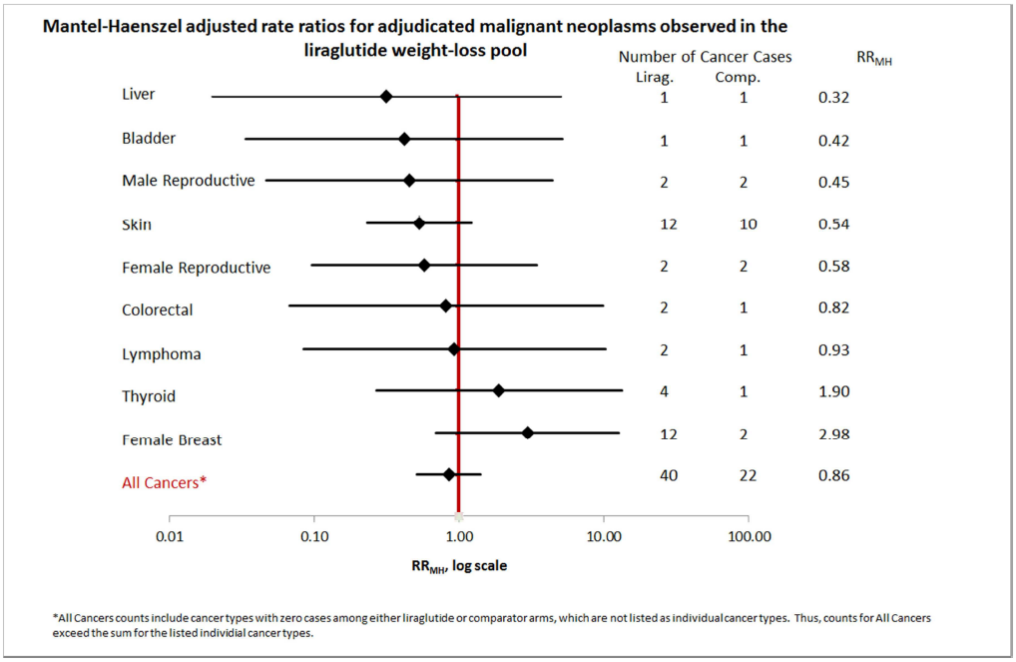
Selected Safety Topics

Neoplasms

After the completion of the first phase 3 trial (1923), prospective adjudication of neoplasms was implemented for the remaining three phase 3 trials. Neoplasms from trial 1923 were adjudicated *post hoc*, and neoplasms from the phase 2 trial (1807) were not adjudicated. In her review, Dr. Golden describes the sources of events sent for adjudication by the external adjudication committee (EAC) as well as the EAC procedures. Of all neoplasm events sent for adjudication, the EAC confirmed 29% of events in the liraglutide group and 22% in the placebo group. Dr. Golden noted that a limitation of MedDRA coding became evident when evaluating the data for neoplasms in non-adjudicated trials (i.e., trial 1807 or any of the trials in the diabetes pool): the MedDRA categories of neoplasms "malignant and unspecified" included both benign (i.e., "unspecified") as well as malignant neoplasms. In my summary that follows, I will focus on the adjudicated results. See Dr. Golden's review for additional analyses.

In addition to the discussion of neoplasms in Dr. Golden's clinical review, Dr. Hampp (Division of Epidemiology) reviewed cancer incidence rates in the liraglutide clinical development program, including both internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates.[9] He presents data for three clinical trial pools: weight management (with an additional subset that only included the 4 of 5 trials that adjudicated potential events of neoplasm), a diabetes pool from the Victoza program (25 clinical trials), and the combination of the weight management and diabetes trials (30 clinical trials). Selected results from Dr. Hampp's review of specific cancers are presented in the subsections below. Here, however, I will note that liraglutide was not associated with an increased risk for all adjudicated malignant cancers combined, but the upper bound of the 95% CI was a 42% increased risk as shown in the figure below, excerpted from Dr. Hampp's review. (This analysis included the 4 of 5 weight management trials that employed adjudication.)

Figure 1. Mantel-Haenszel-Adjusted Rate Ratios for Adjudicated Malignant Neoplasms Observed in the Liraglutide Weight Management Pool



Across the liraglutide trials in the weight management and diabetes pool combined, 202 "malignant and unspecified neoplasms" were reported among patients exposed to liraglutide and 61 among patients exposed to comparators (RR_{MH} 1.16; 95% CI, 0.86-1.57). It should be noted that events reported as "thyroid nodule" would be considered "thyroid neoplasms" in MedDRA-based analyses.

Thyroid

The potential risk for MTC was a major focus of the initial review of Victoza based on the dose-dependent and treatment-duration-dependent increase in thyroid C-cell tumors, in both rats and mice, in two-year carcinogenicity studies (see Carcinogenicity, p. 4). During the review of Saxenda, this risk

[9] For external comparisons, Dr. Hampp compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data from the Surveillance, Epidemiology, and End Results (SEER) database. Dr. Hampp discusses several limitations of making these external comparisons; I agree that they should be interpreted with caution.

remained a major focus of the safety review and was evaluated using information from clinical trials as well as post-marketing data streams.

In the weight management program, if a patient underwent a thyroidectomy for any reason, the pathology was centrally reviewed in addition to the routine local examination; the EAC reviewed both reports. The central pathologist, with expertise in thyroid and C-cell pathology, was blinded to trial treatment and diagnosis by the local site.

There have been no cases of MTC among liraglutide-treated patients in the clinical trials for weight management. All thyroid neoplasms in liraglutide-treated patients were of papillary or follicular origin, which are pathophysiologically distinct from MTC. Four (0.1%) of 3291 patients treated with liraglutide 3 mg were diagnosed with a malignant (3) or pre-malignant (1) thyroid neoplasm during the main period of the phase 3 weight management trials. The pre-malignant case was the single adverse event of C-cell hyperplasia reported in a liraglutide-treated patient (with papillary microcarcinoma), and this was adjudicated to have an onset date prior to baseline. A single thyroid neoplasm, which was a case of MTC, was reported among the 1843 patients treated with placebo. In addition, two liraglutide-treated patients were diagnosed with pre-malignant thyroid neoplasm (papillary microcarcinoma) after withdrawal of therapy, and one liraglutide-treated patient has been diagnosed with a 3-mm papillary microcarcinoma in the ongoing extension of trial 1839. See Dr. Golden's review for further descriptions of these cases.

In Dr. Hampp's analyses, Mantel-Haenszel-adjusted rate ratios for thyroid neoplasms were largely consistent across the various pools of trials but did not reach statistical significance, especially in the adjudicated weight management trials (RR_{MH} 1.90; 95% CI, 0.27-13.35), an analysis that only included 4 events among liraglutide-treated patients and 1 event (of MTC) in a placebo-treated patient as described above.[10] The non-adjudicated MedDRA-based analysis using the pool of weight management and diabetes trials combined yielded a RR_{MH} 2.00 (95% CI, 1.02-3.91).

Calcitonin was measured at screening and at regular intervals during the phase 2 and 3 clinical trials. Dr. Golden notes that calcitonin values exceeding 30 to 50 ng/L increase the likelihood of MTC, and values exceeding 100 ng/L are highly predictive. Using data from trials 1807, 1839, and 1922, there did not appear to be a clear exposure-response relationship between liraglutide AUC and change in calcitonin levels from baseline. The proportions of patients with calcitonin concentrations ≥20 ng/L at the end of trial (or last measured) were 0.5% and 0.2% in the liraglutide 3 mg and placebo groups, respectively. None of the liraglutide-treated patients with elevated calcitonin levels, with onset at any time during treatment, had EAC-confirmed C-cell hyperplasia or MTC.

During this NDA review, the post-marketing experience related to MTC was reviewed. Since the approval of Victoza on 25 January 2010, the Agency has received 13 case reports of MTC in liraglutide-treated patients as of 20 October 2014. These cases were reviewed by Dr. Marina Zemskova, a medical officer and thyroid expert in our Division; refer to her review and presentation at the 11 September 2014 EMDAC meeting for full details. Briefly, of the 10 cases that reported duration of liraglutide exposure, 6 had exposure <12 months and the remaining 4 had exposure ranging from 18 to 43 months. For 4 of the 13 cases, no clinical information other than a diagnosis of MTC and duration of exposure was available; thus, Dr. Zemskova focused on the 9 cases with clinical information. Her review lists the demographics, exposure information, reason for workup, information regarding the method and results of MTC diagnostic testing, and surgical pathology when available. Dr. Zemskova notes that the

[10] The four events among liraglutide-treated patients comprised the three malignant events mentioned in the preceding paragraph and the one papillary microcarcinoma in the ongoing extension of trial 1839.

"causality assessment between MTC and liraglutide is complicated by low number of reported cases and relatively short duration of exposure prior to diagnosis. Clinical presentation of MTC in the reported cases appears to be consistent with what is expected in the general population. Lastly, important clinical information such as baseline assessment for thyroid disorder, family and past medical history, RET genetic testing and staging information is missing from all case reports. Thus, no firm conclusion regarding causal relationship of MTC with liraglutide can be drawn from these cases."

Taken together, given the strong nonclinical signal for thyroid C-cell tumors, I remain concerned about the possibility that liraglutide could contribute to MTC in humans. Given the relatively short time since approval of Victoza, I would not expect to have seen a particularly strong signal of MTC in the post-marketing setting at this time. Providers and their patients should be informed of this risk so that they may make individualized decisions regarding the benefit/risk of using liraglutide chronically for weight management, and this conversation should continue during therapy as the patient's weight is re-evaluated over time. Saxenda will be approved with a REMS to ensure that the benefits of the drug outweigh the potential risk of MTC, as well as the risk of acute pancreatitis (discussed below). The REMS consists of a communication plan and a timetable for submission of assessments.

Breast

In the phase 3 weight management program, EAC-confirmed breast neoplasms occurred in 12 (0.5%) of 2379 women assigned to liraglutide 3 mg compared with 3 (0.2%) of 1300 women assigned to placebo. Among the 12 cases in the liraglutide group, 9 were malignant and 3 were pre-malignant (ductal carcinoma *in situ*); among the 3 cases in the placebo group, 2 were malignant and 1 was pre-malignant. These cases were reviewed by the Division of Oncology Drug Products 1, and the reviewer noted that "[t]here is nothing in the case narratives to support or deny a role of liraglutide in the promotion or progression of breast cancer." It was also noted that there was no distinct pattern in the timing of the events or an association of the events with baseline BMI. In the 120-day safety update, two additional EAC-confirmed malignant breast neoplasms were reported in the ongoing extension of trial 1839, both in liraglutide-treated patients.

In Dr. Hampp's analysis, the Mantel-Haenszel rate ratio for female breast cancer (excluding *in situ*) in the adjudicated weight management trials was 2.98 (95% CI, 0.69-12.81). The non-adjudicated MedDRA-based analysis using the pool of weight management and diabetes trials combined yielded a RR_{MH} 2.01 (95% CI, 0.69-5.89).

The potential risk for breast cancer received considerable attention by the EMDAC at the 11 September 2014 meeting. In fact, the single member who voted against approval was an oncologist who stated that currently there is not enough information to mitigate the risks of malignancy and that the sponsor should look at placebo-controlled arms in the studies already conducted to determine whether or not there was lead-time bias as it relates to malignancies and that FDA should address high-risk populations (e.g., women with BRCA mutations or with a personal history of breast cancer) in the label. Following the meeting, the review team sought any additional evidence for imbalances in breast cancer in the clinical reviews of other approved GLP-1 agonists that may have supported a class effect; no similar imbalances were identified. Furthermore, on 19 September 2014, the Division requested an additional update regarding the incidence of breast cancer in the ongoing trial 1839 as well as a blinded tabulation of cases from the ongoing cardiovascular outcomes trial for Victoza (LEADER). With the caveat that both trials are ongoing, neither provided additional data that heightened a concern for breast cancer at this time. (b) (4)

Considering all available data at the present time, I agree with the review team that this imbalance in breast cancer events should be labeled in Adverse Reactions but does not rise to the level of a Warning and Precaution at this time. Further evaluation of this risk through ongoing clinical trials will be the basis for two post-marketing requirements.

Pancreas

Pancreatic safety, comprising both pancreatitis and pancreatic cancer, is an ongoing focus of interest for incretin mimetics, including liraglutide.[11] There have been no reports of exocrine pancreatic cancer from the weight management program to date.[12]

Colorectum

In the phase 3 clinical trials for weight management, 2 (0.06%) of 3291 patients treated with liraglutide 3 mg and none of the 1843 patients treated with placebo had EAC-confirmed colorectal cancers. One was a rectal adenocarcinoma with onset on day 274 in a 67-y/o man who had a family history of colon carcinoma, cervical carcinoma, gastric carcinoma, and bladder carcinoma; the other case was a Stage III malignant colon carcinoma with onset on day 168 in a 37-y/o woman who reportedly had anemia and rectal bleeding at the start of the trial. In addition to these malignant cases, 17 (0.5%) and 4 (0.2%) of liraglutide- and placebo-treated patients, respectively, were confirmed to have benign colorectal neoplasms (mostly colon adenomas).

Gallbladder Events

Gallstone disease was pre-defined as a medical event of special interest (MESI) in the weight management program. Events were identified by MedDRA search and were not adjudicated. Dr. Golden notes that in the weight management pool, the proportion of patients with "acute gallstone disease" was consistently higher with liraglutide 3 mg than placebo (2.3% vs. 0.9%, or 31 vs. 12 events per 1000 PY), based on a predefined SMQ search. This imbalance was largely the result of AEs that fell under the MedDRA HLGT *Gallbladder disorders* (2.1% vs. 0.7%), comprising cholelithiasis (1.5% vs. 0.5%), acute cholecystitis (0.4% vs. 0.1%), cholecystitis, gallbladder disorder, and chronic cholecystitis. Notably, 19 of 22 events of treatment-emergent cholecystitis reported in liraglutide-treated patients required cholecystectomy.

None of the events of acute gallstone disease were fatal, although the reported events were more likely to be SAEs in liraglutide-treated patients (53% vs. 30% were SAEs in the liraglutide 3 mg and placebo groups, respectively). Seven (0.2%) patients treated with liraglutide, and none of the patients treated with placebo, discontinued drug therapy because of these acute gallstone disease events.

As Dr. Golden points out, obesity and rapid weight loss are associated with an increased risk for gallstone formation. She notes, however, that these events were more common among patients treated with liraglutide 3 mg than placebo even when stratified by degree of weight loss observed while on study drug.[13] Although this is an exploratory analysis across subgroups defined by post-randomization criteria (i.e., weight loss), and therefore not randomized comparisons, the possibility exists that liraglutide promotes gallbladder-related events independent of its effect on weight. A study to

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[11] Egan AG, *et al.* Pancreatic safety of incretin-based drugs – FDA and EMA assessment. *N Engl J Med* 2014; 370(9):794-7.

[12] One case of a neuroendocrine tumor of the pancreas, later determined to be part of the genetic syndrome MEN1, was reported for a patient treated with liraglutide 3 mg in trial 1839.

[13] See Table 72 on p. 146 of her review.

characterize the effect of liraglutide on gallbladder motility will be the subject of a post-marketing commitment.

Pancreatitis

Post-marketing reports of acute pancreatitis with GLP-1 receptor agonists and DPP-4 inhibitors, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, have led to warnings regarding pancreatitis in drug labeling. Furthermore, Victoza is approved with a REMS communication plan that includes informing prescribers about the risk for pancreatitis. In the weight management program, all suspected cases of pancreatitis were prospectively adjudicated by an external event adjudication committee (EAC) in trials 1839, 1922, and 3970; suspected cases in trial 1923 were adjudicated *post hoc*, and events of pancreatitis were considered MESI in year 2 of the phase 2 trial 1807 but were not adjudicated. In her review, Dr. Golden describes how potential cases were identified by predefined MedDRA searches in an attempt to capture events that were not reported by investigators.

In the main treatment periods of the phase 3 weight management trials, 7 (0.2%) of 3291 patients assigned to liraglutide 3 mg had EAC-confirmed acute pancreatitis compared with 1 (0.05%) of 1843 patients assigned to placebo.[14] All seven cases occurred in trial 1839. Dr. Golden notes that this 4:1 imbalance is similar to the 4:1 imbalance observed by AE monitoring in the Victoza pre-approval trials. Furthermore, of the 7 cases in the liraglutide group, 5 were SAEs; the 1 event in the placebo group was reported as mild in severity and not an SAE. Four of the seven events in the liraglutide group occurred within the first two months of exposure, and the remaining three occurred after more than nine months. The confirmed event in the placebo group occurred after more than nine months of exposure. Two of the liraglutide cases and the single placebo case were associated with cholelithiasis.

Taken together, these observations are consistent with an association between liraglutide and acute pancreatitis. As mentioned previously, this risk will be mitigated through a REMS as well as product labeling.

Cardiovascular Safety

Major Adverse Cardiovascular Events

In March 2012, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss and vote on how CV risk should be assessed for drugs being developed for obesity, a topic stimulated by the withdrawal of sibutramine from the U.S. market and by the approach taken with antidiabetic drugs in the 2008 FDA Guidance for Industry, *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The EMDAC voted 17 to 6 to require pre-approval assessments to exclude some degree of CV risk for all drugs being developed for chronic weight management, even in the absence of a CV signal or theoretical risk.

The Victoza development program had been completed prior to the publication of the 2008 guidance referenced above; however, a meta-analysis using a customized set of MedDRA preferred terms for an assessment of major adverse cardiovascular events (MACE) ruled out an upper bound of the 95% CI of the HR of 1.8. A cardiovascular outcomes trial, LEADER, is being conducted with Victoza as a post-marketing requirement to rule out an upper bound of 1.3.

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[14] In addition, there were 2 confirmed cases of acute pancreatitis in the ongoing extension of trial 1839 (both in the liraglutide arm), yielding a total of 9 (0.3%) vs. 1 (0.05%) for liraglutide and placebo, respectively.

For the Saxenda development program, prospective adjudication of MACE was implemented for trials 1839, 1922, and 3270; a similar adjudication process was established for trial 1923, which was ongoing at the time prospective adjudication was implemented in the other trials. Furthermore, *post hoc* adjudication was conducted for all completed Victoza trials, the phase 2 trial 1807, and a semaglutide phase 2 dose-finding trial.[15]

Dr. Zhang has reviewed the meta-analysis conducted by the applicant to investigate the effect of treatment with liraglutide for weight management compared with a pooled comparator group (placebo and active comparators) on CV safety. Per prior agreement, there was no pre-specified risk margin. The primary endpoint was MACE (CV death, nonfatal MI, nonfatal stroke), and the primary CV meta-analysis was performed using an on-treatment population, which included all subjects who received at least one dose of study drug and which included events occurring up to 30 days after the last dose of study drug. The primary analysis included 5908 subjects (3872 liraglutide; 2036 comparator, which included 1941 placebo and 95 orlistat). There were only 17 MACE confirmed by the EAC: 8 (0.2%) in the liraglutide group and 9 (0.4%) in the comparator group. The on-treatment estimated HR had an upper bound of the 95% CI of 1.05. Inclusion of two more events identified in the liraglutide group during the off-drug periods in trials 1839 and 1922 (i.e., an "on-study" analysis) resulted in an upper bound of 1.23. Other sensitivity analyses were consistent with the primary analysis. The following table, excerpted from Dr. Zhang's review (p. 20), shows the breakdown of the type of events that contributed to the MACE composite, by trial and arm.

Table 8: Summary of first MACE by trial, treatment group, and type of events in the WM primary analysis.

Trial		N	MACE n(%)	non-fatal MI n(%)	non-fatal Stroke n(%)	CV death n(%)
NN8022-1807	Liraglutide	371	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Comparator	193	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NN8022-1839	Liraglutide	2481	3(0.1)	2(0.1)	0(0.0)	1(<0.1)
	Comparator	1242	3(0.2)	1(0.1)	1(0.1)	1(0.1)
NN8022-1922	Liraglutide	632	5(0.8)	3(0.5)	2(0.3)	0(0.0)
	Comparator	212	3(1.4)	2(0.9)	1(0.5)	0(0.0)
NN8022-1923	Liraglutide	212	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Comparator	210	1(0.5)	0(0.0)	0(0.0)	1(0.5)
NN8022-3970	Liraglutide	176	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Comparator	179	2(1.1)	2(1.1)	0(0.0)	0(0.0)
Overall	**Liraglutide**	**3872**	**8(0.2)**	**5(0.1)**	**2(0.1)**	**1(<0.1)**
	Comparator	**2036**	**9(0.4)**	**5(0.2)**	**2(0.1)**	**2(0.1)**

Source: created by the reviewer using dataset "mace.xpt".

In addition, a meta-analysis of 20 T2DM trials was conducted, which included 8233 subjects (5498 liraglutide and 2735 comparator) and a total of 49 confirmed MACE. The results were consistent with the weight management analysis (the upper bound of the 95% CI for the estimated HR for MACE was 1.15).

Dr. Zhang concludes that there is no apparent increase in CV risk identified in the liraglutide group versus the comparator. Limitations, however, include the small number of confirmed MACE and the relatively short exposure times, limiting the ability to extrapolate the results beyond one year of

[15] Adjudication was external, independent, and blinded to treatment allocation.

treatment. Furthermore, subjects enrolled in the weight management trials that contributed to this analysis may be at lower risk for CV disease than many who will use Saxenda when approved.[16]

Other Cardiovascular Considerations

In her review, Dr. Golden devotes considerable attention to effects of liraglutide on heart rate and also explores arrhythmias, hypotension, and heart failure. I will focus on the effects on heart rate here; refer to her review for discussions of the other topics.

Regarding heart rate, Victoza labeling notes that mean increases from baseline of 2 to 3 bpm were observed with liraglutide compared with placebo in the diabetes program. Given that a higher dose of liraglutide is under consideration for weight management, Dr. Golden sought data that may inform whether there is a dose-response with respect to heart rate. She noted that in a clinical pharmacology trial that used 24-hour continuous heart rate monitoring, both liraglutide 1.8 mg and 3 mg were associated with an increase in mean heart rate of 6 to 7 bpm, averaged over the entire 24-hr period, compared with placebo. The increase was more pronounced during the night than during the day. Supportive of this effect, in trial 3970 (obstructive sleep apnea), polysomnography demonstrated that liraglutide 3 mg attenuated the noctural decline in heart rate observed in the placebo group.

In the weight management clinical trials, resting heart rate increased within the first 2 weeks of treatment and remained consistently higher than placebo throughout the trial duration; the estimated treatment difference between liraglutide 3 mg and placebo at the end of treatment was 2.5 bpm (95% CI, 2.0 to 3.0). Results derived from ECG data were similar. Increases in heart rate occurred whether or not a patient lost at least 5% of body weight. Various categorical analyses related to heart rate consistently demonstrated a difference between liraglutide and placebo (see Table 117 of Dr. Golden's review, pp. 218-9); for example, in the weight management pool, the proportions of patients with a heart rate increase from baseline >10 bpm at ≥2 consecutive visits were 34.0% and 19.1% for the liraglutide 3 mg and placebo groups, respectively; the proportions with an increase >20 bpm at ≥2 consecutive visits were 4.9% and 1.7%, respectively. In trials that investigated both liraglutide 1.8 mg and 3 mg, Dr. Golden shows that there was no clear indication of a dose-response with respect to heart rate measured at trial visits, which was supported by a lack of an exposure-response relationship based on population PK samples from trials 1839, 1922, and 1807. Last, given that modest reductions in blood pressure have been observed with liraglutide treatment, it should be noted that the rate-pressure product was higher in the liraglutide group than the placebo group in the weight management trials.[17]

There is an ongoing cardiovascular outcomes trial that is a PMR for Victoza (NDA 22341; PMR 1583-9) to evaluate the effect of Victoza on the incidence of MACE in patients with T2DM. This trial will randomize approximately 9000 patients with T2DM who have known vascular disease or other equivalents of high CV risk. Although this trial will study a maximum dosage of liraglutide 1.8 mg per day and will not enroll non-diabetic patients with obesity, it is expected that its results will inform the CV risk of Saxenda. If an adverse effect on MACE is observed, it would certainly cause concern for Saxenda as well. In contrast, if the results exclude an increased risk of MACE ≥30% (i.e., upper bound of the 95% CI for the HR of liraglutide vs. placebo is <1.3), it will then be a subject of review whether there is any suggestion that the overall result may not apply to patients treated with Saxenda. Although there will be limitations with such analyses, the lack of a clear dose- or exposure-response

[16] In the weight management meta-analysis overall, the mean age was 47 years, 71% were women, 14% had diabetes, 14% were current smokers, 39% had hypertension, and only 9% had a history of CV disease at baseline.

[17] The rate-pressure product is the product of heart rate and systolic blood pressure (bpm*mmHg), serving as an estimate of myocardial oxygen demand.

between 1.8 mg and 3.0 mg with regard to heart rate as well as the fact that this trial is well underway justify awaiting its results instead of requiring a new cardiovascular outcome trial for Saxenda at the time of approval. The EMDAC discussed this topic at the 11 September 2014 meeting and generally concurred with this approach.

Hypoglycemia

Liraglutide lowers fasting and postprandial glucose in a glucose-dependent manner. In the weight management programs, patients without T2DM were not provided with glucometers or hypoglycemia diaries, and hypoglycemic symptoms were not systematically recorded. Routine fasting plasma glucose (FPG) measurements ≤70 mg/dL were to be reported as "hypoglycemia" AEs regardless of symptoms,[18] as was "hypoglycemia" (definition not specified) during oral glucose tolerance tests (OGTT) conducted in trials 1807 and 1839; I find neither of these particularly clinically informative.[19] Adverse events of "hypoglycemia" reported outside FPG and OGTT visits were referred to as "spontaneously reported hypoglycemia," which were not confirmed by glucose measurements since patients did not have glucometers. These events occurred in 46 (1.6%) of 2962 patients treated with liraglutide 3 mg and in 19 (1.1%) of 1729 patients treated with placebo. None of these events fulfilled the American Diabetes Association (ADA) criteria of a severe hypoglycemic episode (i.e., requiring third-party assistance).

In patients with T2DM (trial 1922), there was systematic collection of hypoglycemic symptoms and concomitant glucose data via provided glucometers. The following table, excerpted from Dr. Golden's review, summarizes the hypoglycemic episodes by classification in this trial.

Table 133. Hypoglycemic Episodes by Classification, Trial 1922

	Lira 3 mg N=422 PY=379.86		Lira 1.8 mg N=210 PY=189.70		Placebo N=212 PY=179.71	
	n (%)	Events / 100 PY	n (%)	Events / 100 PY	n (%)	Events / 100 PY
ADA	188 (44.5)	259	83 (39.5)	257	58 (27.4)	82
Severe	3 (0.7)	1	2 (1.0)	2	0	0
Documented symptomatic	97 (23.0)	87	47 (22.4)	95	27 (12.7)	31
Asymptomatic	136 (32.2)	151	52 (24.8)	142	35 (16.5)	46
Probable symptomatic	6 (1.4)	2	4 (1.9)	2	1 (0.5)	1
Relative	27 (6.4)	17	14 (6.7)	16	7 (3.3)	5
Sponsor: 'Minor'	58 (13.7)	34	34 (16.2)	46	14 (6.6)	13

Source: ISS, Table 2-24
Severe: hypoglycemia that requires third-party assistance
Documented symptomatic: symptoms of hypoglycemia + plasma glucose ≤70 mg/dL
Asymptomatic: plasma glucose ≤70 mg/dL without symptoms of hypoglycemia
Probable symptomatic hypoglycemia: symptoms of hypoglycemia with no glucose measurement
Relative hypoglycemia: symptoms of hypoglycemia + plasma glucose >70 mg/dL

[18] FPG ≤70 mg/dL occurred at routine clinic visits in 3.1% and 0.8% of non-diabetic patients treated with liraglutide 3 mg and placebo, respectively.

[19] A laboratory glucose of ≤70 mg/dL after an overnight fast is not concerning unless it is accompanied by signs and symptoms of hypoglycemia (particularly those consistent with neuroglycopenia). Healthy individuals on no medications could have FPG in that range as a result of prolonged fasting, and this would not be considered adverse or worrisome. Glucose values post-OGTT are unreliable because they usually represent an artifact of the procedure (i.e., venous rather than arterial glucose concentration is measured in the non-fasting state).

Sponsor's "Minor": plasma glucose <56 mg/dL (or blood glucose <50 mg/dL), with or without symptoms, which the patient can handle themselves

A total of 8 severe hypoglycemic episodes were reported by 5 patients, all of whom were assigned to liraglutide, and all of whom were also taking a sulfonylurea. None of these events were reported as SAEs, and all patients with severe hypoglycemic episodes continued on liraglutide without dose interruption or adjustment. Documented symptomatic hypoglycemia also occurred more frequently among patients treated with liraglutide than placebo, as shown in the table above. Note, however, that there was not a convincing dose-related relationship between liraglutide 1.8 mg and 3 mg with respect to the most clinically significant hypoglycemic events.

Dr. Golden notes that at screening in trial 1922, patients treated with a sulfonylurea (either as monotherapy or in combination with other oral anti-diabetic drugs) were required to reduce their sulfonylurea dose by ~50% in order to prevent potential hypoglycemia induced by the combination of a sulfonylurea and liraglutide ± weight loss. Because of these protocol-imposed changes in concomitant medications, it is likely that hypoglycemia will be more common in clinical practice than observed in clinical trials. Labeling for Saxenda will convey a warning regarding the risk for hypoglycemia with concomitant use of antidiabetic therapy and suggest that prescribers consider dose reductions of concomitant insulin secretagogues. Patients taking insulin have not been studied.

Psychiatric Events

Consistent with FDA recommendations for centrally acting obesity drugs, the weight management program included assessments of depression and suicidal ideation/behavior using the PHQ-9 and C-SSRS questionnaires. Dr. Golden reviewed the questionnaire data as well as adverse events identified using a predefined psychiatric SMQ. Dr. Golden identified suicidal ideation reported by 6 (0.2%) of 3384 patients treated with liraglutide 3 mg (including the extension phase of trial 1839) compared with no patients treated with placebo. One of the liraglutide patients, who had a history of depression, reported a suicide attempt on day (b) (6) of treatment. Dr. Golden recommends that this risk warrants inclusion in the Warnings and Precautions section of labeling, and psychiatric adverse events should be followed in the post-marketing setting and ongoing trials. I agree with her recommendation.

Liver Events and Related Laboratory Data

There have been no cases of Hy's law or fulminant hepatic failure identified in any clinical study in the liraglutide development program. In the weight management pool, at least one post-baseline ALT ≥10x ULN was recorded during the main treatment period for 5 (0.1%) of 3384 patients treated with liraglutide 3 mg and 1 (0.05%) of 1941 patients treated with placebo. Of these, 2 (0.06%) of the liraglutide-treated patients had a peak ALT ≥20x ULN. Dr. Golden reviewed the narratives of all liraglutide-treated patients with any recorded ALT ≥10x ULN. Most cases had confounding features, such as baseline abnormalities, cholelithiasis, or other medications that could have contributed. Adverse events related to *Hepatobiliary investigations* were reported for 1.4% and 1.2% of patients treated with liraglutide 3 mg and placebo, respectively, with most being increases in ALT and/or AST. Dr. Golden notes that analyses of central tendency show that mean decreases in ALT and AST among liraglutide-treated patients, compared with placebo-treated patients, were observed during the trials and/or at the end of the trials.

Liver-related adverse events did not undergo adjudication in the weight management program. The most common preferred term reported in the *Hepatic and hepatobiliary disorders* HLGT was "hepatic steatosis," which was reported more frequently in the placebo group (0.4% vs. 0.7% for liraglutide 3 mg and placebo, respectively). There were two SAEs of "hepatitis," both in patients randomized to

liraglutide in trial 1839. One patient had multiple comorbidities with several confounding features, and the other was in the setting of acute pancreatitis. Last, Dr. Golden reviewed one recently published case report that described a potential case of autoimmune hepatitis in a patient receiving Victoza;[20] she concluded that "[i]t does not appear that the pathology, serology, or clinical course to date definitively rules in or rules out the potential for an autoimmune and/or liraglutide-mediated etiology." The Division of Pharmacovigilance I evaluated this case as well, including consultation with an OSE hepatologist, and concluded that the cause of liver injury in this patient remains in question.

Renal Events and Related Laboratory Data

As stated in Victoza labeling, cases of acute kidney injury and worsening of chronic kidney disease have been reported in the post-marketing setting, sometimes requiring hemodialysis. A majority of the reported events have occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In the weight management program, events of acute renal failure were identified using a pre-specified MedDRA search: 18 (0.5%) of 3384 patients treated with liraglutide 3 mg compared with 8 (0.4%) of 1941 treated with placebo. There was one "renal failure acute" event that was an SAE in a 64-y/o woman with chronic kidney disease, cardiomegaly, and pulmonary hypertension who developed worsening renal function on day 49 in the setting of nausea, vomiting, and diarrhea while also taking an ACE inhibitor and thiazide diuretic; she reportedly recovered after withholding study drug for 6 days and receiving intravenous fluids.

At least one serum creatinine value ≥1.5x baseline was recorded for 1.2% and 1.6% of patients treated with liraglutide 3 mg and placebo, respectively. The corresponding percentages of patients with at least one serum creatinine value ≥0.3 mg/dL above baseline were 3.0% and 2.5%. In her review (Figure 48), Dr. Golden shows that at 6 months, 1 year, and end of trial (LOCF), the mean change from baseline in CKD-EPI eGFR is slightly higher for liraglutide 3 mg than placebo. Taken together, these data do not suggest a renal safety signal, but prescribers should be warned about the possibility of renal impairment given the gastrointestinal adverse effects and the prevalent use of concomitant medications that impair GFR autoregulation (e.g., ACE inhibitors) in this population.

Pregnancy

At the time of the July 2013 data cut-off, 46 women had become pregnant in the completed weight management trials: 31 (1.1%) of 2763 women in the liraglutide group and 15 (1.1%) of 1374 women in the placebo group. The mean exposure following conception was approximately 1 month in both treatment groups. Of these women, 21 gave birth (15 liraglutide, 6 placebo) to healthy babies without congenital abnormalities. Spontaneous abortion was reported more frequently among liraglutide-treated women (9 [29%] vs. 2 [13%] for liraglutide and placebo, respectively), and elective abortions were reported more frequently among placebo-treated women (4 [13%] vs, 3 [20%]). In the extension phase of trial 1839, as of 14 Mar 2014, there have been 14 pregnancies: among 9 in the liraglutide group, outcomes have included 3 healthy babies, 1 spontaneous abortion, 1 miscarriage of partner (male patient treated with liraglutide), and 4 await follow-up. Among the 5 pregnancies in the placebo group, outcomes have included 1 healthy baby, 1 ectopic pregnancy, 1 lost to follow-up, and 2 awaiting follow-up. Although Victoza is pregnancy category C, Saxenda will be pregnancy category X – similar to other drugs approved for chronic weight management – because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm.

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[20] Kern E, *et al*. Liraglutide-induced autoimmune hepatitis. *JAMA Intern Med* 2014; 174(6):984-7.

Assessment of Abuse Potential

In an advice letter dated 14 September 2012, the Controlled Substance Staff agreed that studies to evaluate the abuse potential of liraglutide would not be required to support an NDA for a weight management indication based on nonclinical information submitted to Victoza NDA 22341 and the clinical and nonclinical rationale provided by the applicant. Dr. Golden did not identify any events related to abuse, dependence, or misuse. Furthermore, she detected no evidence of withdrawal or rebound symptoms during the randomized withdrawal portion of trial 1839.

8. ADVISORY COMMITTEE MEETING

The efficacy and safety of Saxenda for chronic weight management were discussed at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on 11 September 2014. Dr. Golden summarized the discussion in her review, and the meeting minutes/transcript will be available at www.fda.gov. I will note that the committee agreed that there remains concern about whether liraglutide promotes MTC, and there was considerable discussion regarding whether liraglutide may promote breast cancer. Both of these safety concerns will be labeled as well as evaluated further in post-marketing requirements. Regarding cardiovascular safety, the committee generally agreed that the ongoing CV outcomes trial to assess the CV risk of Victoza in T2DM mellitus (at a maximum dose of 1.8 mg/day) should be sufficient to characterize the CV risk of Saxenda 3 mg/day for weight management, at least initially; analyses of patient subgroups that would be expected to have higher exposures to liraglutide (e.g., women with low body weight) may inform the CV risk of 3 mg/day for weight management.

There was a single voting question: "Considering the currently available data and the proposed Risk Evaluation and Mitigation Strategy (REMS), is the overall benefit-risk assessment of liraglutide 3 mg per day favorable to support its approval for chronic weight management in individuals with a BMI 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity?" Fourteen members voted "yes" and one member voted "no." The member who voted against approval was an oncologist who stated that currently there is not enough information to mitigate the risks of malignancy and that the sponsor should look at placebo-controlled arms in the studies already conducted to determine whether or not there was lead-time bias as it relates to malignancies, and FDA should address high-risk populations in the label. Following the meeting, the review team discussed these recommendations at length and obtained additional data from ongoing clinical trials with liraglutide as discussed previously. Ultimately, the team recommended labeling the potential risks using the currently available data and obtaining additional information through post-marketing requirements. I agree with this approach.

9. PEDIATRICS

In consultation with the Pediatric Review Committee (PeRC), pediatric studies will be waived for ages 0 to 6 years (inclusive) because the necessary studies would be impossible or highly impractical: weight loss is not recommended for children younger than 2 years of age, and weight maintenance, not weight loss, is the clinical goal for obese children 2 to 6 years of age. Pediatric studies for ages 7 to 17 years (inclusive) are deferred because the product is ready for approval for use in adults prior to the pediatric studies being completed. The deferred pediatric studies are required post-marketing studies and will include a juvenile toxicity study with liraglutide treatment from pre-puberty through reproductive maturity; two clinical pharmacology trials to assess PK and PD parameters of Saxenda in obese pediatric patients ages 7 to 11 years and 12 to 17 years; and two 56-week safety/efficacy trials in obese pediatric patients ages 7 to 11 years and 12 to 17 years. The safety/efficacy trial involving

children ages 7 to 11 years will not be initiated until results from the safety/efficacy trial involving adolescents have been submitted to and reviewed by the Agency.

10. OTHER RELEVANT REGULATORY ISSUES

Financial Disclosure

Dr. Golden noted that the applicant adequately disclosed financial interests/arrangements with clinical investigators (p. 28 and pp. 300-304 of clinical review).

Clinical Inspections

Inspections of six clinical sites (five domestic, one foreign) and the sponsor were conducted as part of routine PDUFA pre-approval clinical investigation data validation. Two clinical sites were each issued a Form FDA-483 with preliminary classifications for these inspections as Voluntary Action Indicated (VAI). Although regulatory violations were noted, Dr. Kleppinger believes they are unlikely to significantly impact primary safety and efficacy analyses; therefore, reliability of data from these sites is acceptable to support this application. The other four sites and the sponsor were classified No Action Indicated (NAI). Dr. Kleppinger concluded that the inspectional findings support validity of data as reported by the sponsor under this NDA.

Proprietary Name Review

The Division of Medication Error Prevention and Analysis (DMEPA) has considered the risks and the safety issues involved in potentially having a second name for this active ingredient from the same manufacturer in the marketplace. The options considered included (1) using the name Victoza, (2) using the name Victoza plus a modifier; and (3) using a dual proprietary name. The first option was deemed least viable because the devices themselves are different and the name should convey some distinction as typically done with other combination products available in multiple platforms. The latter two options were both deemed viable, each with some corresponding risks for error that could not be quantified with certainty. DMEPA concluded that since omission of a modifier when a provider writes a prescription is a risk not readily addressed by labeling, the dual proprietary name option may present less risk since thoughtful labeling could warn against the concurrent use of Victoza and Saxenda. Thus, DMEPA and the Office of Prescription Drug Promotion concluded that the proposed proprietary name, Saxenda, is acceptable from a safety and promotional perspective.

11. LABELING

Key aspects of labeling negotiations included:

- A boxed warning will convey the risk for thyroid C-cell tumors based on the strong nonclinical signal.
- The human cases of MTC among liraglutide-treated patients, identified through FAERS during this review cycle, will be mentioned in Section 5.1 (Risk of Thyroid C-cell Tumors), stating that the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.
- Victoza labeling includes a limitation of use that "Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise" as one strategy to mitigate the risk for MTC (i.e., only using this product after first-line glucose-lowering therapies have been determined insufficient for the treatment of T2DM). The Division recognizes that patients with T2DM with overweight or obesity could receive Saxenda for overweight/obesity before they are initiated on drugs indicated for the treatment of T2DM.

This would effectively move liraglutide, at a higher dose than that approved for T2DM, into position as "first-line therapy." The applicant has not, however, evaluated the safety and efficacy of liraglutide 3 mg/day for the treatment of T2DM (i.e., common scenarios for clinical use of this dose have not been characterized adequately). Thus, Saxenda labeling will contain the limitation of use, "Saxenda is not indicated for the treatment of type 2 diabetes mellitus."

- (b) (4) Clinicians simply need to be aware that Saxenda can lower blood glucose so that they can mitigate the risk of hypoglycemia; this information will be conveyed primarily through the Warnings and Precautions and Adverse Reactions sections of labeling.
- Dosage and Administration will include the recommendation, "Evaluate the change in body weight 16 weeks after initiating Saxenda and discontinue Saxenda if the patient has not lost at least 4% of baseline body weight, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment." The recommendation of discontinuing the drug at an early timepoint is consistent with the approach taken with Qsymia, Belviq, and Contrave. Although the Division does not yet have a standardized method to develop such a recommendation, the general approach has been similar: an assessment after 12 weeks at the intended maintenance dose should allow a prescriber to re-evaluate benefit/risk. For this application, Dr. McEvoy binned weight loss at week 16 (i.e., 12 weeks at the 3 mg dose) and determined the proportion in each category who had ≥5% weight loss at week 56. These data were used to derive a recommendation for labeling.
- Efficacy results (i.e., changes in weight) in Section 14 will reflect an ITT approach and will use imputation approaches for missing data that use information observed from the retrieved dropouts. The applicant conducted their own analyses based on the approach taken by Dr. McEvoy. The results that will appear in the approved labeling have been confirmed by Dr. McEvoy.
- I support the inclusion of cumulative frequency distributions in Saxenda labeling.
- Figures of weight loss over time represent all observed values at each visit (b) (4) The clinical and statistical reviewers believe this is more informative (b) (4) I agree.
- (b) (4) will not be included in labeling for the reasons described earlier in this summary review.
- (b) (4) I agree with Dr. Golden and the SEALD reviewer that these data should not be included in Section 14.
- (b) (4) will not appear in Section 14, (b) (4)

12. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

Risk/Benefit Assessment

Approximately one out of every three people in the United States is obese, increasing their risk for multiple weight-related comorbidities, their attendant complications, and death. Only four drugs approved since 1999 are currently on the U.S. market for chronic weight management.

In the Saxenda clinical development program, the drug proved effective for weight loss in trials up to approximately one-year duration. Using the estimates of the treatment effect determined by the FDA statisticians, treatment with liraglutide 3 mg/day reduced fasting body weight 4.6%, on average, compared with placebo in the largest phase 3 trial, which enrolled patients without type 2 diabetes. In the phase 3 trial that enrolled patients with type 2 diabetes and overweight, treatment with liraglutide 3 mg/day reduced fasting body weight 3.4%, on average, compared with placebo. Both effects were highly statistically significant. Although some may argue that these treatment effects seem too modest to declare clinically meaningful, it is notable that among patients without diabetes, the proportions that lost at least 5% body weight by week 56 were 62% and 34% in the liraglutide and placebo groups, respectively; the proportions that lost at least 10% body weight were 34% and 15%, respectively. Among patients with type 2 diabetes, the proportions that lost at least 5% body weight by week 56 were 50% and 20% in the liraglutide 3 mg/day and placebo groups, respectively; the proportions that lost at least 10% body weight were 23% and 7%, respectively. Although an individual patient who successfully loses weight with Saxenda will never know, with certainty, what they would have done during the same time period had they not been treated (and, therefore, whether the risks of treatment were acceptable), the differences in these proportions certainly support the conclusion that Saxenda would promote clinically meaningful (i.e., ≥5-10%) weight loss for a substantial number of patients. Because weight is a measurement followed regularly by patients, and because each patient can elect to discontinue therapy if they do not achieve a degree of weight loss that is meaningful to them, benefit/risk can be readily reevaluated by both patients and their providers over time.

Modest changes in cardiometabolic parameters (e.g., blood pressure, lipid parameters), which are presumed to be salutary, accompanied the weight loss observed with liraglutide. In addition, although I consider the results exploratory, it is reassuring that changes in two of the patient-reported outcomes questions were directionally favorable for domains related to physical functioning, suggesting that the magnitude of weight loss achieved with liraglutide may impact how patients feel or function.

The safety and efficacy of liraglutide 3 mg daily have not been determined for the treatment of T2DM. Data from trial 1922 suggest that the incremental effect of increasing liraglutide 1.8 mg to 3 mg is quite modest; therefore, if the primary benefit one is hoping to achieve for a patient with T2DM is an improvement in glycemic control, the drug of choice should be Victoza at its recommended dosage of 1.8 mg daily. The "benefits" of Saxenda on HbA1c should not be promoted, as its effects on glucose and HbA1c are likely to be largely direct effects rather than indirect effects mediated by weight loss; promotion of liraglutide-induced effects on HbA1c should be reserved for Victoza. It would be inappropriate, for example, to suggest that Saxenda is a more effective drug for weight loss, compared with other drugs approved for the same indication, because it yields greater reductions in HbA1c. Labeling will include a Limitation of Use that Saxenda is not indicated for the treatment of T2DM.

(b) (4)

; safety sections of labeling will provide warnings regarding hypoglycemia and how to mitigate this risk.

It is worth noting that the effects of drug-induced weight loss on "hard" clinical outcomes (e.g., morbidity and mortality) have not been established. Whether weight loss confers cardiovascular benefit, for example, has been called into question to some extent with the results of the Look AHEAD (Action for Health in Diabetes) trial. [21] This was a randomized, controlled trial in which 5145 overweight or obese patients with type 2 diabetes were assigned to participate in either an intensive lifestyle intervention or to receive diabetes support and education for a median follow-up of 9.6 years. The primary outcome was a composite of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for angina. Despite greater weight loss in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end) as well as greater reductions in glycated hemoglobin and initial improvements in fitness and all cardiovascular risk factors (except LDL-C), the trial was stopped early for futility; the HR was 0.95 (95% CI, 0.83-1.09; p=0.51). Although I would not suggest that this trial disproves the benefits of weight loss, its results should provide caution in making assumptions that drug-induced weight loss is certain to confer cardiovascular benefit.

Taken together, I agree with Dr. Golden (as well as the members of the 11 September 2014 EMDAC) that the clinical trials with Saxenda provided substantial evidence of clinically meaningful efficacy with respect to its effect on body weight.

These benefits, however, do not come without risk. The risk for cancer, especially MTC, remains a serious concern. The nonclinical signal for liraglutide-induced thyroid C-cell tumors is strong and dose-dependent, raising a concern that approval of 3 mg daily for weight management could place patients at greater risk than the approval of Victoza 1.8 mg daily. Although MTC was not observed in liraglutide-treated patients in the weight management program, I agree with Dr. Golden that this is not reassuring given the relatively short duration of exposure. The identified post-marketing cases of MTC were presented in detail for the EMDAC members, who generally agreed with the review team that although there were no compelling features of these cases to implicate liraglutide, it is not time to exonerate the drug, either. The risk for MTC will be labeled in a boxed warning and described in Warnings and Precautions, as well as contributing to the basis for a REMS (see below).

A potential increased risk for breast cancer was identified in this application. As discussed in the body of my review, the observed imbalance in breast cancer events in the weight management clinical trials is of uncertain clinical significance at this time. Given the number of comparisons made with respect to potential effects of liraglutide on various cancer types, it is certainly plausible that the imbalance in breast cancer was simply a result of chance. Some have also speculated that ascertainment bias could have contributed to the imbalance. Regardless, this signal warrants special attention in the post-marketing period, and given that this is a common cancer, it will be unlikely that spontaneous reporting will inform us further. After much discussion with the Division of Epidemiology and the Division of Pharmacovigilance I, we have determined that the best data to inform this risk will be obtained from controlled clinical trials. These trials may also better describe the effect of liraglutide on some of the other neoplasms with modest imbalances in the weight management program, such as papillary thyroid cancer and colorectal neoplasms (predominantly benign adenomas to date).

Acute pancreatitis remains a safety concern with Saxenda given both the post-marketing reports with Victoza and the higher incidence of adjudicated acute pancreatitis observed in the weight management trials among patients treated with liraglutide compared with placebo. This risk will also contribute to

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[21] The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369:145-54.

the basis for a REMS. The cause of pancreatitis associated with liraglutide treatment is unknown. In the case of Saxenda, it may also be influenced by the increase in gallstone-related disease associated with liraglutide treatment in patients with overweight/obesity. These risks will be labeled such that patients and providers are aware to be vigilant for early symptoms that could signal underlying pathology.

Liraglutide increases heart rate, although this does not appear to be dose-dependent between 1.8 mg and 3 mg daily. The applicant adjudicated MACE in the weight management and type 2 diabetes programs (prospectively and retrospectively, depending on the trial) and, at present, there is no evidence for an increase in CV risk with liraglutide. This conclusion, however, relies on very few MACE: there were only 17 positively adjudicated MACE in the entire weight management program. The ongoing LEADER trial is assessing the CV risk of liraglutide, albeit at a maximum dose of 1.8 mg daily, in approximately 9000 patients with T2DM at high risk for cardiovascular events. The primary endpoint is time to first occurrence of CV death, nonfatal MI, or nonfatal stroke. The planned duration is at least 3.5 years. Despite the limitations of being conducted in a different population and using a different dose, the EMDAC opined that this trial ought to yield information to help characterize the CV risk of the 3 mg dose for weight management. I agree with their assessment; therefore, we will not require a second CV outcomes trial at this time.

Several other adverse events are associated with liraglutide treatment, although many of the imbalances involved relatively few numbers of events in the weight management program. The experience with Victoza to date helps to inform some of the risks, such as renal impairment, hypersensitivity, and severe hypoglycemia in patients on insulin secretagogues; these will be labeled in Warnings and Precautions. Because of an unfavorable imbalance in the small number of events involving suicidal ideation and behavior, this risk will also be included in Warnings and Precautions; the number and nature of the events were insufficient, however, to rise to the level of a boxed warning or preclude approval.

With adequate labeling, a REMS, and agreement with the applicant regarding several post-marketing requirements, I believe that the benefit/risk balance is favorable for Saxenda as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with obesity or with overweight in the presence of at least one weight-related comorbid condition.

Recommendation for Risk Evaluation and Mitigation Strategies

Victoza has a REMS in place, consisting of a communication plan and a timetable for submission of assessments, which addresses the potential risk for MTC and the risk for acute pancreatitis associated with Victoza. In collaboration with the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Saxenda as well to ensure that the benefits of the drug outweigh (1) the potential risk of MTC identified in nonclinical studies of liraglutide and other GLP-1 receptor agonists; and (2) the risk for acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, identified in the post-marketing reports for liraglutide. As described above, cases of pancreatitis have been described in association with liraglutide 3 mg/day during clinical trials. On this background, it is notable that the safety concerns that led to the requirement of the Victoza REMS are no less of an issue today than they were in 2010. Thus, similar to Victoza, the Saxenda REMS will consist of a communication plan and a timetable for submission of assessments of the REMS. See Dr. Pippins's REMS memorandum and the REMS reviews by Dr. Vega and Ms. Oswell for further details.

Recommendation for Post-marketing Requirements and Commitments

The following safety-based PMRs will be included in the action letter:

- An MTC registry-based case series of at least 15 years duration, which will also establish a registry of incident cases of MTC and characterize their medical histories related to diabetes and use of Saxenda.
- Collection of information on baseline breast cancer risk and potential confounders for all identified cases of breast cancer in the ongoing CV outcomes trial (LEADER) and trial 1839.
- Reminder that the aforementioned CV outcomes trial is being conducted as a PMR for Victoza.

In addition, to further characterize the effect of liraglutide on gallbladder motility, a study evaluating gallbladder ejection fraction in liraglutide-treated subjects will be a post-marketing commitment.

Regulatory Recommendation

- Approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
11/10/2014